Magnetic Resonance Imaging of Myelin

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Summary: The ability to measure myelin *in vivo* has great consequences for furthering our knowledge of normal development, as well as for understanding a wide range of neurological disorders. The following review summarizes the current state of myelin imaging using MR. We consider five MR techniques that have been used to study myelin: 1) conventional MR, 2) MR spectroscopy, 3) diffusion, 4) magnetization transfer, and 5) T₂ relaxation. Fundamental studies involving pe-

ripheral nerve and MR/histology comparisons have aided in the interpretation and validation of MR data. We highlight a number of important findings related to myelin development, damage, and repair, and we conclude with a critical summary of the current techniques available and their potential to image myelin *in vivo*. **Key Words:** Myelin, MR, histologic validation, T₂, diffusion, magnetization transfer, MR spectroscopy.

INTRODUCTION

The ability to measure myelin *in vivo* has far reaching consequences both for our understanding of normal development of the nervous system, as well as for the characterization of a wide variety of neurological disorders. Until fairly recently, our knowledge of myelin development and pathology was limited to that acquired from postmortem studies. Although pathological studies still remain the gold standard, advances in imaging now allow us to image changes in the brain *in vivo* using MR. Unfortunately, despite much effort and progress in MR in recent years, there is still no MR technique capable of assessing the myelin bilayer explicitly. However, a number of MR techniques are available that attempt to study myelin by indirect methods, through which we may further our understanding of myelin development, damage, and repair.

The following review provides a comprehensive summary of the current state of imaging myelin using MR. We begin with a background of the structure and function of myelin, and then briefly review the current MR techniques used to assess myelin (i.e., conventional MR, MR spectroscopy, diffusion, magnetization transfer, and T₂ relaxation). We present an expanded section on T₂

relaxation, because this approach is not as well known as the others and is not covered elsewhere in this special issue. We highlight fundamental studies in peripheral nerve and summarize a number of important histological validation studies. We explore what we have learned about myelin development, myelin damage, and myelin repair from MR and, finally, we conclude with a critical summary of the current techniques available and their potential to image myelin *in vivo*.

MYELIN

Myelin is a lipid-protein lamellar membranous structure enveloping axons in both the central and peripheral nervous system of vertebrates.^{1,2} In the CNS, myelin is primarily found in white matter (WM), making up approximately 50% of the dry weight and giving WM its distinctive color. Myelin is also present in gray matter (GM), although in much smaller quantities.

Myelin structure

The CNS myelin is produced by oligodendrocytes and is comprised of tightly compacted oligodendrocyte cell membranes, which are wrapped around the axon in a concentric lamellar fashion (FIG.1). Each oligodendrocyte has the ability to produce roughly the same amount of myelin³ and can produce 5000 mm² to 50,000 mm² of myelin surface area per cell per day, during the period of active myelin assembly.⁴ The axon is not continuously wrapped by my-

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FIG. 1. The CNS myelin sheath surrounding an axon with inset depicting close up of bilayer, including myelin basic protein (MBP), proteolipid protein (PLP), cyclic nucleotide phosphodiesterase (CNP), and myelin-associated glycoprotein (MAG).

elin, but it is focally unmyelinated at loci, termed nodes of Ranvier; the myelinated region between adjacent nodes of Ranvier is referred to as an internode. Each oligodendrocyte can form multiple myelin internodes with multiple axons, and the number of internodes is regulated by axons. When myelination is initiated, all axons are the same size; however, oligodendrocytes appear to have the ability to predict the future diameter of axons and create myelin internodes that are thinner and shorter on those axons that will remain smaller, while myelinating longer and thicker internodes on those axons that will attain a large diameter.³ Each myelin internode can be divided into two ultrastructurally and functionally distinct domains: 1) paranodal loops and 2) compact myelin. Paranodal loops facilitate ion exchange at the node of Ranvier by providing a high concentration of sodium channels and compact myelin inhibits ion exchange during nerve conduction.³

The myelin bilayer is made up of approximately 80% lipid and 20% protein and it is composed of repeating units of the major dense line formed by fusion of the cytoplasmic aspects of the oligodendrocyte process, alternating with the extracellular space between adjacent processes, the intraperiod line. The intraperiod line is thus an extension of the extracellular space and as such

should have a relatively high-water content (WC). The intracellular and extracellular space in between the bilayers is filled with water, which makes up approximately 40% of the weight of myelin¹ (FIG. 1). Myelin has a periodicity of about 150 angstrom to 160 angstrom.⁵

A variety of proteins contribute to myelin's ultrastructure including³:

1. **Myelin Basic Protein (MBP)** is a basic protein making up approximately 30% of the myelin proteins and is localized at the cytoplasmic surface of compact myelin.
2. **Proteolipid Protein (PLP)** is a hydrophobic protein with four membrane-spanning domains, making up about 50% of the myelin proteins. The PLP maintains the 30 angstrom extracellular spacing of compact myelin by electrostatic interactions with myelin lipids.
3. **Cyclic Nucleotide Phosphodiesterase (CNP)** makes up about 4% of the myelin proteins and is concentrated on the cytoplasmic side of the myelin lamellae.

