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Review

White matter aging and its impact on brain function

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SUMMARY

Aging has a detrimental impact on white matter, resulting in reduced volume, compromised structural integrity of myelinated axons, and an increase in white matter hyperintensities. These changes are closely linked to cognitive decline and neurological disabilities. The deterioration of myelin and its diminished ability to regenerate as we age further contribute to the progression of neurodegenerative disorders. Understanding these changes is crucial for devising effective disease prevention strategies. Here, we will discuss the structural alterations in white matter that occur with aging and examine the cellular and molecular mechanisms driving these aging-related transformations. We highlight how the progressive disruption of white matter may initiate a self-perpetuating cycle of inflammation and neural damage.

INTRODUCTION

In his pioneering work, *De Humani Corporis Fabrica* (1543), Renaissance anatomist Andreas Vesalius provided one of the earliest descriptions of white matter structure, noting the corpus callosum as a whitish substance distinct from the softer, yellowish cerebrum.[1] Although Vesalius recognized that the corpus callosum connected the two hemispheres, he did not understand that its fibers originated from nerve cell bodies. At the time, white matter was believed to be composed of excretory ducts filled with a "spongy substance" and was thought to be the center of spirit and imagination.[1] Now, we know that white matter primarily consists of myelinated axons, glial cells, blood vessels, and extracellular matrix. Oligodendrocytes, the main cells in white matter, produce myelin sheaths that are crucial for fast signal transmission and for maintaining the functional and structural integrity of axons.[2,3] Because white matter largely lacks neuronal cell bodies and mainly serves to connect different gray matter areas, it has not received as much as attention as the cortical areas of the brain. Yet, its significance becomes evident when looking at its evolution in primates. Unlike neocortical gray matter, which grows in direct proportion to brain size, white matter mass has increased at a much higher rate, highlighting the crucial role of enhanced connectivity for higher brain function.[4] Consequently, the proportion of white matter in the human brain has risen to about 40%, with myelinated axons being a major component.[4] However, this expansion of white matter also introduces risks, providing a surface for diseases and the effects of aging. As we age, our white matter undergoes several changes. It experiences a reduction in overall volume and exhibits a decline in its microstructural integrity, and there is an accumulation of focal lesions, contributing to a decline in cognitive functions and to the risk for age-related neurological diseases, including dementia and stroke.[5–8] Many of these changes follow non-linear kinetics, starting slowly and then accelerating at a certain age.[9] In this context, we explore the structural changes in white matter associated with aging and investigate the cellular and molecular mechanisms underlying these age-related transformations. We hypothesize that chronic inflammation and vascular changes are closely linked to the degeneration of myelin and axons with age.

AGING-RELATED HUMAN WHITE MATTER ALTERATIONS

Age-related changes in human white matter have been extensively documented through neuroimaging techniques. For example, a recent study involving over 120,000 magnetic resonance imaging (MRI) scans has mapped brain morphology across the human lifespan.[10] White matter volume increases rapidly during early childhood, peaks around age 30, and then begins to decline after age 50.[10] This decline is accompanied by an exponential increase in ventricular volume. Non-traditional MRI techniques, such as diffusion tensor imaging, have been used to assess changes in white matter by measuring the diffusion of water molecules in the brain.[11,12] In white matter, water diffusion is more directional due to the alignment of axonal fibers and myelin sheaths, unlike in gray matter and fluid-filled areas.[12] Studies using these methods show that water diffusivity generally changes with age, indicating deterioration in white matter composition and integrity.[13] Furthermore, these MRI-based anatomical reconstructions of white matter tracts demonstrate distinct patterns of age-related changes, with more significant alterations observed in the anterior regions compared with the posterior ones.[7] This finding supports the notion that myelinated tracts, which complete myelination later in development, are affected at an earlier stage during aging.

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Additionally, white matter hyperintensities (WMHs), which appear as increased signal intensity on T2-weighted MRI scans, are commonly associated with normal aging.[14] These hyperintensities often indicate pathological changes in the white matter, potentially resulting from chronic ischemic small vessel disease, hypertension, diabetes mellitus, and other vascular risk factors. The distinction between normal aging and disease is often not sharp, especially regarding the vascular changes that accompany aging. The reported prevalence of WMHs is notably high. In the general population, it ranges from approximately 40%–95%.[15–19] The numbers vary based on the sensitivity of the neuroimaging method used and the study population. For example, studies such as the Cardiovascular Health Study and the Rotterdam Scan Study, which focused on participants over 60 years old, reported a high prevalence rate of around 95%.[19,20] Initially, WMHs can be focal, affecting specific areas, or multifocal, impacting multiple regions. As they progress, these lesions may become confluent, covering large areas of white matter. Thus, WMH should be seen as a continuum, with the mildest form possibly reflecting alterations associated with normal aging of white matter and the more severe forms, which are linked to clinical symptoms, being considered a disease.[21] In its most severe form, WMHs, often along with lacunar infarcts and microbleeds, can cause vascular dementia.

