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Harnessing myelin water fraction as an imaging biomarker of human cerebral aging, neurodegenerative diseases, and risk factors influencing myelination: A review

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Abstract

Myelin water fraction (MWF) imaging has emerged as a promising magnetic resonance imaging (MRI) biomarker for investigating brain function and composition. This comprehensive review synthesizes the current state of knowledge on MWF as a biomarker of human cerebral aging, neurodegenerative diseases, and risk factors influencing myelination. The databases used include Web of Science, Scopus, Science Direct, and PubMed. We begin with a brief discussion of the theoretical foundations of MWF imaging, including its basis in MR physics and the mathematical modeling underlying its calculation, with an overview of the most adopted MRI methods of MWF imaging. Next, we delve into the clinical and research applications that have been explored to date, highlighting its advantages and limitations. Finally, we explore the potential of MWF to serve as a predictive biomarker for neurological disorders and identify future research directions for optimizing MWF imaging protocols and interpreting MWF in various contexts. By harnessing the power of MWF imaging, we may gain new insights into brain health and disease across the human lifespan, ultimately informing novel diagnostic and therapeutic strategies.

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CONFLICT OF INTEREST STATEMENT

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Keywords

human brain aging; imaging biomarker; magnetic resonance imaging; myelin water fraction; neurodegenerative diseases; risk factors

1 | INTRODUCTION

The increasing prevalence of neurodegenerative diseases worldwide, coupled with the global demographic shift toward an older population, highlights the critical importance of studying aging and neurodegeneration (López-Otín et al., 2023; Wilson 3rd et al., 2023). Neurodegenerative diseases, such as Alzheimer's disease (AD) and related dementias, Parkinson's disease (PD), and multiple sclerosis (MS), lead to progressive brain damage and neural dysfunction, severely affecting millions of individuals. Further, the aging process itself, even in the absence of distinct disease pathology, involves changes in brain structure and function that can dramatically impact cognitive and physical abilities (Grady, 2012; Zapparoli et al., 2022). Understanding these processes is therefore paramount not only for developing effective treatments and interventions but also for creating preventative strategies to maintain brain health and functional independence in older adults.

Post-mortem studies have revealed that myelin deterioration is among the main sequelae of aging and is an important pathophysiologic correlate of neurodegenerative disorders and dementias (Nasrabady et al., 2018). Myelin, an electrical insulator essential for facilitating the conduction of action potentials and for providing trophic support to neuronal axons, is crucial for higher-order integrative functions of the brain. However, myelin and its synthesizing cells, oligodendrocytes, are especially vulnerable to aging and neurodegenerative disease-related insults, such as oxidative damage and neuroinflammation (Nave & Werner, 2014). Therefore, accurate and detailed in vivo assessment of myelin is particularly relevant and useful in tracking and differentiating age-related myelin changes from those caused by neurodegenerative diseases, of which myelin loss is a hallmark feature (Ettle et al., 2016; Festa et al., 2024; Nasrabady et al., 2018).

Quantitative advanced magnetic resonance imaging (MRI) has revolutionized the ability to assess and monitor aging and neurological conditions in a way that is both non-invasive and highly informative. The application of advanced MRI techniques has greatly accelerated the development of imaging biomarkers for early diagnosis, monitoring of disease progression, and evaluation of treatment efficacy in neurodegenerative conditions. Of these many techniques, myelin water fraction (MWF) imaging stands out for its high specificity measurement of in vivo myelin content (MacKay et al., 1994; MacKay & Laule, 2016). Further, histological validation studies in animal and human brain and spinal cord tissue have demonstrated the high sensitivity and specificity of MWF imaging for quantifying myelin content and identifying myelin abnormalities associated with aging and neurological syndromes (Chen et al., 2017; Harkins et al., 2013; Laule et al., 2006, 2008; Soustelle et al., 2019).

Given the rapidly growing significance of this research, the current review aims to provide a comprehensive overview of the role of MWF imaging in the study of aging

and neurodegenerative diseases. First, we will briefly discuss the theoretical principles underlying MWF imaging, its applications in studies of aging and neurodegenerative diseases, and the insights it offers into the impact of modifiable and non-modifiable risk factors on myelination. Next, we will explore the current challenges and future directions in the field of MWF imaging, highlighting its potential for advancing our understanding of myelin dynamics and its implications for the diagnosis and treatment of neurodegenerative diseases. Through this review, we hope to contribute to the growing body of knowledge surrounding myelin imaging techniques and their significance in the study of human brain aging and neurological disorders.

2 | MWF IMAGING: BACKGROUND, TECHNIQUES, AND LIMITATIONS

While various MRI methods, such as diffusion tensor imaging (DTI), magnetization transfer imaging (MTI), relaxation times (T_1, T_2, and T_2*), and diffusion-weighted imaging (DWI), are sensitive to myelin, they lack specificity to any particular determinant of white matter tissue. Indeed, although these methods are sensitive to changes in brain tissue demyelination, the underlying structural and molecular mechanisms responsible for these derived indices are difficult to define because of their sensitivity to other intrinsic methodological and physiological factors, such as macromolecular content, axonal degeneration, iron, cell membrane permeability, and architectural features, such as fiber fanning and crossing. To overcome these limitations, advanced MRI methods have been developed based on multi-component relaxometry (MCR) that provides much greater sensitivity and specificity in non-invasive MRI myelin mapping (MacKay et al., 1994; O'Brien, 2014). MCR analysis has characterized two main water pools in white matter, with distinct relaxation times and fractions (Figure 1, Upper panel). The pool exhibiting the more rapid transverse relaxation and smaller fraction size has been attributed to myelin-bound water, while the more slowly relaxing pool has been assigned to relatively unbound intra- and extra-cellular water (Does, 2018; MacKay et al., 1994). The fraction of the former pool, representing the water trapped between the myelin sheaths, is calculated as the MWF and has been shown to represent a specific measure of myelin content (Chen et al., 2017; Harkins et al., 2013; Laule et al., 2006, 2008; MacKay et al., 1994; O'Brien, 2014; Soustelle et al., 2019) (Figure 1, Upper panel).

Several MRI methods exist to quantify MWF (Figure 1, Bottom panel). Multi-spin-echo (MSE)-based sequences, such as the Carr–Purcell–Meiboom–Gill sequence (CPMG) (MacKay et al., 1994), and its accelerated version, gradient, and spin echo (GRASE) (Does & Gore, 2000; Oshio & Feinberg, 1991; Prasloski, Rauscher, et al., 2012), are widely used because of their availability on most pre-clinical and some clinical MRI systems, their simple signal model, and the histological validation conducted over the past two decades (Chen et al., 2017; Harkins et al., 2013; Laule et al., 2006, 2008; Soustelle et al., 2019) (Figure 1). MWF(MSE) can be measured from MSE imaging data using multi-component T_2 analysis with the non-negative least-squares algorithm (NNLS), which does not require a priori assumptions about the number of relaxation components (Bonny et al., 2020; Bouhrara, Reiter, Maring, et al., 2018; Does & Gore, 2000; Drenthen et al., 2019; Dvorak et al., 2019; Oshio & Feinberg, 1991; Prasloski, Madler, et al., 2012; Prasloski, Rauscher, et al., 2012; Yoo et al., 2015), with available open-source tools (Doucette et al., 2020).

However, MSE-based sequences suffer from long echo times and echo spacings limiting dense signal decay sampling, particularly for the fast-relaxing water pool trapped within the myelin bilayers. To allow denser sampling, methods based on multi-gradient-echo (MGE) sequences have been developed, which account for myelin, intracellular, and extracellular water pools using an extended three-pool model (Du et al., 2007; Hwang et al., 2010; Nam, Lee, et al., 2015; Sati et al., 2013; van Gelderen et al., 2012). However, MGE-based methods are susceptible to field inhomogeneities, although corrections have been made to account for local field inhomogeneities and to incorporate external information derived from diffusion tensor imaging to improve accuracy (Chan & Marques, 2020; Du et al., 2007; Hwang et al., 2010; Nam, Lee, et al., 2015; Sati et al., 2013; van Gelderen et al., 2012) (Figure 1) or through the use of low field (LF) MRI (Schäper & Bieri, 2024). The small difference between T_2* and T_2 at LF MRI makes MGE imaging a viable method for LF MRI applications. For improved spatial resolution and reduced acquisition time, the multi-component driven equilibrium single pulse observation of T_1 and T_2 (mcDESPOT) method has been introduced (Deoni, 2011; Deoni et al., 2008; Deoni, Matthews, & Kolind, 2013). Based on steady-state MRI sequences, mcDESPOT simultaneously maps multi-component T_1 and T_2 relaxation times and MWF(mcDESPOT), providing improved sensitivity and specificity to tissue changes (Figure 1). Additionally, mcDESPOT uses conventional MR acquisition sequences, allowing for clinical feasibility. MWF(mcDESPOT) is determined using a two-component system with the stochastic region contraction algorithm (MWF-mcDESPOT) or the Bayesian Monte Carlo (BMC) analysis (MWF(BMC-mcDESPOT)) (Bouhrara & Spencer, 2015, 2016, 2017; Deoni & Kolind, 2015). While histological validation of MWF-derived values using mcDESPOT is lacking, MWF values derived using BMC-mcDESPOT have been shown to exhibit strong correlations with gene expressions related to myelin and its transcription (Bae et al., 2024). Nevertheless, mc-DESPOT has received criticisms for its instability in the accurate determination of MWF when water exchange is included in the signal model (Bouhrara et al., 2016; Lankford & Does, 2013; West et al., 2019), calling for further improvements and developments. Finally, MWF can also be estimated using Look-Locker-type sequences combined with multi-component longitudinal relaxometry analysis (MWF-LL-T_1) (Labadie et al., 2014), or a T_2-prepared module for magnetization-preparation (MWF-FAST-T_2) (Nguyen et al., 2012, 2016; Oh et al., 2006, 2007). However, these techniques have not been extensively applied in clinical investigations. For further technical details, we refer the reader to the following review papers (Alonso-Ortiz et al., 2015; Does, 2018; Lee et al., 2021; Piredda, Hilbert, Thiran, & Kober, 2021).