4. **Myelin-Associated Glycoprotein (MAG)** constitutes approximately 1% of the myelin proteins and may have a role in helping oligodendrocyte processes distinguish between myelinated and unmyelinated axons in the CNS.
5. **Myelin Oligodendrocyte Glycoprotein (MOG)** is confined to oligodendrocyte bodies and the outermost surface of the myelin sheath. The precise function of MOG is unknown, but it is believed to be important in defining the structural integrity of the myelin sheath.

A variety of lipids also contribute to myelin's ultrastructure including⁴:

1. **Cholesterol** accounts for about 30% of the total lipids and is a critical element in the assembly and integrity of myelin.
2. **Phospholipids** constitute approximately 40% of the total lipids in myelin and play a role in biomembrane structure.
3. **Glycosphingolipids** make up approximately 30% of the total lipids in myelin and are sometimes also called glycolipids, include cerebrosides, sulfatides, globosides, and gangliosides.

Figure 1 (inset) shows a close-up diagram of the myelin bilayer.

The composition of myelin in the brain is largely, although not completely, conserved among mammalian species (e.g., myelin from rat brain has been shown to have less sphingomyelin than human and bovine myelin). Regional variations also exist within a single species with spinal cord myelin having a higher lipid to protein ratio than myelin from brain tissue from the same species.⁴

Myelin function

Myelin acts as an electrical insulator for neurons and increases the speed of action potential transmission by 10 to 100 times compared to that along an unmyelinated axon. Myelin is of critical importance because speed of conduction is fundamental in allowing complex motor, sensory, and behavior of neuronal functions to occur. The action potential is mediated by voltage-gated sodium channels located at the nodes of Ranvier, and it jumps from one node of Ranvier to another, with the internodal myelin acting as an insulator of high electrical resistance and low conductance. The resulting saltatory conduction of the action potential is much faster than the continuous conduction by sodium channels evenly distributed along the unmyelinated axon.

Along with its conduction function, myelin has also been implicated in regulating axonal transport,⁶ maintaining axonal integrity,⁷⁻⁹ altering pH¹⁰, and regulating fluid volume and ion composition.¹¹ This highlights the intimate association between myelin and the underlying

axon. There is increasing evidence that damage to WM can occur either to myelin or to the axon with subsequent damage to the other.¹² Consequently, one might anticipate a high correlation between myelin and axonal content; this has indeed been observed in several pathological studies.^{13,14} Therefore, using MR to measure axonal damage and myelin damage separately is often difficult.

REVIEW OF MR TECHNIQUES USED TO ASSESS MYELIN

Unfortunately, with current technology, it is very difficult, if not impossible to directly image nonaqueous protons in myelin; this is because: 1) their signal decays to zero in a few tens of microseconds, and 2) the MR signal from lipids and proteins in myelin is indistinguishable from that arising from protons on other nonaqueous constituents of CNS tissue.¹⁵ Two approaches for directly imaging myelin *in vivo* have been investigated: with ultrashort echo time (TE) imaging¹⁶ and ³¹P spectroscopy.¹⁷ A difficulty with ultrashort TE imaging of myelin is removal of the contaminating signal from water, and with ³¹P spectroscopy there are challenges in quantitative characterization of the signal from phosphatidylcholine head groups. Much more research is required before these approaches will be ready for clinical use. Therefore, practically speaking, MR of myelin is acquired by indirect means. At least five different approaches for indirect myelin imaging have been explored in the literature: 1) conventional T₁-weighted and T₂-weighted imaging, 2) spectroscopy, 3) diffusion tensor imaging, 4) magnetization transfer imaging, and 5) separation of T₂ relaxation components.

Due to their excellent soft tissue contrast, T₁-weighted and T₂-weighted images play a large role in clinical MR. Unfortunately, this pathological sensitivity is accompanied by a relatively low specificity because many brain pathologies give rise to similar bright lesions, and for adults there is not a fixed relationship between relaxation time-weighting and myelination. However, the situation is different for newborns and young children in which conventional T₁-weighted and T₂-weighted imaging has been used extensively in studies of myelin development.¹⁸ There is consensus in the literature today that T₁ relaxation is primarily determined by WC.^{19,20} It is important to note that this technique implicitly assumes that the only nonaqueous tissue added in early brain development is myelin. Conventional T₁-weighting and T₂-weighting should be considered a qualitative measure of myelination and has limited application for subjects older than 2 years of age.