Histopathological analysis reveals significant heterogeneity, ranging from slight matrix disentanglement to varying degrees of demyelination and axon loss.[22,23] Despite this variability, the most consistently reported features of WMHs include diffuse myelin loss, astrogliosis, axonal damage, and widened perivascular spaces. Although it is widely accepted that WMHs primarily stem from vascular origins, the specific reasons behind the susceptibility of white matter to ischemic damage remain a topic of debate. WMHs were once primarily attributed to chronic reductions in blood flow to the white matter.[24] Such lesions predominantly occur in the deep white matter, which is nourished by the distal ends of long, deep arteries.[25] This distal location can lead to lower blood flow compared with the more superficial white matter regions. The role of reduced cerebral blood flow in the development of WMH is still under discussion and is not considered the only factor. Some have suggested that the deep white matter is situated in watershed areas—regions at the boundary between different blood supply territories—where blood flow is already limited and particularly vulnerable to ischemia.[26] Moreover, hypertension and atherosclerosis are major contributors to white matter vascular pathology. Additionally, age-related stiffening of blood vessels might contribute to the problem by impairing cerebrovascular reactivity.[27–29] This can lead to increased permeability and subsequent leakage of fluids and proteins into the perivascular spaces, potentially harming brain tissue and arterial walls. The perivascular spaces are essential for removing interstitial fluids and waste products.[30] Their function depends on vascular pulsatility, which can be affected by aging.[31] Aging can disrupt fluid circulation within the perivascular spaces, causing waste accumulation, perivascular space enlargement, and increased distances for oxygen and nutrient diffusion, ultimately contributing to the formation of white matter lesions. Although most studies indicate that age-related white matter lesions are primarily due to vascular causes, it is crucial not to assume that this is always the case. For instance, the commonly observed periventricular caps thin rims along the walls of the lateral ventricles can result from subependymal gliotic demyelination caused by changes in the ependymal lining rather than ischemic damage.[32] Additionally, as will be discussed below, aging-related perturbation of glial cells and inflammation are additional mechanisms by which white matter lesions may develop.

AGING-RELATED MYELIN PATHOLOGY

Structural changes of myelinated axons

Although MRI imaging changes do not always indicate myelin degeneration, there is a wealth of evidence documenting age-related morphological alterations in myelin and myelinated axons. Early light microscopy studies first highlighted these myelin alterations, showing reduced staining intensity in the aged human cortex.[33] This was especially evident as increased pallor in the staining of intracortical fibers in older brains, notably in association with cortical areas and fiber tracts that myelinate later in life. Stereological analysis has demonstrated that older adults have approximately ~15% less white matter and ~25% shorter total length of myelinated fibers compared with younger individuals.[34] These changes may result from a combination of aging-related factors, including increased demyelination, axonal degeneration, and impaired myelinogenesis. Peters et al. performed extensive electron microscopy analyses on brain sections of aged monkeys and detected distinct patterns of myelin alterations.[35,36] A common degenerative change in myelin with aging is a local splitting of the major dense line, which represents the closely compacted cytoplasmic surfaces, creating pockets of cytoplasm likely belonging to the oligodendrocyte forming the sheath. These pockets appear degenerative, as they are dense and often contain amorphous bodies. Another change is the formation of blebs resulting from splitting of compact myelin at the apposed outer membranes. Other age-related alterations include the formation of redundant myelin sheaths, circumferential splits in myelin sheaths, axonal damage, and some paranodes appearing to be in disarray, stacked closely together. Ultrastructural studies on myelin of aged rodents confirm these patterns of myelin alterations (Figure 1).[37,38]

Cellular and molecular changes of myelinating oligodendrocytes and their precursors

These observations collectively prompt the question of how these ultrastructural features develop. One possibility is that they arise as a response to neuronal degeneration. However, most studies have concluded that there is no significant or only mild loss of cortical neurons with age, making primary neuronal cell death an unlikely cause.[39–41] Instead, the cause appears to reside within the myelin sheath itself and/or the axon it ensheathes. To understand how brain aging affects myelin integrity, it is important to recall some of its basic properties. In the CNS, the production of essential myelin components starts when oligodendrocyte precursor cells (OPCs) complete their terminal differentiation and transform into pre-myelinating oligodendrocytes.[42–45] After synthesis and targeted delivery, these components must organize into a multilayered membrane