While MWF imaging has shown great promise in investigating brain function and disease, several limitations must be acknowledged. One major limitation is the relatively low spatial resolution, which can make it difficult to accurately detect myelin content in small brain regions, such as the cortex, hippocampus, or amygdala. Additionally, MWF is susceptible to various sources of artifacts, including head movement, magnetic field inhomogeneities, and instrumental noise, which can significantly impact measurement accuracy and introduce variability into the data (Bonny et al., 2020; Bouhrara, Reiter, Maring, et al., 2018). Moreover, MWF values could be affected by various physiological factors, such as iron content (Birkl et al., 2019), fiber orientation (Birkl et al., 2021), diffusion (Carney et

al., 1991; Deichmann et al., 1995; Le Bihan et al., 1989; Ziener et al., 2010), exchange (Allerhand, 1966; Deoni et al., 2008; Kalantari et al., 2011; Myint & Ishima, 2009; Spencer & Fishbein, 2000; West et al., 2019), off-resonance effects (Bouhrara & Bonny, 2012; Knopp et al., 2009; Majumdar et al., 1986; Zweckstetter & Holak, 1998), magnetization transfer (Bieri & Scheffler, 2007; Sled & Pike, 2000; Weber et al., 2009; Zhang et al., 2015), J-coupling (Allerhand, 1966; Mayer et al., 2007; Stables et al., 1999), spin locking (Santyr et al., 1988; Suh et al., 1994; Ulmer et al., 1996), internal gradients (Seland et al., 2004; Sun & Dunn, 2002; Washburn et al., 2008), and magnetization spoiling (Preibisch & Deichmann, 2009; Yarnykh, 2010; Zur et al., 1991), which can introduce complexity and variability into the data. The importance of these effects in a particular experiment will depend both on the specifics of the sample or subject under investigation and on the details of the pulse sequence, including the selection of parameters such as echo time, repetition time, flip angle, and gradient durations and amplitudes. Additionally, as MWF is the fraction of water trapped within the myelin sheaths to the total water content, its measurement can be biased by water content changes in the intra- or extra-cellular space as a result of, for example, axonal degeneration or inflammation, which may lead to an artificial underestimation of myelin content. Therefore, external references should be used to mitigate this issue. Further, interpreting MWF values also requires careful consideration of various factors, including age, sex, genetic background, and comorbidities, which can introduce complexity and uncertainty into the analysis. The current lack of standardization in MWF imaging protocols and data analysis methods hinders comparison across different studies and populations, limiting the generalizability of the findings and the ability to aggregate data across studies.

Despite these limitations, MWF remains the most effective measure of myelin content. MWF provides a quantitative assessment of myelin water content, which is highly correlated with myelin density. Therefore, MWF imaging offers a unique advantage in studying demyelination and remyelination processes in various neurological conditions, allowing researchers to specifically target myelin and gain insights into the underlying pathophysiology. By providing a measure of myelin content, MWF imaging can help to better understand the mechanisms of cerebral aging and neurodegeneration, monitor treatment efficacy, and potentially serve as a biomarker for disease progression and remission, as discussed in the following sections.

3 | MWF IMAGING IN AGING AND NEURODEGENERATIVE DISEASES

MWF imaging has proven invaluable for understanding the patterns of white matter maturation and neurodegeneration across the adult lifespan. In a seminal work, Deoni and colleagues investigated the utility of MWF imaging to determine the trajectory of white matter and myelin development from 3 to 60 months of age (Deoni et al., 2012). The spatio-temporal pattern of early brain myelination as demonstrated by MWF(mcDESPOT) follows a sigmoidal shape closely resembling that of histological data, characterized by a lag period followed by exponential growth within the first 12–16 months of age and slower growth from 2 to 5 years of age (Figure 2, Upper panel). Myelination has been observed to begin in posterior brain regions, including the cerebellum, internal capsule, and occipital lobes, and end in anterior brain regions, specifically the frontal and temporal

lobes. MWF imaging also corroborates previous observations from post-mortem (Peters, 2002; Tang et al., 1997), volumetric (Bartzokis et al., 2001; Jernigan et al., 2001; Raz et al., 2005), and diffusion imaging studies (Colmenares et al., 2023; Cox et al., 2016) of cerebral aging following an inverted U-shaped trajectory across the adult lifespan, in which myelination typically peaks at middle age then gradually declines at older ages (Arshad et al., 2016; Bouhrara et al., 2019; Dvorak et al., 2021; Uddin et al., 2019) (Figure 2, Bottom panel). Further, consistent with the retrogenesis (last in–first out) hypothesis, these MWF studies also reported differential rates of demyelination across various brain regions, in which early-myelinating posterior brain regions exhibit delayed demyelination with age compared to late-myelinating anterior brain regions and thus may be selectively spared from the aging process and degeneration (Bender et al., 2016; Brickman et al., 2012). As such, the age-related demyelination of anterior brain regions, including the frontal and temporal regions known to subserve higher-order neural functions, may explain related cognitive, behavioral, and functional deficits exhibited at advanced ages.

In the context of neurodegenerative disorders, MWF imaging has been extensively utilized in studies of MS, a chronic inflammatory and immune-mediated neurodegenerative disease that directly targets the myelin sheath and oligodendrocytes, leading to widespread myelin and axonal damage with concomitant cognitive and motor deficits (Figure 3). A recent comprehensive scoping review by Khormi and colleagues encapsulates the breadth of MS studies that employ myelin water imaging (Khormi et al., 2023). Notably, multiple MWF studies have shown heterogeneity in myelin profiles across different types of MS lesions (Faizy et al., 2016; Hurtado Rúa et al., 2022; Johnson et al., 2023; Kitzler et al., 2022; Panou et al., 2021; Rahmanzadeh et al., 2021). For example, Faizy et al. observed that mean MWF(MSE) values significantly differ between three different lesion types, with contrast-enhancing lesions demonstrating the lowest mean MWF values (Faizy et al., 2016). Recently, Rahmanzadeh et al. found that periventricular lesions exhibit significantly lower MWF(FAST-T_2) values compared to juxtacortical lesions, implying greater myelin damage (Rahmanzadeh et al., 2021). Overall, MWF values in MS-related white matter lesions were markedly lower compared to those of normal-appearing white matter (NAWM) and healthy tissue. Longitudinal MWF studies have also shown that chronic MS lesions lead to demyelination over time, particularly in the occipital lobes (Pandya et al., 2020), while acute MS lesions demonstrate a trend of increasing MWF(FAST-T_2) over time, which is likely indicative of a combination of reduced edema and myelin recovery (Vargas et al., 2015). Further, MWF(mcDESPOT) imaging has been shown to be robust in detecting changes in tissue pathology and clinical symptoms in primary progressive MS (Figure 2) (Kolind et al., 2012). Recent studies have also applied MWF imaging to examine changes in myelin after pharmacological interventions. For example, a recent MS clinical trial study found that MWF(mcDESPOT) in NAWM and chronic lesions is higher in participants administered ocrelizumab compared to those administered interferon beta-1a, suggesting that ocrelizumab shows greater efficacy in protecting against demyelination in MS (Kolind et al., 2022). Additionally, a recent seminal MWF(MGE) study provided the first biologically validated, imaging-based evidence of myelin repair in MS via pharmacological intervention (Caverzasi et al., 2023), demonstrating that MS patients exhibit increased MWF in the NAWM of the corpus callosum after administration of clemastine fumarate, an antihistamine compound.

These studies underscore the pivotal role of MWF imaging in MS research, offering a sensitive measure of myelin changes for improved diagnosis, monitoring of disease progression, and evaluation of clinical treatment outcomes.