The MR spectroscopy potentially provides indirect information about myelin through the existence of peaks from neutral lipids associated with myelin loss and, in some cases, increases in the choline peak presumably associated with the breakdown of phosphatidylcholine

FIG. 2. (A) T_2 decay curve and (B) T_2 distribution from human white matter. Inset in (B) shows a cross-section through an axon with the locations of intra/extracellular water and myelin water.

head groups from myelin lipids. Proton magnetic resonance spectroscopy (MRS) is an excellent technique for detecting active demyelination; however, it is not capable of assessing intact myelin.

Diffusion tensor imaging (DTI) measures the kinetics of water molecules. It can be formulated in terms of mean diffusivity ($\langle D \rangle$) and fractional anisotropy (FA), or more specifically by the axial and radial elements of the water diffusion tensor, $\lambda_{\parallel}$ and $\lambda_{\perp}$, respectively. It has long been known that myelin is not required for the existence of anisotropy in water diffusion in nerves.²¹ However, it has recently been demonstrated^{22,23} in animal models that loss of myelin results in an increase in $\lambda_{\perp}$. Hence, DTI can provide information on changes in myelination; however, it is not a reliable indicator of absolute myelination because the diffusion tensor components depend on the degree of fiber tract orientational order within the imaging voxel.

Magnetization transfer imaging involves detecting the exchange of magnetization between nonaqueous tissue and water.²⁴ It is usually measured as a magnetization transfer ratio (MTR), but it has also been modeled to extract tissue parameters (e.g., the fraction of protons on nonaqueous tissue [F]).^{25–27} The large amount of literature on magnetization transfer imaging makes it clear that MTR is a very sensitive measure of tissue damage. However, MTR has been shown to be influenced by other processes such as inflammation,²⁸ and it is unlikely to be validated as a specific measure of myelination.

Whereas T_2 -weighted images are acquired at a single TE time, T_2 relaxation studies collect the MR signal at a large number of TE times to produce a T_2 decay curve. Multi-echo T_2 relaxation studies in CNS tissue have revealed the existence of at least two distinguishable water environments;²⁹ a short T_2 component from water trapped in the myelin sheath, and a longer T_2 component arising from intracellular and extracellular water. The signal from the “myelin water” can be separated, leading to an indirect measure of myelin, the myelin water frac-

tion (MWF). Figure 2 shows a typical T_2 decay and corresponding T_2 distribution from human WM.

USE OF T_2 RELAXATION TO MEASURE MYELINATION *IN VIVO*

As diffusion, MTR and MRS are reviewed in depth elsewhere in this issue, we present an expanded section on T_2 relaxation. The MR signal from the brain is almost entirely from water. Using T_2 relaxation, the water signal in the brain can be separated into three components: 1) a long T_2 component (~ 2 s) due to cerebrospinal fluid, 2) an intermediate component (~ 100 ms) arising from intracellular and extracellular water, and 3) a short T_2 component (~ 20 ms) believed to be due to water trapped between the myelin bilayers (myelin water) (see FIG. 2). The MWF is calculated by dividing the signal area of the T_2 distribution attributed to myelin water ($10 \text{ ms} < T_2 < 50 \text{ ms}$) by the total area of the T_2 distribution. A myelin water map can be created by displaying the MWF for each pixel in the image. Total WC estimates can be obtained by normalizing the total area of the T_2 distribution to an external water standard.³⁰

T_2 data acquisition

The first step in a T_2 study is the acquisition of high-fidelity T_2 decay curves. The most common approach is to collect multiple echoes in a single MR sequence. Many investigators have used the Poon–Henkelman multiple echo sequence³¹ that uses rectangular composite 180° pulses flanked by crushers of decreasing amplitude and alternating sign. This sequence excites the entire signal from the selected slice and results in negligible contributions from a signal originating outside the selected slice. Although this sequence is proven to yield robust T_2 decay curves, it suffers from the disadvantage of being a single-slice technique. Modification of the sequence with slice selective refocusing pulses for multiple-slice acquisition is problematic due to

magnetization transfer effects from off-resonance excitations. This off-resonance effect is complicated by the evidence that exchange between myelin water and nonaqueous myelin occurs at a more rapid rate than exchange between other nonaqueous tissue and the intracellular and extracellular water pool.^{32–34} However, a more practical approach to collecting T_2 decay curves was introduced by Oh et al.³⁵ who used a novel spiral acquisition technique³⁶ that collected images at 12 TE times for 16 slices in 10 minutes. Mädler et al.³⁷ developed a three-dimensional multi-echo pulse sequence that was capable of collecting 32 echoes for multiple slices in less than 20 minutes. Research is underway on variations of the three-dimensional multi-echo sequence, which could reduce scan times for multiple slice T_2 decay curves to under 10 minutes.