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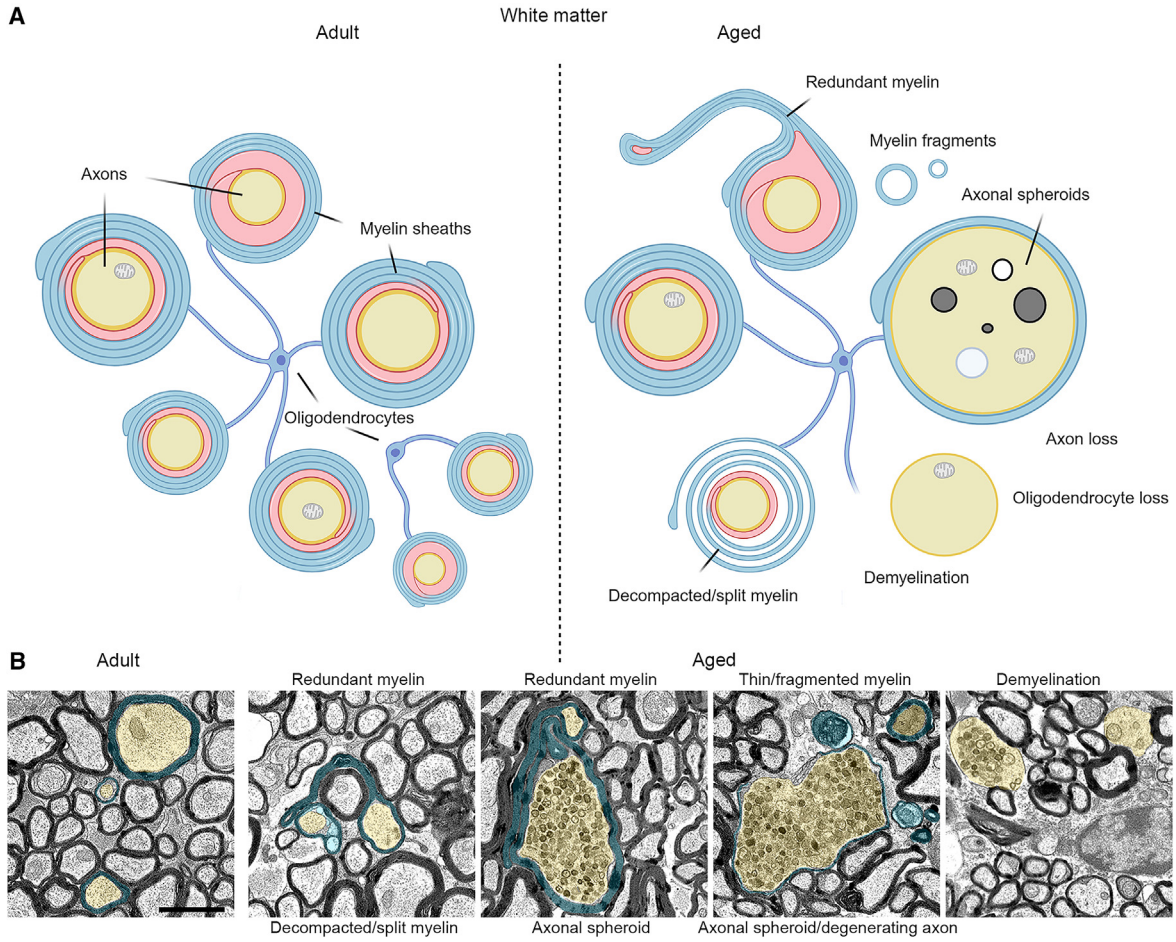

Figure 1. Ultrastructural changes associated with white matter aging

(A) Schematic representation of myelinated axons in adult (left) and aged (right) white matter. Oligodendrocytes wrap myelin sheaths around multiple axons to provide fast signal transmission and axonal support. Myelin thickness varies with axonal caliber. Aging leads to structural changes of myelin and axons that result in impaired function and degeneration.

(B) Representative electron micrographs of optic nerve cross-sections from adult and aged mice show structural alterations of myelin and axons. Selected fibers are pseudocolored (myelin blue; axons yellow) to exemplify aging-related changes. These comprise the formation of decompacted/split myelin, redundant myelin, myelin fragments, axonal spheroids, and demyelination, and can culminate in axon and oligodendrocyte loss. Scale bar, 2 μm.

structure, characterized by the tight compaction of its layers.[46] Once formed, myelin exhibits extraordinary stability with minimal turnover.[47,48] The lifespan of myelin membrane components has been estimated to exceed half a year.[47–49] This stability comes with a risk because molecules that are not replaced can accumulate damage over time. Oxidative damage from reactive oxygen species (ROS) is a hallmark of aging.[50] ROS can oxidize amino acid side chains and backbones, potentially altering protein structure and function. Additionally, ROS-induced lipid peroxidation can damage membranes and produce reactive by-products that further harm the cell or some of its compartments. For example, damage to myelin basic protein (MBP) may alter its adhesive properties in keeping the cytoplasmic leaflets of the opposing myelin bilayer together, resulting in pathology at the major dense line. Such loss of MBP function has been shown to be a critical factor in triggering myelin breakdown in models of demyelination.[51] It is important to note that normal myelin also contains areas with a less-compacted structure, allowing molecules to move and exchange more freely.[52,53] These narrow, cytoplasm-rich spaces comprise small regions of less-compacted membranes, located at the innermost and outermost edges of myelin membranes, at the paranodes, and throughout myelin as an interconnected system of cytoplasmic channels. The integrity of these cytoplasm-rich regions is crucial for maintaining myelin and its associated axons.[53] Disruption of these domains, which may occur with aging, could impair the metabolic and biophysical connection with the axon and lead to axonal damage and degeneration.