MWF imaging has also been instrumental in demonstrating a direct relationship between myelin breakdown and prevalent neurodegenerative diseases, including AD, PD, and related dementias. Studies have shown that individuals with AD, mild cognitive impairment (MCI), and vascular dementia have significantly lower MWF compared to healthy controls, with AD patients exhibiting the most substantial reduction, particularly in the parietal and medial temporal lobes and segments of the corpus callosum (Bouhrara, Reiter, Bergeron, et al., 2018; Kavroulakis et al., 2018; Lim et al., 2022). Further, individuals with PD exhibit altered MWF(mcDESPOT), particularly in frontal and temporal white matter, with the extent of MWF reduction associated with disease severity (Dean et al., 2016). Specific regional patterns of MWF(MSE) alterations are also associated with distinct clinical phenotypes of PD (Baumeister, Kim, et al., 2019) and are uniquely associated with rigidity symptoms compared to other MRI metrics (Cai et al., 2022). These findings may therefore enable more accurate disease classification and personalized treatment strategies based on individual myelin profile.

While the primary focus of this review is on normative aging, neurodegenerative diseases, and risk factors influencing myelination, it is noteworthy that MWF MR imaging has also been successfully applied to study a wide range of psychiatric, autoimmune, genetic, metabolic, and vascular conditions, including schizophrenia (Flynn et al., 2003; Vanes et al., 2018), psychosis (Lang et al., 2014; Vanes et al., 2019), autism (Deoni et al., 2015), neuromyelitis optica (Jeong et al., 2016, 2017; Manogaran et al., 2016), neurofibromatosis (Billiet et al., 2014), Niemann-Pick disease (Davies-Thompson et al., 2016), Huntington's disease (Casella et al., 2021), phenylketonuria (Sirrs et al., 2007), stroke (Borich et al., 2013; Lakhani et al., 2017; Park, Cho, et al., 2022), primary and amyotrophic lateral sclerosis (Kolind et al., 2013), among others. These conditions all involve demyelination, as is measurable using MWF MRI. Recent comprehensive reviews highlight the sensitivity and utility of MWF imaging in addressing clinical applications, further underscoring its potential as a diagnostic and research tool (Balaji et al., 2022; MacKay & Laule, 2016; Mancini et al., 2020; Stellingwerff et al., 2023; van der Weijden et al., 2021, 2023). While there is some overlap between these papers and our manuscript, together they offer a thorough understanding of myelin mapping. Our review complements previous works by delving deeper into the hallmarks, outcomes, and risk factors affecting myelination as measured by MWF MRI.

Collectively, these MWF studies offer a unique window into the myelin integrity of the brain, providing insights into the processes of myelin deterioration and repair that underlie cognitive decline, motor dysfunction, and the pathogenesis of neurodegenerative diseases. The ability of MWF imaging to detect subtle changes in myelin content across different brain regions and disease states not only aids in early disease detection but also offers the potential as a reliable and powerful biomarker for assessing treatment efficacy and disease progression. Utilization of MWF imaging in future interventional studies of neurodegenerative diseases will enable more precise monitoring of therapeutic interventions,

facilitating the development of targeted treatments that can halt or slow the progression of demyelinating conditions.

4 | MWF IMAGING AND HALLMARKS OR OUTCOMES OF NEURODEGENERATION

Hallmarks and outcomes of neurodegeneration associated with cerebral aging and diseases constitute a vital area of study for understanding the biological underpinnings of these conditions. Clinical in vivo research utilizing MWF imaging has provided fundamental insights into the cellular and molecular pathways that form the basis of these hallmarks and how cerebral myelination may either affect or be affected by these processes.

4.1 | Protein aggregation

Protein aggregation, in the context of both healthy cerebral aging and neurodegenerative diseases, is increasingly believed to be a key mechanism underlying demyelination. However, the precise relationship between protein aggregation and demyelination—whether one is a cause or a consequence of the other—remains to be definitively determined. In the context of AD, the myelin model, as introduced by Bartzokis (2004), posits that because of the unique vulnerability of oligodendrocytes to oxidative stress and injury, age-related myelin breakdown may predispose to the development of AD and related dementias through a variety of mechanisms, including promoting the aggregation of amyloid-beta (Aβ) and tau oligomer fibrils and subsequent neuronal death, as increasingly demonstrated in animal models (Depp et al., 2023). In PD, although it is primarily characterized by alpha-synuclein aggregation in dopaminergic neurons of the substantia nigra, alpha-synuclein-positive inclusions have also been found in oligodendrocytes and are associated with myelin abnormalities in animal models (Bae et al., 2023; Wakabayashi et al., 2000). Other neurodegenerative diseases that are well-characterized by protein aggregates, such as huntingtin aggregation in Huntington's disease or protein inclusions containing *TDP-43*, *FUS*, and *SOD1* protein in amyotrophic lateral sclerosis, also exhibit oligodendrocyte dysfunction and myelin deterioration (Bartzokis et al., 2007; Raffaele et al., 2021).

Currently, MWF imaging studies focused on the relationship between myelin integrity and protein aggregation have been predominantly conducted in the context of AD. For example, in a study of pre-clinical AD, reduced MWF(mcDESPOT) was closely associated with cerebrospinal fluid (CSF) biomarkers of AD pathology, including reduced concentrations of $A\beta_{42}$ and elevated concentrations of total tau, phosphorylated tau 181 (pTau181), and soluble amyloid precursor protein ($sAPP\beta$) (Dean et al., 2017). Further, in a multimodal MWF-MRI, functional MRI, and tau-positron emission tomography (PET) imaging study, higher MWF(MSE) levels were associated with lower susceptibility of functionally connected cortical regions to accumulate fibrillary tau (Rubinski et al., 2022). Additionally, in a study investigating the relationship between plasma biomarkers of AD and MRI metrics of myelin and axonal integrity in cognitively unimpaired adults, it was observed that lower MWF(BMC-mcDESPOT) was significantly associated with higher glial fibrillary acidic protein (*GFAP*), a marker of reactive astrogliosis and neuroinflammation, in the temporal lobes, a well-known region of AD pathology (Walker et al., 2023). Collectively, these studies

provide compelling evidence of the association between myelin loss and protein markers of AD pathology in humans. Future work should aim to explore this relationship longitudinally, as well as to investigate the relationship between MWF and other protein aggregates, such as alpha-synuclein in PD.

4.2 | Iron accumulation

Iron participates in several key biological processes critical for the maintenance of normal neurological function, including the transport of oxygen to the brain, mitochondrial respiration, oxidative phosphorylation, and the synthesis of neurotransmitters. Oligodendrocytes, which are the main iron-containing cells of the central nervous system, incorporate iron as an essential cofactor for enzymatic activities related to myelin production and maintenance (Khattar et al., 2021; Möller et al., 2019; Todorich et al., 2009). However, emerging evidence reveals that aging and neurodegenerative diseases, including in AD, PD, and MS, are associated with iron accumulation, which, if not sufficiently cleared, may catalyze free radical reactions that promote oxidative damage to cerebral tissues (Emerit et al., 2001). Yet, the etiology of iron accumulation remains elusive. One emerging paradigm suggests that myelin breakdown and oligodendrocyte degeneration release substantial stores of iron that lead to overaccumulation and subsequent neurodegeneration with cognitive and behavioral dysfunctions (Bartzokis, 2004). To date, only two clinical studies have utilized MWF imaging in combination with quantitative susceptibility mapping (QSM), a sensitive MRI technique capable of detecting local field distortions caused by iron-associated magnetic susceptibility inhomogeneities, to provide direct support for the hypothesis that myelin loss is associated with iron accumulation in human brain aging (Khattar et al., 2021), and neurodegenerative diseases, namely MS (Yao et al., 2018). Although such research is currently limited, these studies provide compelling evidence that excess iron exerts a deleterious impact on myelin integrity, potentially accelerating the process of neurodegeneration and contributing to the cognitive and behavioral deficits observed in aging and neurodegenerative diseases. Future work that combines QSM and MWF imaging to investigate the relationship between iron and myelin loss in the context of other neurodegenerative diseases, including AD and PD, could further elucidate the intricate mechanisms by which iron dysregulation contributes to the pathogenesis of these conditions. However, it is important to reemphasize the impact of iron on MWF determination so that careful experimental designs and results' interpretation are needed (Birkl et al., 2019).

4.3 | Cognitive and physical declines

Cognitive decline and motor dysfunction associated with aging and neurodegenerative diseases have been strongly linked to demyelination in numerous studies. Myelin sheaths are essential for the saltatory conduction of action potentials across the axon, facilitating rapid signal transmission and integration of information across neural networks. Degeneration of myelin is thus believed to result in disruptions in the timing and synchronization of neural impulses on which normal brain functions, including cognition and motor function, depend. As such, accurate quantification of changes in myelin integrity through MWF imaging is crucial for understanding the underlying mechanisms of cognitive and motor dysfunctions in human brain aging and disease. Furthermore, direct observation of myelin changes may facilitate the identification of early demyelinating events that precede clinical symptoms,

thereby allowing for timely and targeted intervention strategies aimed at mitigating the adverse effects of myelin loss on cognitive and motor function.