For quantitative analysis, T_2 decay curves must have high signal-to-noise ratios with the minimum acceptable noise standard deviation being approximately 1% of the signal strength at the shortest echo time.^{38,39} The echo spacing should ideally be as short as feasible and the echo train length should be such that the last echoes report only noise. For *in vivo* human brain studies, the echo spacing should be 10 ms or less, and the echo train length should exceed 1 s to measure the shortest T_2 components and be sensitive to T_2 times on the 400 ms timescale, respectively. Unfortunately, the number of echoes acquired is often limited by considerations of power deposition and MR scanner pulse programmer restrictions.

T_2 decay curve analysis

A second challenge in extracting the myelin water signal is the analysis of the T_2 decay curves in terms of a sum of exponential components. The approach applied most frequently in the literature is non-negative least squares,^{40,41} which uses a χ^2 minimization algorithm to fit the decay curve with a T_2 distribution (i.e., a plot of amplitude vs T_2 time [FIG. 2B]). Non-negative least squares produces a T_2 distribution consisting of a few discrete spikes; however, most investigators prefer a smooth distribution. A continuous distribution can be achieved by minimizing χ^2 as well as a regularizer. A common regularizer is the sum of the squares of the solution amplitudes—the so-called “small model.”⁴⁰ Another approach fits the decay curves to a limited number of Gaussian-shaped T_2 peaks.⁴²

A very different approach to extracting the myelin water signal is to derive a filter that produces either a myelin water image or a total water image when applied to a series of images acquired at different TE times. Using this novel approach, Jones et al.⁴³ and Vidarsson et al.⁴⁴ created myelin water images from a linear combination of as few as three echoes. This linear combination approach could lead to techniques for very fast acquisition of myelin water images.

T_2 interpretation

A third challenge to myelin imaging using T_2 relaxation is developing the model for interpretation of the T_2 decay curve as a superposition of signals from different water environments in nervous system tissue. The convention is to interpret the signal with T_2 times less than 50 ms as arising from water in the myelin sheath and the signal with T_2 times greater than about 50 ms as intracellular and extracellular water. In peripheral nerves, the three T_2 peaks normally observed are attributed to myelin water, axonal water, and extracellular water (FIG. 3). Use of these models presumes that exchange between the various reservoirs is slow on the T_2 time scale. The presence of exchange would result in a decreased MWF. Evidence thus far^{32–34} suggests that exchange between myelin water and the rest of the water is relatively slow but not completely negligible in CNS tissue and very slow in peripheral nerve system (PNS) tissue.⁴⁵ A further issue with this approach is the assumption of a fixed relationship between myelin water and nonaqueous myelin—approximately 40% by weight in healthy mature WM.¹ More work is required to explore this relationship in the newborn brain and in pathological WM.

In recent years, a number of groups have embarked on research in the area of T_2 relaxation in CNS tissue. Work on myelin water imaging has been published by at least nine groups.^{29,35,44,46–51} Although myelin water imaging is not yet a widely used technique, we are confident that the added participation of these excellent research groups will accelerate technical developments.

PERIPHERAL NERVE

Although the focus of this review is on CNS myelin, much of the pioneering work using MR to study myelin has been done in the PNS. Both CNS and PNS myelin are functionally similar, but they have slightly different lipid and protein compositions and minor structural differences.³ Each internodal segment of PNS myelin is connected to a single Schwann cell, whereas a single oligodendrocyte is connected to several tens of internodal segments of CNS myelin. The internodal distances are longer and the lamellar periodicity is slightly larger in PNS than CNS myelin. Based on the previous statements, one would expect MR results from PNS myelin to be generally translatable to CNS myelin. However, the aforementioned increased lamellar periodicity may lead to a higher WC in PNS myelin.

Almost 40 years ago, Swift and Fritz⁵² demonstrated in bullfrog sciatic nerve that T_2 relaxation was not monoexponential. Several decades later, Vasilescu et al.⁵³ examined the frog sciatic nerve using a multi-echo technique and found a multiexponential decay giving rise to three distinct T_2 components. The authors suggested that the physical compartments associated with these three

FIG. 3. T₂ distribution from peripheral nerve for (a) normal, (b) 7 days after crush injury, (c) 14 days after crush injury, and (d) 32 days after crush injury.⁶⁰ (Reprinted from Magnetic Resonance in Medicine, Does MD, Snyder RE. Multiexponential T₂ relaxation in degenerating peripheral nerve. Vol. 35, No. 1, 1996, pgs 207–213. Copyright 1996, with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

water pools were extracellular, axoplasmic, and myelin water. Authors Does et al.⁵⁴ have since conducted a number of studies investigating frog sciatic nerve also using multi-echo MR. In 1995 they demonstrated *in vivo* three T₂ relaxation components: 1) myelin (19 ms, 26%), 2) axon (63 ms, 29%), and 3) connective tissue water (241 ms, 45%).⁵⁴ This longest T₂ component had previously only been identified *in vitro*.^{53,55}