Once formed, myelin sheaths exhibit remarkable resilience, persisting for a long time. Longitudinal intravital imaging in mice shows that most are extraordinarily stable, with only 1% changing in length over several weeks.[54] Moreover, these studies indicate that the generation of myelin sheaths occurs lifelong, with more than half of cortical oligodendrocytes produced after the developmental myelination period is completed. New oligodendrocytes are continuously generated through the

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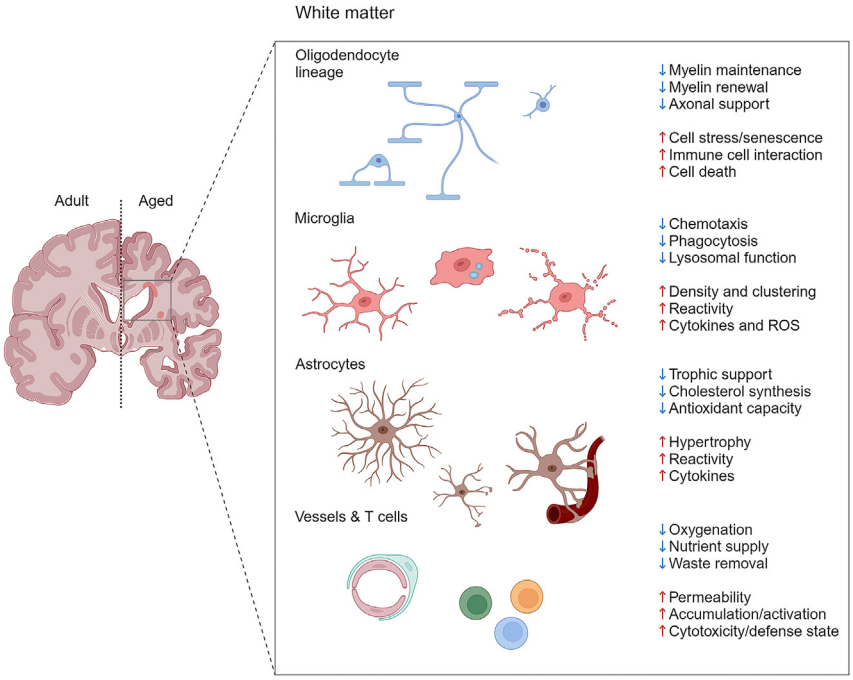

Figure 2. Cellular and molecular mechanisms associated with white matter aging

Schematic representation of how aging affects various glial, vascular, and immune cells and their function in the white matter. Aging results in impaired homeostatic functions and reactive cell state changes that promote chronic inflammation and poor resolution of accumulating damage.

differentiation of OPCs, some of which incorporate into existing neural structures to actively produce myelin.[54,55] In addition to this gradual and ongoing formation of mature oligodendrocytes, there is also a regenerative response to myelin pathology aimed at restoring the ensheathment and functionality of axons following myelin loss.[56] This regenerative process is mediated by OPCs, which can detect injury—either directly or through communication with microglia.[57] Upon sensing damage, OPCs become activated, proliferate, migrate to the site of injury, and eventually differentiate into myelinating oligodendrocytes.[56] Both modes of myelination could theoretically contribute to the replacement of degenerated myelin that accumulates with aging. However, imaging in aged mice reveals a significant decline in myelination and pre-myelinating oligodendrocytes.[58,59] This aligns with previous research showing that aging is a key factor contributing to remyelination failure in multiple sclerosis (MS) models.[60–63] The slowing of remyelination with aging is marked by the impaired recruitment of OPCs to the lesion area and their reduced differentiation into oligodendrocytes.[64,65] Chronically demyelinated lesions either have few OPCs or, more commonly, contain OPCs that have not successfully differentiated.[65,66] The underlying mechanisms that alter OPCs during aging are complex and multifaceted. These mechanisms encompass a wide range of biological processes, including epigenetic modifications, metabolic shifts, and the onset of cellular senescence.[67–69] Additionally, these processes can be influenced by extrinsic factors such as inflammatory signals from the aging microenvironment.[70,71] With aging, the extracellular matrix of the brain also becomes stiffer, which restricts the potential of adult OPCs to develop into myelinating oligodendrocytes, contributing to the decline in CNS myelin.[72]

As oligodendrocytes age, they transition into a disease-associated state.[73] This phenomenon was initially observed in mouse models of amyloidosis and in experimental models of MS through single-cell transcriptomic profiling.[73–77] In models of Alzheimer's disease (AD), disease-associated oligodendrocytes appear after the formation of disease-associated microglia (DAM) and the accumulation of amyloid plaques. During aging, a significant proportion of oligodendrocytes, especially in the white matter, enter this disease-associated state.[73] Analysis of differentially expressed genes in these oligodendrocytes shows a marked upregulation of immune-related genes, such as *Serpina3n* (a serine protease inhibitor linked to immune proteases) and the complement component *C4b*. Other upregulated pathways involve cell-stress-related signaling, immune signaling, interferon (IFN)-response, and several major histocompatibility complex genes. Additionally, disease-associated oligodendrocytes downregulate cholesterol biosynthesis pathways, indicating a shift from their usual role in maintaining myelin sheaths to functions related to inflammation, cell stress, and survival.

OPCs also show changes in gene and protein expression with aging, consistent with the induction of mitotic senescence, immune signaling, and dysfunctional myelinogenesis.[78,79] The transition of oligodendrocyte-lineage cells into such states in aging and disease likely stems from a combination of cell-autonomous effects and reactions to the changing microenvironment.[80] Together, these diverse mechanisms contribute to the diminished functionality and regenerative potential of OPCs and oligodendrocytes and their detrimental impact in the aging central nervous system (Figure 2).