Recent studies have investigated the relationship between MWF and cognition, revealing a complex interplay between myelin integrity and cognitive function during development and aging. For example, one study explored the relationship between white matter development and cognitive ability in children from 3 months to 5 years old (Deoni et al., 2016). The study found a significant positive relationship between MWF(mcDESPOT) and cognitive ability in the posterior portion of the corpus callosum. Additionally, there were age-related differences in the relationship between MWF and cognitive ability, with significant positive associations identified in different brain regions across various age groups. Other studies discovered that lower MWF in different brain regions including the fornix was linked to poorer memory performance in adults (Bangen et al., 2021; Mendez Colmenares et al., 2024) (Figure 4a). Recently, it has been reported that lower MWF(BMC-mcDESPOT) is associated with more rapid cognitive decline, particularly in processing speed and executive functions in cognitively unimpaired adults (Gong, Bilgel, Kiely, et al., 2023; Gong, Bilgel, Resnick, et al., 2023) (Figure 4a). Multiple MWF studies have also investigated the relationship between myelin and cognition in various neurodegenerative diseases. In individuals with MS, lower MWF and higher myelin heterogeneity have been associated with worse information processing speed (Abel, Vavasour, Lee, Johnson, Ackermans, et al., 2020; Abel, Vavasour, Lee, Johnson, Ristow, et al., 2020; Ouellette et al., 2020), verbal memory (Abel, Vavasour, Lee, Johnson, Ristow, et al., 2020), and executive function (Baumeister, Lin, et al., 2019). These findings suggest that MWF may serve as a useful biomarker of cognitive decline, especially in processing speed and executive functioning, and potentially inform early intervention strategies. However, further research is needed to fully elucidate the relationship between MWF and cognition across various domains and populations.

Recent studies have also investigated the relationship between MWF and motor function in the context of aging and neurodegenerative diseases. For example, both lower cerebral myelination (Faulkner et al., 2023) (Figure 4b), and brainstem myelination (Akhonda et al., 2023), have been associated with slower gait speed, a reliable functional metric and biomarker of health status, in cognitively unimpaired adults. Further, in older adults with cerebral small vessel disease and MCI, lower MWF(MSE) in specific white matter tracts, including the cingulum, superior longitudinal fasciculus, posterior corona radiata, and body of the corpus callosum, was associated with higher gait variability, a strong marker of fall risk and mobility impairment (Boa Sorte Silva et al., 2022). In individuals with MS, the ratio of MWF(MSE) in lesions to NAWM also significantly predicted changes in functional mobility after a rehabilitation intervention of downward slope walking (King et al., 2018). Moreover, in individuals with PD, sex differences in MWF(MSE) were found to be associated with sex differences in motor symptom profiles of PD, with women exhibiting more symptoms of tremor and brady-kinesia and men exhibiting more rigidity and axial symptoms (Cai et al., 2023); these findings provide further insight into the underlying mechanisms that contribute to the well-established differences in clinical characteristics between male and female PD patients.

The prominent relationship between myelin, executive function, and processing speed, and motor function underscores the intricate interdependence of white matter integrity and cognitive-motor abilities throughout the aging process. Given that white matter and myelin are believed to be the most vulnerable to the aging process and exhibit early age-related degeneration compared to neurons (Bartzokis, 2004; Wang et al., 2018), it is plausible to suggest that this vulnerability may explain why processing speed and executive functions, and the brain regions associated with them, are especially sensitive to aging (Nilsson et al., 2014; Reuter-Lorenz et al., 2021), and are hypothesized to lead to general cognitive deficits, including memory decline, as a consequence (Albinet et al., 2012; Salthouse, 1996; West, 1996). These cognitive functions, essential for efficient information processing and decision-making, also play a fundamental role in coordinating motor responses. In neurodegenerative diseases like AD, PD, and MS, deficits in processing speed and executive function often accompany motor symptoms. This convergence suggests a shared underlying pathology involving disruptions in myelin integrity, leading to impairments in both cognitive and motor functions in aging and neurodegenerative diseases.

5 | RISK FACTORS INFLUENCING MYELINATION

Mounting evidence from MWF imaging reveals that various reversible and non-reversible risk factors linked to aging and neurodegenerative diseases are associated with human demyelination. Elucidating the precise relationship between these risk factors and myelin loss is crucial for developing effective strategies to safeguard and enhance myelin integrity. This knowledge will guide the development of lifestyle changes and pharmacological interventions aimed at mitigating these risk factors and promoting myelin health.

5.1 | Age

Age is known as the primary contributing risk factor of neurodegeneration. During the aging process, myelin sheaths undergo natural degradation, leading to a decline in cognitive and motor functions. This process, known as demyelination, results in slower neural transmission and reduced neural plasticity. Studies have shown that aging is associated with a decrease in myelin thickness and an increase in myelin damage, particularly in regions vulnerable to aging, such as the prefrontal cortex and the medial temporal lobes, including the hippocampus and entorhinal cortex. Additionally, age-related myelin loss has been linked to neurodegenerative diseases, including AD and PD. While age-related changes in white matter have been extensively investigated using sensitive MRI methods, the age-related microstructural changes in myelination as measured using MWF have received surprisingly little attention (Arshad et al., 2016; Bouhrara et al., 2019; Dvorak et al., 2021). These limited studies have revealed a complex pattern of myelination across the lifespan, with continued myelination until middle age followed by a rapid decline thereafter. Additionally, genetic factors, and environmental factors such as exercise and cognitive stimulation, may also influence myelination patterns throughout the aging process, as elaborated below. Further research is therefore urgently needed to uncover the underlying mechanisms driving age-related decline in myelin content and how age interacts with other risk factors. Such research will provide a more comprehensive understanding of brain aging

and the development of neurodegenerative diseases, offering insights that could inform prevention and treatment strategies.

5.2 | Sex

Distinct brain developmental patterns have been reported between sexes during early childhood and adulthood (Dean et al., 2015; Liu et al., 2010). Sex differences in brain structure and function have been observed in adulthood, with females typically having greater volume in the prefrontal cortex, orbitofrontal cortex, superior temporal cortex, lateral parietal cortex, and insula, while males typically having greater volume in the ventral temporal and occipital regions (Liu et al., 2020). These findings suggest that there may be inherent differences in brain development and organization between males and females, which could have implications for understanding sex differences in cognition and behavior. Moreover, recent studies have revealed significant sex differences in MWF, with women showing higher MWF values than men, particularly in regions such as the fornix, corpus callosum, and anterior corona radiata (Arshad et al., 2016; Bouhrara et al., 2019; Brenner et al., 2023; Kiely et al., 2022; Liu et al., 2010). This suggests that female brains may have a greater proportion of myelinated fibers, which could contribute to sex differences in cognitive abilities and vulnerability to demyelinating disorders. Age-related changes in MWF may also vary between males and females, with females experiencing a more rapid decline in MWF with age (Arshad et al., 2016; Bouhrara et al., 2019), which may be exacerbated by menopause. The decline in estrogen and progesterone levels during menopause may contribute to a more pronounced decrease in MWF, potentially impacting cognitive function and increasing the risk of neurodegenerative diseases (Brinton et al., 2015; Morrison et al., 2006). These sex differences in myelin are consistent with previous findings that oligodendrocyte proliferation and myelin protein regulation differ in males and females (Cerghet et al., 2006; Greer et al., 2004). Sex steroids may influence this differential regulation, potentially contributing to sex differences in myelin repair mechanisms (Marin-Husstege et al., 2004). Cross-sectional and longitudinal studies highlight sex differences in brain maturational processes, emphasizing the importance of myelination in understanding neuropsychiatric disorders. However, other MWF-based studies failed to identify sexual dimorphism in MWF (Burzynska et al., 2024; Dvorak et al., 2021; Faizy et al., 2020). While the limited sample sizes and differences in MRI methodology to estimate MWF may have precluded the detection of sex-related differences in MWF, these studies underscore the need for further research to confirm these findings and explore the underlying hormonal and genetic factors contributing to sex differences in MWF. Further research in this area may also have important implications for the diagnosis and differential treatment of neurological disorders in both men and women.