A second study by Does et al.⁴⁵ investigated the T₁, T₂, and MTR properties of frog sciatic nerve at 3 Tesla (3T). Here the authors demonstrated that in addition to multiexponential T₂ relaxation, each T₂ component had its own T₁ relaxation and magnetization transfer (MT) properties providing further support for the assignment of these components to unique physical compartments of water. Surprisingly, similar MTR values were found for myelin water and axonal water; this was interpreted as having arisen from different magnetization exchange rates and T₁ relaxation times for the two environments. Therefore, similar MTRs do not necessarily indicate similar myelination states. The authors warned that “interpreting changes in MTR solely to reflect a change in

degree of myelination could lead to erroneous conclusions.”

Myelination has been shown to result in decreased T₁ and T₂ in PNS tissue.⁵⁶ This decrease was attributed to the interaction of water with myelin lipids. In garfish, the lipid content of the unmyelinated olfactory nerves was higher than that in the myelinated cranial nerves; however, the T₁ and T₂ times were longer in the unmyelinated nerves.⁵⁶ The lipid composition was not analyzed and this may be important, because in model membranes, galactocerebroside was found to be a particularly effective molecule at reducing T₁ and T₂, presumably due to its large head group with four hydroxyl groups.⁵⁷ The WC was similar for both types of nerves; therefore, the interactions with water molecules inside compartments may be important in determining relaxation times.

One of the earliest studies to examine peripheral nerve degeneration using nuclear MR was conducted by Jolesz et al.⁵⁸ in 1984. In this study, Wallerian degeneration was induced in rat sciatic nerve. Prolonged T₁ and T₂ relaxation times were observed in the excised injured nerve, accompanied by an increase in WC, as well as decreased myelin

content on histology. Their results demonstrated the ability of MR to detect secondary changes in myelinated nerve fibers, and the authors hypothesized that it should be possible to detect Wallerian degeneration on MR scans. Several years later, Titelbaum et al.⁵⁹ studied peripheral nerve injury *in vivo* in a series of animals also to investigate the role of MR in Wallerian degeneration. High-signal intensity was observed along the injured nerve, which corresponded to edema and myelin breakdown from Wallerian degeneration. The authors suggested that the duration and extent of signal abnormality might indicate the severity of the nerve injury.

In a crush injury model for Wallerian degeneration, Does and Snyder⁶⁰ found that as degeneration progressed, a reduction in the fraction of the shortest T_2 component was observed and attributed to a combination of interstitial edema and myelin loss. Subsequently, the T_2 spectra evolved from three distinct peaks to one which was hypothesized to arise from the collapse and loss of myelinated fibers.⁶⁰ Figure 3 shows the evolution of the T_2 spectrum after a crush injury in the experiment by Does et al.⁶⁰ In the injured rat peripheral nerve, the size of the short T_2 component was correlated with a quantitative histological assessment of myelin during myelin loss and repair.⁶¹ However, the short T_2 component was unable to distinguish between intact myelin and myelin debris, and instead it represented all myelin present in the sample.⁶¹

Experiments in peripheral nerve continue to play a role in the study of myelin. Recently, Wessig et al.⁶² reported on a study in which lyssolecithin, which focally dissolves myelin sheaths while sparing axons, was injected into the sciatic nerve of 30 male rats and imaged using conventional MR and Gad T_1 , as well as with a novel micellar contrast agent gadofluorine M (Gf). Conventional MR and Gad T_1 did not identify regions of demyelination, whereas Gf T_1 images distinctly highlighted areas of focal demyelination that remained until remyelination occurred. This novel contrast agent may provide a new method of imaging focal areas of demyelination *in vivo*.

HISTOLOGICAL VALIDATION STUDIES

Although great effort has been put into finding a myelin-specific MR marker, pathological validation of any technique claiming to be such a marker is also necessary. However, pathological MR comparison studies are technically challenging and sometimes difficult to interpret. Tissue begins to degrade due to autolysis immediately upon death, often making it difficult to replicate *in vivo* MR measurements. Also, extensive tissue processing occurs in preparation for the application of histological stains that can change the shape of the tissue sample from the time it underwent MR, making subsequent comparisons difficult. Other limitations in histological staining include challenges in obtaining staining homogeneity and consistency; however, new

antigen specific stains may make comparison across samples more quantitative. Also, some methods for quantifying pathological stains, such as manual cell-counting, can be labor intensive and prone to error. New methods such as optical density or automated counting may be beneficial. Another problem arises from the differences in slice thickness with the lower limit of MR resolution, being typically on the order of 1 mm, whereas histopathology slices are typically 3 microns to 10 microns thick, creating partial volume effects. Because of these obstacles, only a relatively small number of studies have quantitatively investigated the correlation between MR-derived measures and histopathology.