AGING-RELATED INFLAMMATORY RESPONSES IN WHITE MATTER

Compared with peripheral organs, the brain, including its white matter, enjoys a certain degree of "immune privilege," characterized by limited immune surveillance, patrolling, and cell turnover.[81] This immune restraint likely helps prevent unnecessary immune reactions and tissue damage, as well as protects against the aging-related decline in cellular turnover. However, despite this privilege, the brain and the immune system maintain a strong and dynamic interaction, both within the brain's parenchyma and at specialized interfaces between the CNS and the immune system at the brain's borders.[82] Consequently, aging-related changes in either system inevitably impact the other.

As the immune system ages, it becomes increasingly senescent, marked by a diminished ability to detect and clear pathogens and cellular debris. Innate immune cells exhibit reduced efficiency in phagocytosis and resolution, whereas adaptive immune responses lose efficacy and diversity, often shifting toward chronic inflammation and cytotoxicity.[50,83,84] This phenomenon, known as "inflammaging," also influences the aging brain's immune system, leading to altered immune reactivity and diminished capacity for resolution.

Microglia reactions

Microglia are well known to undergo "priming" with aging, leading to an enhanced expression of their pro-inflammatory machinery.[85] This heightened reactivity can have lasting negative effects on brain function, even in the absence of disease or trauma. As microglia age, their functional capacity gradually declines, particularly in their ability to respond to chemotactic signals and engage in phagocytosis.[86] These changes may be indicative of the cellular senescence, dystrophy, and degeneration of these long-lived cells.[87] Interestingly, aging seems to primarily affect microglia in the white matter, likely due to their active role in maintaining and protecting the structural and functional integrity of the myelin sheath.[88,89] Indeed, the above-described white matter changes and oligodendrocyte dysfunction associated with aging can trigger microglial activation. In aged white matter, microglial density increases, with some of these cells clustering into nodules and undergoing morphological changes such as hypertrophy and decreased ramification.[90–92] Within these nodules, microglia actively clear abnormal myelin, leading to the formation of insoluble lipofuscin-like lysosomal inclusions, which can overwhelm their phagocytic function over time.[37] Aging-related changes in myelin integrity also result in a distinct transcriptional state of microglia in white matter. These white-matter-associated microglia (WAM) exhibit characteristics similar to DAM or the microglia-neurodegenerative phenotype (MGnD), partially activating disease-related transcriptional programs.[92–94] WAM show increased expression of proteins involved in inflammation, phagocytosis, and antigen presentation, and their transition into this aging-related state is critically dependent on triggering receptor expressed in myeloid cells 2 (TREM2). Additionally, microglia in the aging hippocampus accumulate cytoplasmic lipid droplets, exhibit impaired phagocytosis, produce high levels of ROS, and release pro-inflammatory cytokines.[95] The precise roles of these varied microglial responses during brain aging are not yet fully understood, with both detrimental and beneficial effects being proposed. These diverse functions likely stem from microglial heterogeneity, but a common thread suggests that enhancing phagocytic capacity and reducing chronic inflammation in microglia could be beneficial for maintaining cognitive function as the brain ages.[96,97]

Astrocyte reactions

Aging and the inflammatory activation of microglia have been closely linked to increased astrocyte reactivity.[98,99] Astrocytes play a crucial role in maintaining the proper function of the CNS, supporting neurons, glial cells, and brain border cells and maintaining overall homeostasis. However, like microglia, the state and function of astrocytes change as we age. With aging, astrocyte density and cell morphology shift, potentially due to changes in neural stem cell differentiation and reduced neurogenesis, which may contribute to cognitive decline.[100] Astrocytes also show regional differences in their vulnerability to aging, with more pronounced reactive states in myelin-rich brain regions.[98] Similar to aged microglia, aged astrocytes begin to resemble those seen in disease states, showing an upregulation of immune-related genes and a downregulation of genes associated with homeostatic functions.[101] When exposed to inflammatory stimuli—whether from the periphery (such as systemic inflammation) or within the CNS—astrocytes undergo compartment-specific inflammatory transitions.[102] As astrocytes and microglia age, they engage in abnormal intercellular communication. Astrocytes support reparative microglia states by secreting anti-inflammatory factors and cholesterol, but these regulatory functions decline with aging and neuroinflammation.[103] Microglia also play a role in inducing reactive phenotypes in astrocytes; for example, blocking microglia-secreted cytokines (such as interleukin [IL]-1α, tumor necrosis factor alpha [TNF-α], and complement component [C1q]) through genetic or pharmacological interventions can prevent the development of reactive astrocyte states in both disease and normal aging.[98,99] Although aged astrocytes have been proposed to secrete factors harmful to nearby neurons and oligodendrocytes, this appears to be more common in degenerative conditions rather than during normal aging.[104] However, the changes in astrocyte function still suggest a significant shift in their role, potentially contributing to the overall decline in CNS function as the brain ages.