5.3 | Genetic risk factors

Genetic risk factors play a significant role in myelination, with various genes contributing to the development and maintenance of myelin. For example, the apolipoprotein E ε4 (*APOE-ε4*) allele, a well-established risk factor for AD, has been linked to disrupted myelination and cholesterol transport, which are both crucial for myelin formation and maintenance (Blanchard et al., 2022). Similarly, mutations in the TMEM106B gene cause hypomyelinating leukodystrophy, a condition characterized by impaired myelin formation

and maintenance (Simons et al., 2017). Additionally, genetic causes of familial AD, such as mutations in the *APP* gene, which gives rise to amyloid precursor protein, and the *PSEN* gene, which gives rise to the protein presenilin, lead to proteinopathies and subsequent neurodegeneration, including myelin degeneration (Bartzokis, 2011; Lopera et al., 2023). Recent findings unveiled by MWF(BMC-mcDESPOT) imaging indicate that, among a cohort of cognitively healthy individuals, carriers of the *APOE-ε4* allele were found to have lower MWF in several brain structures compared to non-carriers, while carriers of the *APOE-ε2* allele, which is believed to confer neuroprotection, have higher MWF values in most cerebral structures investigated (Triebswetter et al., 2022). The *APOE-ε4* results are complementary to Dean and colleagues' results of significantly lower MWF(mcDESPOT) in infant carriers of *APOE-ε4* as compared to non-carriers (Dean et al., 2014), and to Remer and colleagues' finding of altered rates of myelination, as measured using MWF(mcDESPOT), in childhood carriers of *APOE-ε4* in a longitudinal study cohort of infants and young children (Remer et al., 2020) (Figure 5a). Similarly, another study found that reduced MWF(MGE) in cognitively impaired individuals is more prominent in *APOE-ε4* carriers than non-carriers, particularly in NAWM but not in white matter hyperintensities (Park, Lee, et al., 2022). The results of these studies therefore suggest the significant impact of *APOE* genotypes on myelin integrity and reveal the potential mechanistic pathway by which the *APOE-ε4* allele contributes to myelin deterioration and overall development of AD. Further, genetic variation in *PLP1*, a gene that encodes for proteolipid protein, was found to be significantly associated with asymmetries in MWF(MSE) values, particularly in the parietal lobes (Ocklenburg et al., 2019). These findings support the notion that *PLP1* affects white matter myelination in the human brain, and *PLP1* mutations associated with rare demyelinating disorders, including MS and Pelizaeus-Merzbacher disease, may lead to distinct patterns of white matter vulnerability, as reflected in the observed asymmetries in MWF. These discoveries underscore the critical role of considering genetic factors in the development of personalized medicine approaches, while also calling for further investigations.

5.4 | Metabolic and vascular risk factors

Metabolic and vascular risk factors have been linked to disrupted myelination, contributing to cognitive and functional impairments. Specifically, conditions such as obesity, insulin resistance, type 2 diabetes, hypertension, and other cardiovascular diseases have all been shown to impact myelin integrity. The high metabolic burden of myelin maintenance and repair by oligodendrocytes makes white matter particularly vulnerable to metabolic stressors that accumulate with age (Roth & Nunez, 2016). The implications of mitochondrial dysfunction and impaired glucose and lipid metabolism in the pathophysiology of AD, PD, and MS may in part explain the underlying mechanisms by which myelin deterioration contributes to the progression and manifestation of neurodegenerative diseases (Lin & Beal, 2006). Further, given the energy-intensive nature of oligodendrocyte metabolism, myelin is also particularly susceptible to damage by hypoperfusion which can impede sufficient cerebral blood flow, substrate delivery, and waste removal of metabolic byproducts and toxins (Bouhrara et al., 2020). Such conditions are also known to accumulate with age and are strongly related to neurodegenerative pathologies.

Multiple MWF studies have shown the direct association between myelin integrity and metabolic and cerebrovascular dysfunctions. For example, elevated insulin levels and insulin resistance have been linked to reduced myelin content in white matter regions (O'Grady et al., 2019) (Figure 5b). These findings may possibly be attributed to altered synthesis and metabolism of cholesterol, the main constituent of myelin, caused by insulin dysregulation. Additionally, in cognitively healthy adults, lower MWF has been associated with obesity (Bouhrara, Khattar, et al., 2021), and higher adiposity and metabolic syndrome (MetS) risk scores (Figure 5b), particularly in late-myelinating brain regions (Burzynska et al., 2023). Obesity and higher adiposity may cause myelin injury through proposed mechanisms such as low-grade chronic inflammation, disrupted energy utilization and regulation, abnormal cholesterol metabolism, and oxidative stress (Fernández-Sánchez et al., 2011). Further, a direct relationship was demonstrated and further corroborated between lower MWF(BMC-mcDESPOT) and lower cerebral blood flow in the context of healthy aging (Bouhrara et al., 2020, 2022; Kiely et al., 2023) (Figure 5b). Hypertensive adults have also been shown to exhibit significantly lower MWF(BMC-mcDESPOT) compared to healthy controls (Laporte, Faulkner, Gong, Akhonda, et al., 2023) (Figure 5b). These findings provide further evidence that vascular dysregulation caused by arterial remodeling and altered blood pressure may lead to impaired cerebral blood flow and, consequently, reduced glucose and oxygen transport and concomitant myelin injury. In addition, individuals with cerebrovascular diseases, including stroke and vascular dementia, were shown to have local and global reductions in MWF compared to healthy controls (Borich et al., 2013; Dao et al., 2021; Ferris et al., 2022), thereby indicating the broad disruptive effects of cerebral ischemia on white matter integrity. These findings highlight the importance of addressing metabolic and vascular health in the prevention and treatment of neurodegenerative diseases, emphasizing the intricate interplay between systemic health and brain function.

5.5 | Depression

Depression, or major depressive disorder (MDD), is often a comorbidity of neurodegenerative diseases, including AD and PD. Previous studies suggest that MDD and neurodegenerative diseases share some of the same pathophysiological and molecular mechanisms (Galts et al., 2019), including morphological brain changes, disturbances in monoaminergic neurotransmitters, dysregulation of the hypothalamic–pituitary–adrenal axis and neuroinflammation, oxidative stress, mitochondrial dysfunction, and impaired trophic support to neurons, all of which can result in neuronal death and atrophy (Dexter & Jenner, 2013; Gil & Rego, 2008; Kumar et al., 2015). Further, both pre-clinical and clinical studies, including structural and diffusion MRI studies, have shown that MDD is also associated with abnormalities in brain white matter and myelin content (Boda, 2021; Dalby et al., 2010; Hemanth Kumar et al., 2014; Sacchet & Gotlib, 2017). However, it remains unclear whether MDD is a prodromal disorder that can predict the onset of neurodegenerative diseases, or simply is an accompanying disorder that occurs in tandem with the early neuropathological changes of these diseases.

While the available literature remains limited, a few MWF imaging studies have provided more direct evidence of the association between MDD and altered myelination, including in individuals with neurodegenerative diseases. For example, in individuals with probable

AD and MCI, reduced MWF(MSE) is significantly associated with the severity of neuropsychiatric impairment, including memory impairment and depressive symptoms (Kavroulakis et al., 2018). In individuals with PD, higher depression and apathy scores are associated with reduced MWF(MSE), particularly in the association and projection tracts (Baumeister, Kim, et al., 2019). However, in individuals with MS, anxiety and depression symptoms were not significantly associated with MWF(MSE) values (Panou et al., 2021). Further work is therefore needed to elucidate the relationship between depressive symptoms and myelin integrity across different stages and types of neurodegenerative diseases. Longitudinal MWF studies assessing changes in myelin integrity and depressive symptoms over time could help determine if changes in myelin integrity are a consequence of the depressive state, a contributing factor to its onset, or a marker of disease progression. Additionally, exploring the effects of antidepressant treatment on myelin integrity and neurodegenerative disease progression could offer insights into potential therapeutic mechanisms and strategies for managing comorbid MDD in patients with neurodegenerative diseases.

5.6 | Lifestyle and environmental risk factors

Various modifiable lifestyle risk factors influence brain aging and the onset and progression of neurodegenerative diseases. Further, lifestyle factors, such as physical exercise (Graciani et al., 2023; Kujawa et al., 2023), education and literacy level (de Resende et al., 2022; McPhee et al., 2019), cognitive training (Antonenko et al., 2023; Engvig et al., 2012; Metzler-Baddeley et al., 2017), nutrition and dietary habits (Langley et al., 2020), smoking and alcohol use (Gons et al., 2011; Rice & Gu, 2019; Yu et al., 2016), and environmental agents (Costa et al., 2004), have been shown to affect white matter integrity. Understanding the mechanisms underlying the relationship between these risk factors and myelination is essential for developing lifestyle interventions aimed at preserving cognitive function, slowing brain aging, and preventing development and further progression of neurological disorders. Although the impact of lifestyle factors on brain health is well-established, there currently remains only a paucity of MWF studies lending support for the direct impact of lifestyle risk factors on human brain myelination. Higher physical activity has been associated with higher MWF in healthy young adults (Bracht et al., 2016) and older adults with cerebral small vessel disease and MCI (Boa Sorte Silva et al., 2023). Higher physical activity in post-stroke individuals has also been shown to improve myelin content to a level comparable to that of healthy older adults (Greeley et al., 2022). Other MWF studies on nutrition, cognitive stimulation, or education are currently limited to investigations on infancy and early childhood white matter development. For example, Deoni et al. found that breastfeeding, which provides essential oligosaccharides and other critical nutrients for neurodevelopment, was associated with higher MWF(mcDESPOT) and cognitive ability in infants (Deoni et al., 2018; Deoni, Dean, et al., 2013). Dietary nutrients rich in long-chain fatty acids, iron, choline, sphingomyelin, and folic acid are also associated with early MWF(mcDESPOT) trajectories (Deoni et al., 2018; Schneider et al., 2023). Studies on prenatal exposure to maternal nicotine (Björnholm et al., 2020) and alcohol use (McLachlan et al., 2019) observed no significant associations to MWF(mcDESPOT), yet significant associations with DTI metrics, suggesting that these toxins may be more greatly associated to axonal integrity as opposed to myelin integrity.