Magnetization transfer ratio, T_1 and T_2 relaxation

Pioneering studies by Dousset et al.^{63,64} in both primates and guinea pigs, respectively, found that the MTR was only slightly reduced in edematous lesions (5% to 8%), whereas a much more dramatic decrease was observed in areas of demyelination (26%). In a rat model, demyelinating and remyelinating corpus callosum lesions showed a good correlation between the MTR and myelin damage and repair as measured by histology.⁶⁵ The MTR histogram parameters were also found to correlate with histopathological results including the myelination state.⁶⁶ However, other pathological conditions may be responsible for a decrease in MTR, as was demonstrated by both Brocet et al.⁶⁷ and Gareau et al.,²⁸ who showed a reversal of MTR decreases due to modulation of inflammation after inducing experimental autoimmune encephalomyelitis (EAE) in the guinea pig brain. Furthermore, Cook et al.,⁶⁸ using an EAE model in guinea pigs, found equal reductions in MTR in areas of edema compared to areas of demyelination in the spinal cord. Also, in a very recent study, Blezer et al.⁶⁹ examined an EAE model in the marmoset brain comparing T_1 , T_2 (5 echo, monoexponential fit) and the MTR to axonal density and macrophage count of both early active and inactive macrophages. The MTR was found to correlate significantly with the number of inactive macrophages ($R^2 = 0.26$), as well as with the macrophage inflammation index, which reflects whether macrophages in the lesions express markers of active or inactive lesions ($R^2 = 0.49$), further supporting the possible influence of inflammation and presence of macrophages on the MTR.

The T_2 measurements from animal models in the CNS tissue have also shown the T_2 distribution to be multi-component.^{15,70,71} Stewart et al.¹⁵ studied the T_2 relaxation behavior of the spine and brain from guinea pigs induced with EAE. This was the first study to investigate T_2 relaxation in the spinal cord, and they found decreases in the short T_2 component consistent with histologically measured myelin loss. Decreased MWF levels after spinal cord injury also have been detected in rats.⁷² The relationship between the short T_2 component and myelin

was also studied by Pun et al.⁷³ and Odrobina et al.⁷⁴ They examined the effect of demyelination induced by tellurium on the sciatic nerve of rats, with both MR and histology. Tellurium-treated animals showed a 68% decrease in healthy myelin in the sciatic nerve and a 45% increase in the extracellular matrix. A decrease in the area of the short T_2 component, an increase in average T_1 , and an increase in the T_2 of the intermediate component were also measured. A good correlation was observed between the degree of myelin staining and the size of the short T_2 component ($R^2 = 0.59$), whereas T_1 was found to strongly correlate with the size of the extracellular matrix ($R^2 = 0.85$). The authors postulated that the area of the short T_2 component was the best measure of the process of demyelination.

Examining MTR and T_2 relaxation measures in an EAE model of the guinea pig, Gareau et al.²⁸ showed both measures were reduced in the normal-appearing white matter (NAWM). However, the MTR and myelin water appeared to be influenced by different aspects of EAE, as modulating the inflammation strongly influenced the MTR but did not affect the myelin water. This result suggests that the short T_2 component is specific for myelin, whereas pathological features other than myelin content may be important in the interpretation of MTR.²⁸ In another study, tumor necrosis factor- α was injected into rat sciatic nerve to induce inflammation with little demyelination and axonal loss.⁷¹ The MTR and the quantitative MT measure of the semi-solid pool size, M_{0B} , were found to decrease, whereas the average T_1 and T_2 relaxation times increased. All of these MR measures correlated well with the extracellular volume of the neural tissue as evaluated by quantitative histology. Stanisz et al.⁷¹ also found that multicomponent T_2 was the best at distinguishing between inflammation and demyelination, whereas MT measurements were more likely to be influenced by both changes in myelin and pH.