In summary, aging leads to significant changes in CNS-resident glial cells, creating a more inflammatory microenvironment that directly or indirectly compromises neuroaxonal integrity. Novel transcriptomic approaches have reinforced the observations that these changes are especially pronounced in the aging white matter. By combining spatial and single-nucleus transcriptomics, two recent studies have revealed that glial aging progresses more rapidly in white matter than in cortical regions, with patterns that partially mirror the neuroinflammatory changes triggered by systemic inflammation.[105,106] Furthermore, rejuvenation interventions have shown region-specific effects on gene expression changes, highlighting the spatiotemporal complexity of aging of the brain.

Adaptive immune reactions

White matter aging is also associated with changes in the adaptive immune system, particularly through the increased presence of T cells.[107–110] Notably, most of these T cells are cytotoxic $CD8^+$ cells, which resemble tissue-resident memory T (TRM) cells that typically populate the adult brain at low frequencies.[111] $CD8^+$ TRM cells reside within tissues and at their borders, providing localized protection against reinfection or malignancy. However, they can also cause unintended damage in the nervous system, as observed in autoimmune diseases like MS.[112] In the aging brain, these $CD8^+$ TRM cells accumulate predominantly in white matter tracts, where they closely interact with myelinated axons that show signs of damage, such as focal blocks of axonal transport and the formation of axonal

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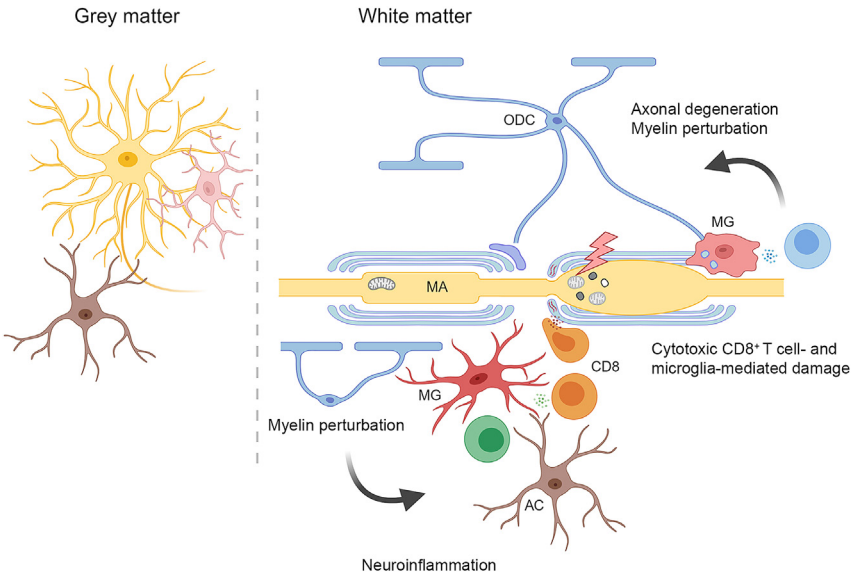

Figure 3. A self-perpetuating cycle of inflammation and neural damage associated with white matter aging

Schematic representation of how neural damage and inflammation may lead to a self-perpetuating vicious cycle in the aging white matter. Aging-related myelin perturbation triggers chronic neuroinflammation, comprising glial reactions and the accumulation of CD8$^+$ T cells. Cytotoxic CD8$^+$ T cell- and microglia-mediated damage of myelinated axons can lead to axonal degeneration and further myelin perturbation. ODC, oligodendrocyte; MA, myelinated axon; MG, microglia; AC, astrocyte; CD8, CD8$^+$ T cell.

spheroids.[38] Importantly, aged *Rag1*$^{-/-}$ or *Cd8*$^{-/-}$ mice, which lack mature adaptive immune cells or the CD8 compartment, exhibit reduced axon degeneration and better preservation of cognitive and motor function. Further investigation has revealed that these CD8$^+$ TRM cells comprise various subsets with distinct characteristics, including variable expression of checkpoint or cytotoxic effector molecules. Bone marrow transfer experiments have indicated that the aging-related axon degeneration induced by these cells is driven by cognate T cell receptor (TCR)-dependent cytotoxic mechanisms, involving the serine protease granzyme B.[38] Although the specific targets and antigens recognized by these T cells remain unclear, their clonal expansion and predominant accumulation in white matter suggest a potential myelin-related autoreactivity. In aged human white matter, CD8$^+$ T cells also accumulate, interact with damaged fibers, and express markers of chronic T cell activation and exhaustion, indicating that they may have similar detrimental effects as observed in mice. Activated CD8$^+$ TRM cells are also known to secrete cytokines, primarily IFN-γ, which can stimulate surrounding tissue to express molecules essential for broad-spectrum host defense. Supporting this, recent findings have identified IFN-responsive glial states near CD8$^+$ T cells within aging white matter.[73] Aged *Rag1*$^{-/-}$ or *Cd8*$^{-/-}$ mice show decreased IFN-responsive oligodendrocyte and microglia states, with less oligodendrocyte loss. Conversely, injection of IFN-γ into aged white matter induces stronger microgliosis and oligodendrocyte loss than into young white matter.

These observations suggest that different subsets of CD8$^+$ TRM cells may use distinct mechanisms and effector molecules to elicit various glial responses, contributing to the complex interplay between the immune system and neurodegeneration in the aging brain (Figure 3).