Notwithstanding the sparsity of these investigations, such research contributes valuable preliminary evidence that signifies the urgent need for expanded research in this field. They serve as a critical foundation for hypothesizing the broader impacts of lifestyle factors on myelination throughout the lifespan, including in the early stages of life. Importantly, these studies highlight the intricate connections between lifestyle behaviors and neurobiological outcomes, advocating for the necessity of longitudinal and cross-sectional studies that could elucidate the temporal and causal relationships between lifestyle modifications and myelin health. The exploration of these associations is paramount for the refinement of preventive and therapeutic strategies aimed at mitigating the risk and progression of neurodegenerative conditions through lifestyle adjustments. Therefore, despite the scarcity of existing studies on the impact of lifestyle factors on MWF and, by extension, myelination, they are indispensable for advancing our understanding of neurodegenerative disease mechanisms and developing comprehensive and tailored approaches to preserve and enhance brain health in aging.

6 | FUTURE DIRECTIONS AND RECOMMENDATIONS

Emerging trends in MWF imaging research, such as combination with multimodal neuroimaging, improved image processing techniques, and integration with deep learning (Akhondi-Asl et al., 2015; Alonso-Ortiz et al., 2017; Björk et al., 2016; Bouhrara et al., 2015; Bouhrara, Reiter, Maring, et al., 2018; Dean et al., 2016; Drenthen et al., 2019; Du et al., 2007; Dvorak et al., 2019, 2023; Gong, Khattar, Kiely, et al., 2023; Guo et al., 2013; Heath et al., 2018; Hwang et al., 2010, 2011; Hwang & Du, 2009; Jones et al., 2003; Jung et al., 2018; Kumar et al., 2016; Kwon et al., 2013; Lenz et al., 2012; Levesque et al., 2010; Mohammadi & Callaghan, 2021; Nam, Kim, & Lee, 2015; Nam, Lee, et al., 2015; Neeb et al., 2012; Nguyen et al., 2016; Piredda, Hilbert, Canales-Rodríguez, et al., 2021), promise enhanced resolution and novel applications across various fields. These advancements hold great potential for refined diagnosis and treatment monitoring in neurological disorders. Specifically, MWF imaging may enable early diagnosis and personalized medicine in aging and neurodegenerative diseases, allowing for timely interventions and improved disease management. With its ability to detect subtle changes in myelin content, MWF imaging may serve as a valuable biomarker for monitoring disease progression and treatment efficacy, ultimately improving patient outcomes. As the field continues to evolve, we can expect MWF imaging to play an increasingly important role in addressing the growing burden of neurological disorders.

One exciting application of MWF imaging is its use for aggregate g-ratio mapping (Bouhrara, Kim, et al., 2021; Campbell et al., 2017; Cortina et al., 2022; Jung et al., 2018; Mohammadi & Callaghan, 2021; Stikov et al., 2015), which allows researchers to quantify the average myelin sheath thickness around different types of nerve fibers in the brain. By combining MWF with diffusion MRI, it is possible to estimate the aggregate g-ratio, a measure of the ratio of the outer and inner diameters of myelinated axons within a voxel. This information can be used to study the organization and maturation of brain connectivity, as well as to investigate abnormalities in myelination and demyelination in various neurological disorders. Aggregate g-ratio mapping has already revealed novel insights into brain development, aging, and disease (Berman et al., 2018; Bouhrara, Kim,

et al., 2021; Cercignani et al., 2017; Cortina et al., 2022; Jung et al., 2018; Kamagata et al., 2019; Laporte, Faulkner, Gong, Palchamy, et al., 2023; York et al., 2021, 2022), and represents one of the promising future directions of brain mapping, holding great potential for advancing our understanding of brain function and dysfunction. However, mapping aggregate g-ratio is a complex and still evolving area of research.

Adopting MWF imaging also poses a significant challenge because of its intrinsic complexity, requiring expertise in multiple fields. MR physics knowledge is essential to understanding the underlying principles and optimizing imaging protocols, while signal processing skills are necessary to extract accurate MWF values from complex data. Moreover, a deep understanding of neurobiology is required to interpret the results and relate them to brain function and disease. This multidisciplinary nature of MWF imaging creates a barrier of entry for many researchers and clinicians, limiting its widespread adoption and hindering the full realization of its potential in understanding brain function and treating neurological disorders. To improve MWF imaging, several recommendations can be made, including standardizing imaging protocols and data analysis methods to ensure consistency across studies and populations; developing higher-resolution imaging techniques to improve detection of myelin content in small brain regions; implementing robust artifact correction methods to minimize the impact of head movement, magnetic field inhomogeneities, and instrumental noise; accounting for physiological factors such as iron content, fiber orientation, and exchangeable protons; standardizing experimental factors such as pulse sequence parameters, echo time, and repetition time across sites and MRI manufacturers to facilitate data harmonization; encouraging multidisciplinary collaboration between MR physicists, engineers, and neuroscientists; conducting large-scale studies to establish normative values and exploring applications in various neurological disorders; establishing publicly accessible databases to share data and facilitate collaboration; developing and applying advanced computational methods such as machine learning and artificial intelligence to improve data analysis and interpretation; and combining MWF imaging with other neuroimaging modalities to provide a more comprehensive understanding of brain function and disease. By addressing these limitations and challenges, MWF imaging can reach its full potential in understanding brain function and treating neurological disorders.

7 | CONCLUSION

MWF imaging has already made significant contributions to our understanding of brain function and disease, providing a unique window into myelin content quantification. By advancing research in MS, MWF imaging has enabled the study of disease progression and treatment response, allowing researchers to investigate the impact of new therapies on myelin integrity. In the realm of neurodegenerative diseases, MWF imaging has shed light on the complex interplay between myelin and neuronal degeneration, providing insights into the underlying mechanisms of AD and PD, and beyond. Additionally, MWF imaging has identified risk factors for neurodegeneration, paving the way for the development of early interventional and prevention strategies. Furthermore, MWF imaging has enabled the study of brain development and aging, providing a greater understanding of the dynamic changes in myelin throughout life. While there are still limitations and challenges to be addressed,

the benefits of MWF imaging are undeniable, and continued refinement and development of this MR imaging biomarker will unlock its full potential, making a meaningful impact on the diagnosis, treatment, and understanding of neurological disorders.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable since no new data were generated or analyzed for this Review article.

Abbreviations:

Aβ	amyloid-beta
AD	Alzheimer’s disease
APOE	apolipoprotein E
BMC	Bayesian Monte Carlo
CPMG	Carr–Purcell–Meiboom–Gill
CSF	cerebrospinal fluid
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
GRASE	gradient and spin echo
mcDESPOT	multi-component driven equilibrium single pulse observation of T1 and T2
MCI	mild cognitive impairment
MCR	multi-component relaxometry
MDD	major depressive disorder
MetS	metabolic syndrome
MGE	multi-gradient echo
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSE	multi-spin echo
MTI	magnetization transfer imaging

MWF	myelin water fraction
NAWM	normal-appearing white matter
NNLS	non-negative least-squares
PET	positron emission tomography
PD	Parkinson's disease
pTau181	phosphorylated tau 181
QSM	quantitative susceptibility mapping
sAPPβ	soluble amyloid precursor protein
T1	longitudinal relaxation time
T2	transverse relaxation time

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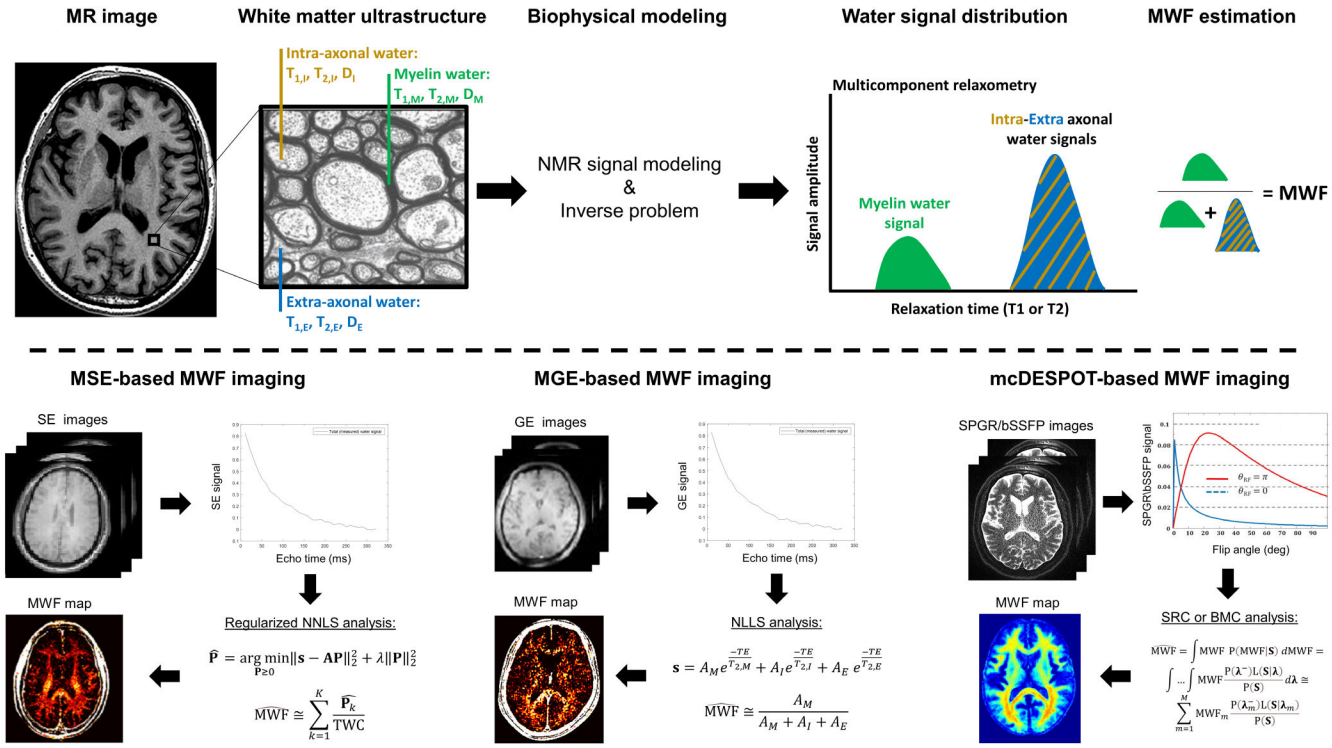