A limited number of studies have also investigated MR histopathologic correlations in human tissue. In a fairly large study of samples collected from 17 multiple sclerosis (MS) subjects immediately postmortem, van Waesberghe et al.⁷⁵ examined MTR and T_1 contrast ratio (i.e., signal intensity of lesions relative to NAWM on a T_1 -weighted image) compared to axonal and myelin density. MTR and T_1 contrast ratio were found to correlate strongly with axonal density in lesions ($R^2 = 0.69$ and 0.55 , respectively), and MTR also correlated strongly with axonal density in NAWM ($R^2 = 0.58$), whereas the correlation of MTR and T_1 contrast ratio with myelin density was much weaker ($R^2 = 0.20$ and 0.36 , respectively). Schmierer et al.¹⁴ also compared MTR and T_1 in fresh postmortem brain tissue from 20 subjects to measures of myelin content, axonal density, and gliosis. Both MTR and T_1 were found to correlate with both myelin content and axonal density ($R^2 = 0.70$ and 0.44 , respec-

tively for MTR; $R^2 = 0.49$ and 0.24 , respectively for T_1). Using multiple regression analysis, the primary MR correlate of myelination appeared to be MTR. No correlation was observed between either MR measure or gliosis. However, the authors do caution that "despite the strong association shown between MTR and myelin content, abnormalities in the former should not be attributed solely to variations in the latter." Bot et al.⁷⁶ investigated the relationship between MTR, T_1 , and T_2 (4 echoes, monoexponential) and staining for myelin and axons in 13 samples of formalin-fixed cervical spinal cord at 4.7 T. All MR measures correlated well with staining for myelin ($R^2 = 0.59$, 0.58 , and 0.50 for T_2 , MTR, and T_1 , respectively) and less well with axonal density ($R^2 = 0.19$, 0.17 , 0.15 for T_2 , MTR, and T_1 , respectively). The T_2 was found to be the strongest independent predictor for myelin density. This was not found in an MS spinal cord study by Mottershead et al.¹³ in which the MTR, T_1 , and anisotropy were strongly correlated with myelin content, but T_2 was more weakly correlated.

Studies in the human brain have shown postmortem formalin-fixed MR is comparable with *in vivo* imaging.⁷⁷ Fortunately, there is little change of the myelin water signal postmortem, both shortly after death *in situ* and on tissue fixation with formalin.⁷⁸ The T_2 distribution from the formalin-fixed brain is qualitatively similar to that from the brain *in vivo*, although quantitatively the T_2 is shifted to shorter times. A good qualitative correspondence was observed between myelin water in the formalin-fixed brain and the anatomic distribution of myelin⁷⁹ as indicated by Luxol fast blue, a stain originally introduced by Klüber and Barrera⁸⁰ in 1953, and widely believed to stain phospholipid components of myelin.^{81–83} A good quantitative correlation between MWF and Luxol fast blue optical density was also observed across 25 samples from the MS brain (average, $R^2 = 0.67$).⁷⁸

A few studies have investigated the relationship between signal intensity and myelination. In a demyelinating model of rabbit sciatic nerve, Teresi et al.⁸⁴ compared image intensity of T_1 and heavily T_2 -weighted images to staining for myelin and glial cells. Different stages of demyelination were identified, each with their own MR properties. Early nerve degeneration exhibited demyelination with corresponding signal increase on the heavily T_2 -weighted sequence; however, no increase in glial cells or changes on the T_1 image was observed. Advanced nerve degeneration, which displayed an increase in glial cells but no further increase in demyelination, showed a corresponding decreased intensity on T_1 -weighted images, as well as a previously observed increase in T_2 intensity. The authors suggested that MR was able to distinguish different stages of demyelination in degenerating nerves. Using T_1 -weighted images, van Walderveen et al.⁸⁵ and Bitsch et al.⁸⁶ found that hypointense T_1 MS lesions (also known as " T_1 black holes")

were correlated with the degree of tissue loss, although correlation with axonal count was most significant. However, the evolution of the hypointensity of the lesion was determined not only by axonal loss, but also by the demyelinating activity with remyelination, causing lesions to become less hypointense.⁸⁶ In a study of MS spinal cord, proton density (PD) and T₂-weighted images obtained from high-resolution MR showed higher signal intensities in areas with lowest axonal density and myelin content.^{87,88} In a recent study from the same group, Bo et al.⁸⁹ found that subpial cortical demyelination in MS was not associated with focal or diffuse WM abnormalities found on MR or by histology, suggesting that the presence of WM pathology does not predict cortical demyelination in a clinical setting.