Immune responses in the aging brain extend beyond their effects on oligodendrocyte-lineage cells and myelinated axons. Previous studies have demonstrated that T cell infiltration in the aged brain can impair the function of neural stem cells within neurogenic niches.[110] Notably, CD8$^+$ T cells secrete IFN-γ, which has been shown to inhibit the proliferation of neural stem cells. This mechanism is likely significant for the oligodendroglial lineage, as aging is associated not only with myelin degeneration but also with a reduced capacity for myelin renewal.[58,113] In addition to these changes, CD4$^+$ regulatory T cells, which typically promote regeneration, show a decline in their pro-regenerative capacity with CNS aging.[114] This further hinders OPC differentiation and the remyelination process, exacerbating the challenges the aging brain faces in maintaining white matter integrity.

These combined observations raise several critical questions about the mechanisms underlying the recruitment and activation of CD8$^+$ TRM cells in the aged white matter. Although the exact processes remain incompletely understood, it is likely that reactive glial cells play a significant role. For instance, systemic inflammation induced by lipopolysaccharide (LPS), a known factor that exacerbates primed microglial reactivity,[115] has been shown to increase both the accumulation and pathogenic impact of CD8$^+$ T cells in aged but not adult white matter.[38] On the other hand, TREM2 deficiency, which impedes the formation of WAM, also results in reduced accumulation of CD8$^+$ cells.[73,92] Additionally, checkpoint inhibition experiments indicate that some CD8$^+$ TRM responses are triggered by peripheral stimuli and that their activation can be detrimental to white matter integrity.[73] As aging leads to systemic and vessel-related changes that promote T cell recruitment into white matter,[116] it seems that a mix of internal mechanisms within CNS and external factors may contribute to the harmful effects these T cells have on myelinated fibers.

How exactly do these activated CD8$^+$ TRM cells exert their harmful effects in white matter? Their close interaction with myelin segments and oligodendrocytes suggests that they might indirectly compromise axonal integrity by disrupting the delicate homeostatic relationship between myelin and axons.[117,118] This disruption could lead to a cascade of effects that ultimately impair the function and structure of the nervous system. Elucidating the exact cellular and molecular mechanisms will require further investigation. Additionally, it will be important to study how other lymphocyte populations may impact the aging white matter, especially because B cells have been shown to influence the

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progression of different diseases associated with myelin defects and neuroinflammation.[119,120]

One of the most perplexing questions is why the immune system appears to attack its own cells in specific compartments during aging. One possible explanation is a maladaptive activation of immune cells, where an inappropriate inflammatory response leads to a pathogenic outcome. Under normal physiological conditions, cellular damage can induce senescence, and immune cells work to eliminate these senescent cells to facilitate tissue repair.[50] However, when the immune system becomes dysfunctional or inefficient, these elimination and repair processes fail, promoting aging or disease. This might be particularly relevant in the brain, given its limited capacity for regeneration, highlighting the context-dependent impact of immune responses on aging and neurodegeneration.

IMPLICATIONS OF WHITE MATTER AGING FOR DISEASE

The susceptibility of white matter to aging has implications for diseases where age is a risk factor. These diseases, which encompass neurodegenerative, vascular, and neuroinflammatory disorders, typically share a prolonged preclinical phase and a tendency for accelerated progression with advanced age. For example, AD has a prolonged pre-clinical phase characterized by the gradual accumulation of Aβ deposits, followed by further pathological changes like the formation of neurofibrillary tangles associated with neurodegeneration, typically occurring at an older age.[121] Another example is small vessel disease, which accounts for about 20% of all dementia cases and is the second most common cause of chronic progressive cognitive impairment, with aging being a major risk factor.[122] MS is typically diagnosed at a young age as a relapsing-remitting disease, but after several decades, approximately two-thirds of the patients subsequently develop secondary progressive MS.[123] These examples, which show that chronic-progressive neurodegeneration is often preceded by a several-decade-long, sometimes clinically silent stage, raise the question of whether normal brain aging is one factor contributing to the worsening of the disease. Interestingly, aging-related white matter changes show a sex bias, with men exhibiting more prominent reductions in volume.[124] This aligns with the known sex-specific differences in progression of the above-mentioned diseases. One possible explanation for the influence of age on these diseases is the gradual buildup of pathological events until reaching a critical threshold, after which the pathology begins to accelerate. We will provide examples illustrating how age-associated white matter alterations can speed up pathology in these diseases.