FIGURE 1.

A schematic overview of myelin water fraction (MWF) determination and the most commonly applied MRI methods. The upper panel provides an overview of the steps involved in multicomponent relaxometry for MWF determination using MRI. This process involves MR physics for appropriate data acquisition, prior knowledge of tissue microstructure for signal modeling, and expertise in mathematics and signal processing for the inverse problem and calculation of MWF. The lower panel highlights the main MRI methods used to map MWF in vivo. While the MSE and MGE-based methods involve the acquisition of imaging data at different TEs, mcDESPOT makes use of data acquired using steady-state imaging at different flip angles. All methods aim to separate the fraction of the water trapped within the myelin sheets for the estimation of MWF using multicomponent relaxometry. BMC, Bayesian Monte Carlo; bSSFP, balanced steady-state free precession; D, diffusion coefficient; mcDESPOT, multicomponent driven equilibrium single pulse observation of T1 and T2; MGE, multi-gradient echo; MSE, multi-spin echo; MWF, myelin water fraction; NLLS, non-linear least squares; NMR, nuclear magnetic resonance; NNLS, non-negative least squares; SPGR, spoiled gradient-recalled; SRC, stochastic region contraction; T1, longitudinal relaxation time; T2, transverse relaxation time; TE, echo time.

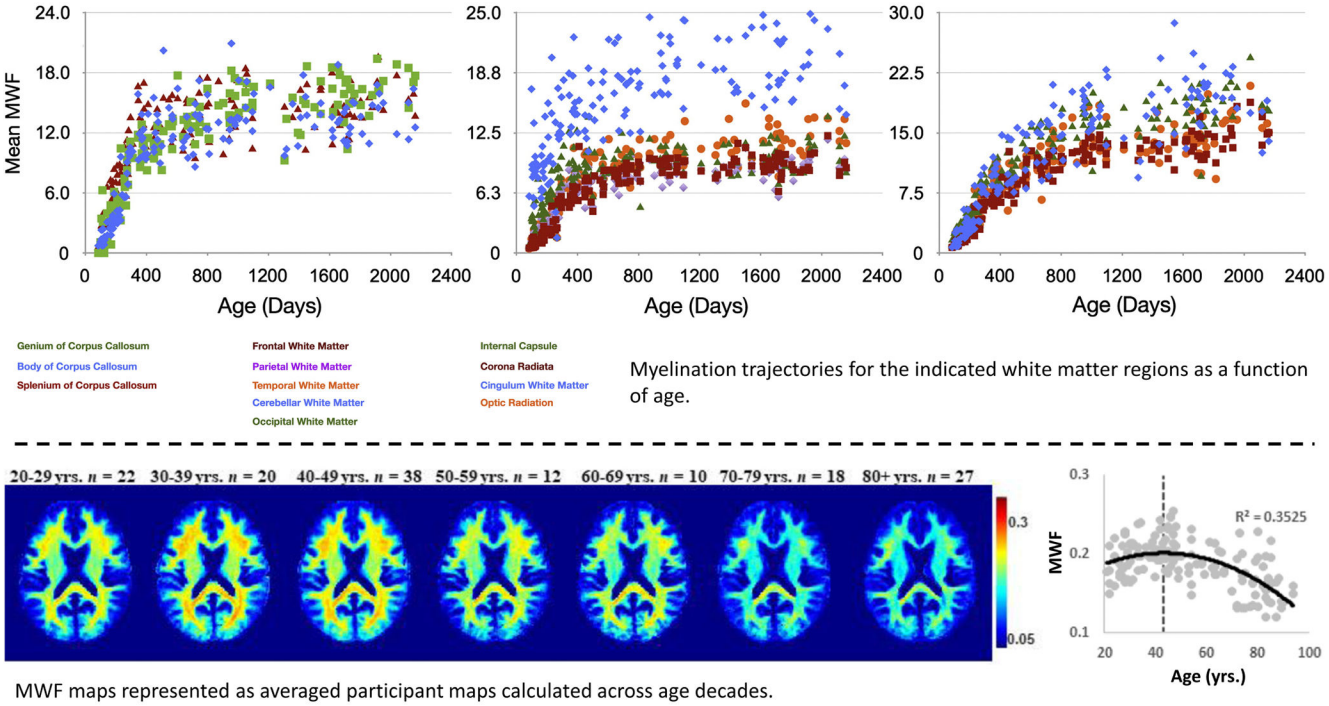

FIGURE 2.

Myelination during brain development, maturation, and aging. Top panel: Myelination trajectories for various white matter regions and pathways spanning 83 through 2040 days of age (N = 153 healthy male and female children). Points represent the mean MWF(mcDESPOT) values with error bars corresponding to the measurement standard deviation. Overall, the myelination trajectories follow a sigmoidal shape, with a lag period followed by exponential growth over the first 12–16 months of age, and slower growth from 2 through 5 years of age (Deoni et al., 2012) (modified without permission required). Bottom panel: MWF(BMC-mcDESPOT) maps represented as averaged participant maps calculated across age decades (N = 147 cognitively unimpaired spanning an age range of 21–94 years). The displayed parameter maps correspond to slice number 90 of the MNI atlas. Visual inspection indicates an increase in MWF(BMC-mcDESPOT) values from early adulthood to middle age, followed by a decrease in values afterward. This pattern is clearly highlighted in the plot of mean MWF(BMC-mcDESPOT) values, calculated over all white matter regions, as a function of age, with the dashed vertical line indicating age at maximum myelination (~44 years) (Kiely et al., 2022) (modified with permission; License No: 5763380763492).

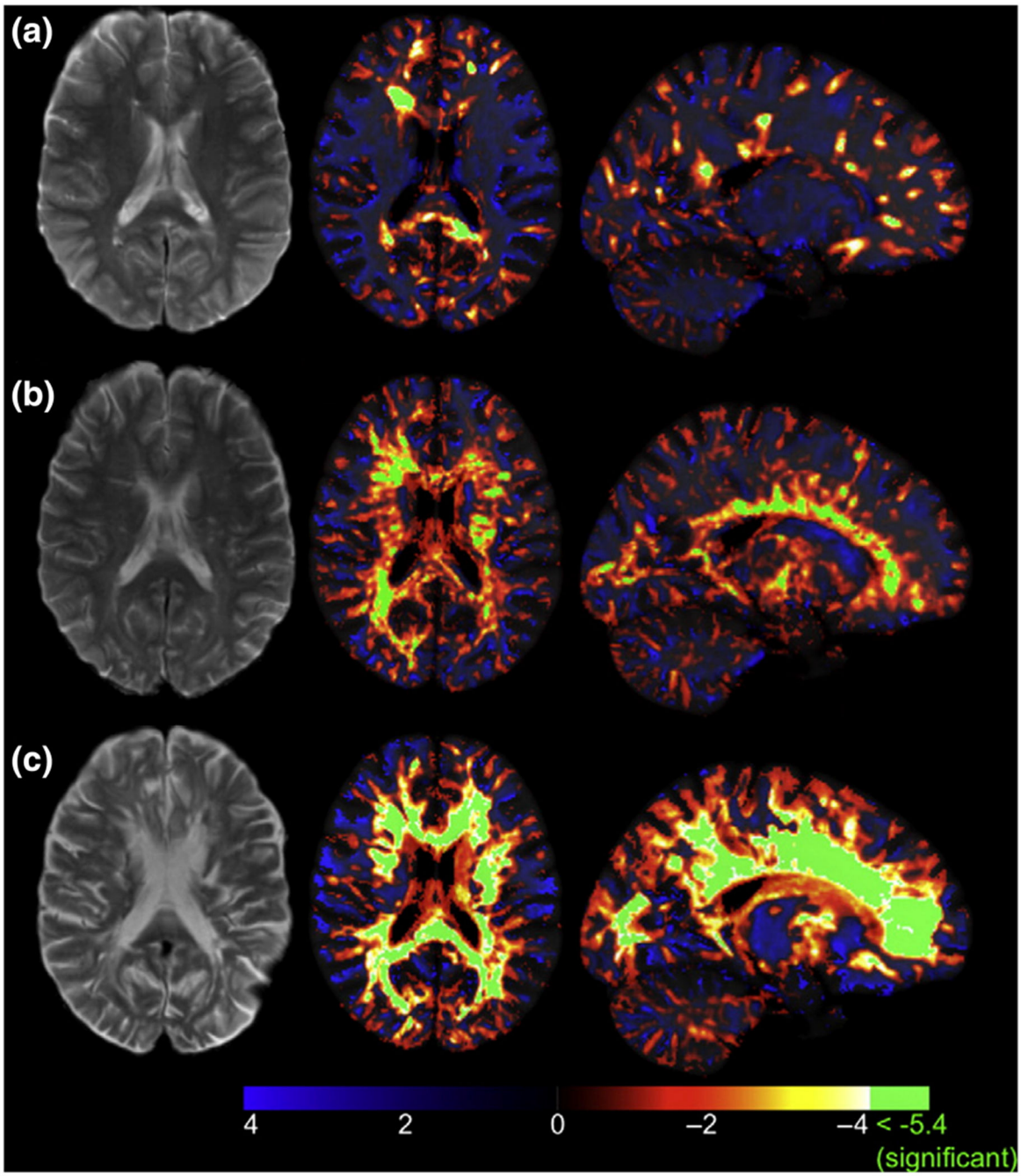

FIGURE 3.

T2-weighted image (left), and axial (middle) and sagittal (right) Z-score map of MWF(mcDESPOT) values compared to the group of matched healthy controls for three primary progressive multiple sclerosis (PPMS) patients. PPMS Patient (a) had an Expanded Disability Status Scale (EDSS) of 1.5, Patient (b) had an EDSS of 6.5 and Patient (c) had an EDSS of 5.5 (Kolind et al., 2012) (modified with permission; License No: 5763380486104).

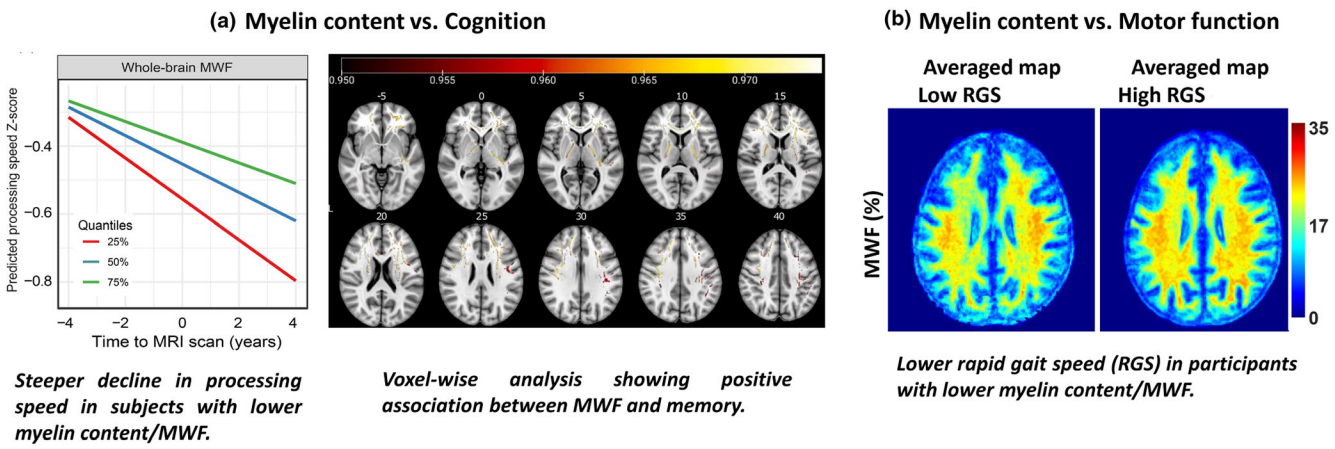

FIGURE 4.

Association of myelination, as measured using MWF(BMC-mcDESPOT) or MWF(MSE) MRI, with hallmarks and outcomes of aging and neurodegeneration. (a) Significant relationships between myelin content and the rates of change in cognitive performance among cognitively normal individuals ($N = 123$) have recently been identified (Gong, Bilgel, Kiely, et al., 2023) (modified with permission; License No: 5763380111061). Voxel-wise analysis shows an association between MWF(MSE) and memory in a cross-sectional study of cognitively unimpaired adults ($N = 141$, age 20–79 year) (Mendez Colmenares et al., 2024) (modified with permission; License No: 1488748-2). (b) Lower myelin content is associated with lower gait speed, as integrative measure of motor function, in a cohort of $N = 118$ cognitively unimpaired adults (Faulkner et al., 2023) (modified without permission required).

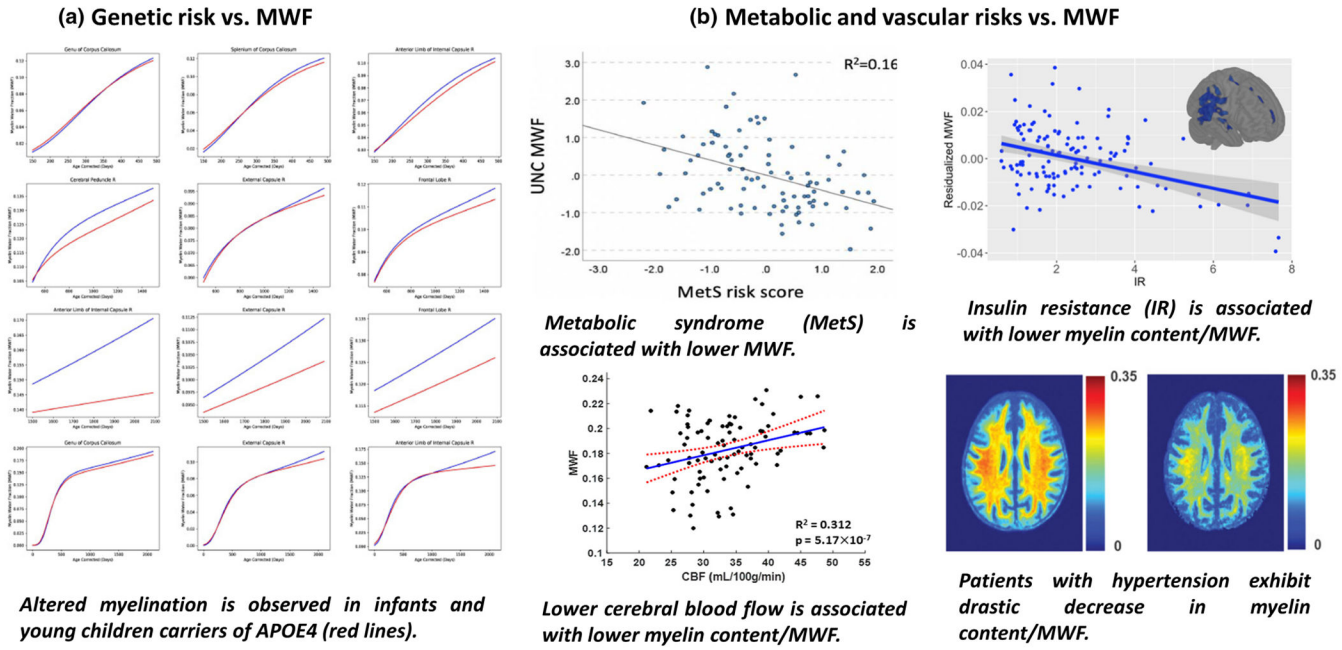

FIGURE 5.

Association of risk factors with myelination as measured using MWF MRI. (a) Differential trajectories of myelination were observed between infant's and young children's carriers (red line, $N = 74$) and non-carriers (blue line, $N = 149$) of APOE4, 2–68 months of age (Remer et al., 2020) (modified with permission; License No: 1490103-1). (b) Greater metabolic syndrome (MetS) risk score in adults correlates with lower brain myelin/MWF(MSE) in a cohort of $N = 90$ cognitively and neurologically healthy adults (Burzynska et al., 2023) (modified with permission; License No: 5763370454403). Elevated insulin resistance (IR) is associated with altered myelination in a cohort of $N = 126$ cognitively unimpaired middle-aged adults (O'Grady et al., 2019) (modified with permission; License No: 5763370139454). Lower cerebral blood flow is associated with lower myelin content in normative aging ($N = 90$) (Kiely et al., 2023) (modified with permission; License No: 5763371494572). Patients with hypertension exhibit lower MWF(BMC-mcDESPOT) as compared to control (Laporte, Faulkner, Gong, Akhonda, et al., 2023) (modified with permission; License No: 501896415).