One of the best-studied examples is the effect of age on the capacity for regeneration of the CNS after a demyelinating insult. As individuals age, the ability of OPCs to differentiate into myelin-forming oligodendrocytes diminishes. One underlying reason is that white matter aging modifies the microenvironment in a way that hinders oligodendrocytes from effectively engaging in the regenerative process. Although various factors contribute to the creation of this non-permissive environment in the aging white matter, one of the primary changes occurs in myeloid cells.[61,63,125,126] Experiments using heterochronic parabiosis—where aged mice with demyelinating white matter injury are paired with younger mice—has demonstrated that monocyte-derived macrophages from the young mice can effectively restore remyelination in the aged mice.[127] This finding underscores the significant impact of age on phagocytes. As described above, microglia become more reactive with age and participate in myelin degeneration. Often described as "primed," these microglia are more sensitive to secondary stimuli.[115] However, contrary to what might be expected, microglia in aging brains exhibit a diminished response to demyelinating injuries.[128] The loss of microglial plasticity results in a failure to activate the necessary transcriptional pathways for clearing myelin debris. Not only is the phagocytosis of myelin debris reduced but its lysosomal degradation and subsequent metabolism are also impaired.[56,70] A particular challenge arises with myelin-debris-derived cholesterol, as aged mice fail to activate the liver/retinoid x receptors (LXR/RXR) pathway.[62,63,129] This results in the accumulation of foamy microglia, with signs of cholesterol overload in the lesions. The reasons behind the microglial unresponsiveness in the aging brain remain unclear but appear to involve epigenetic alterations that can be restored by innate immune training.[130] Ultimately, the inability of microglia and macrophages to effectively phagocytose, degrade, and metabolize myelin debris has significant consequences for the regenerative process, leading to an increased likelihood of accelerated progression of disease pathology in demyelinating disorders.[131]

Another example is the impact of white matter pathology on AD. A recent study has established a connection between myelin dysfunction and amyloid plaque deposition in AD.[132] One important factor appears to be microglial dysfunction linked to increasing myelin pathology. Specifically, myelin dysfunction reduces the number of plaque-associated microglia. Interestingly, these DAM, which typically function to clear amyloid plaques, seem to be attracted to areas of myelin damage. This suggests that engagement of microglia with aberrant myelin as it occurs during aging might be a mechanism contributing to the increased amyloid plaque burden in AD. Moreover, oligodendrocytes have recently been shown to contribute to Aβ production and synaptic dysfunction in models of AD, emphasizing their involvement in the advancement of the disease.[133,134]

A more direct way in which detrimental functions may emerge with age is through dysfunctional myelin. Studies on de- and dysmyelination models show that progressive axon degeneration mainly affects axons with abnormal myelin sheaths that are inefficiently removed.[118,135] Dysfunctional myelin loses its metabolic support capabilities and gains detrimental biophysical properties upon inflammation-related signals such as ROS or direct immune attack.[117,136,137] Possible mechanisms could be the breakdown of non-compact cytoplasmic channels within myelin sheaths, which are essential for the metabolic connection between myelin and neurons, or cytoskeletal alterations within those domains, leading to axonal constriction.[118]

Myelin dysfunction may further contribute to detrimental pathways in aging-related diseases through its pro-inflammatory role. Recent research on amyloidosis in mouse models found a gradual accumulation of disease-associated oligodendrocytes and myelin abnormalities, accompanied by a small population of $CD8^+$ T cells. Myelin injury in AD appears to stimulate

OPC proliferation and differentiation into a pre-myelinating state characterized by high biosynthetic activity and increased susceptibility to stress and cell death.[138–142] In AD models, the differentiation of oligodendrocytes into their mature form is impaired, and, consequently, pre-myelinating oligodendrocytes accumulate, exhibiting severe pathological changes and abnormally swollen processes.[142] This suggests that progressive myelin damage may create a self-perpetuating cycle of inflammation and damage. Notably, depleting $CD8^+$ T cells can interrupt this cycle, potentially by reducing their interaction with abnormally activated microglia with myelin-damaging activity or oligodendrocytes.[142]

Finally, age-related small vessel pathology in the white matter will affect disease progression. The gradual buildup of small perforating arterioles and capillaries with signs of arteriolosclerosis, lipohyalinosis, and fibrinoid necrosis can impair white matter oxygenation and nutrient supply. Additionally, the stiffening of blood vessels that occurs with aging diminishes their ability to adapt to changes in blood flow. This can lead to increased vascular permeability, resulting in fluid and protein leakage into the perivascular spaces, which are essential for waste removal and maintaining homeostasis, thereby accelerating white matter pathology and inflammation.

CONCLUSION

White matter aging is marked by a complex array of structural, molecular, cellular, and functional alterations. Although the primary events driving these changes remain undefined, it is likely a combination of various factors. Among these, alterations in oligodendrocytes and myelin perturbation are considered potential primary events. Disease models with primary oligodendrocyte defects exemplify how such changes can induce chronic inflammation, creating a self-perpetuating cycle that leads to further damage.[118,143,144]

In addition to oligodendrocyte and myelin changes, immunosenescence and vascular alterations are possible contributors to the aging process in white matter. The resulting poor resolution of inflammation and the establishment of pro-inflammatory states further perpetuate immune-mediated tissue damage and degeneration. These processes not only contribute to but also intertwine with major neurodegenerative diseases, explaining the increased risk associated with aging.

From a therapeutic perspective, several strategies could be considered to mitigate degenerative changes associated with white matter aging. Improving myelin integrity, as suggested by rejuvenation studies to restore oligodendrocyte function, may be one approach.[145] Additionally, targeting inflammation by blocking detrimental immune responses while promoting beneficial ones holds promise. For example, selectively inhibiting harmful T cell reactions while fostering regulatory T cell functions could help reduce inflammation and restore the regenerative capacity of the aging brain.[146]

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AUTHOR CONTRIBUTIONS

Both authors researched and wrote sections of the review.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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