Diffusion

An extensive number of studies investigating diffusion measures in animal models have been completed by Song et al.^{22,23,90} and Sun et al.^{91–94} In 2002, this group studied dysmyelination *in vivo* using diffusion tensor imaging in the shiverer mouse,²³ a mutation characterized by an almost total lack of CNS myelin, with MBP in particular being undetectable. They observed increases (relative to age-matched controls) of the water diffusivity perpendicular to the axonal fiber tracts ($\lambda_{\perp}$) in accordance with lack of myelin, whereas the diffusivity parallel to the axon ($\lambda_{\parallel}$) remained unaffected, consistent with axonal preservation. The presence of incomplete myelination with intact axons was confirmed by electron microscopy, and the authors hypothesized that $\lambda_{\perp}$ and $\lambda_{\parallel}$ may be able to differentiate myelin and axonal loss. This hypothesis was supported by work from the same group in which $\lambda_{\perp}$ and $\lambda_{\parallel}$ from the mouse optic nerve with retinal ischemia was examined.²² In the early stages of ischemia, $\lambda_{\parallel}$ was found to decrease, consistent with the observed histological findings of axonal degeneration, whereas $\lambda_{\perp}$ and myelin content were unaffected. The $\lambda_{\perp}$ was then found to increase in the following days due to myelin degeneration, confirmed by histology. Song et al.⁹⁰ and Sun et al.⁹² also examined the cuprizone model of demyelination and remyelination in the corpus callosum of the mouse brain, and they found that increases and decreases in $\lambda_{\perp}$ corresponded to the time course of demyelination and remyelination, respectively, as measured by histology. In the myelin-deficient rat spinal cord, $\lambda_{\perp}$ and $\lambda_{\parallel}$ were higher, whereas FA was the same compared with normal rats,⁹⁵ suggesting that myelin had an effect on the diffusion characteristics of water in WM, but not on the FA. Interestingly, formalin fixation appeared to have little effect on $\lambda_{\perp}$ in mouse brain, supporting the use of diffusion–histology comparisons to gain insight into the underlying mechanisms of observed diffusion measures.^{91,93} The use of $\lambda_{\perp}$ has subsequently been applied to the study of myelin in animal models of various diseases and injury, including Alzheimer's disease,⁹⁴ weight-drop injury in the spinal

cord,⁹⁶ EAE of the spinal cord,⁹⁷ and herpes simplex infection of the CNS.⁹⁸

Measures of diffusion have also been correlated with histological measures of axonal density and myelin content in human tissue. Mottershead et al.¹³ obtained quantitative MR maps of PD, T₂ (2 echo, monoexponential fit), T₁, MT, and diffusion weighting from fresh post-mortem spinal cord from four MS subjects at 7 Tesla (7T). Regions of interest were mapped by eye to histology images stained for axons and myelin. A correlation was detected between axonal density and MTR, PD, T₁, and the diffusion standard deviation index (SDI, a measure of diffusion anisotropy) ($R^2 = 0.61, 0.42, 0.38$, and 0.37 , respectively). Weaker correlations were found for axonal density and T₂ ($R^2 = 0.20$). A correlation was also detected between myelin content in MS WM and T₁, PD, MTR, T₂ and SDI ($R^2 = 0.61, 0.52, 0.42, 0.32, 0.26$, respectively). A weaker correlation was found between myelin content and $\langle D \rangle$ ($R^2 = 0.20$).¹³ A recent study by Schmierer et al.⁹⁹ investigated the relationship between the diffusion measures of $\langle D \rangle$ and FA in the fresh post-mortem brain with myelin content, axonal density, and gliosis. Both FA and $\langle D \rangle$ were found to correlate with both myelin content and axonal count ($R^2 = 0.62$ and 0.49 , respectively for FA, and $R^2 = 0.46$ and 0.44 , respectively for $\langle D \rangle$). A weaker correlation was observed for both FA and $\langle D \rangle$ and gliosis ($R^2 = 0.25$ and 0.30 , respectively). However, multiple regression analysis suggested $\langle D \rangle$ and FA were primarily affected by myelin content, whereas their correlation with axonal count was largely explained by the stronger association of the latter with myelin content.

Summary

The MTR has shown a correlation with myelination, but was influenced by inflammation, axonal density, and the presence of macrophages. The MWF was well correlated with myelin content both in animal and MS studies. The diffusion metrics, $\langle D \rangle$, and FA were related to myelin content, and $\lambda_{\perp}$ changed with myelination state. Tables 1 and 2 summarize all of the correlations between histology and the various MR measures as previously reported.

NORMAL MYELINATION

In humans, myelination begins in the fifth fetal month, developing rapidly for the first 2 years, but continues throughout life until the sixth decade.^{100,101} Generally, myelination begins in posterior regions before anterior regions of the brain.¹⁰² Onset of myelination is accompanied by an increase in lipid and protein content and a corresponding decrease in WC. Decreases in T₁ and T₂ times of the developing brain have been significantly correlated with decreases in WC¹⁰³; therefore, conventional MR of neonates usually assesses myelination us-

TABLE 1. Comparison of Myelin Staining to Proton Density, T_1 Contrast Ratio (Signal Intensity of Lesions Relative to NAWM on a T_1 -weighted image), T_1 time, $\langle D \rangle$, and Diffusion Anisotropy

MR Measure	R ² With Myelin Stain	Plot	Reference
PD	0.52	n/a	Mottershead et al. ¹³
T_1 contrast ratio	0.36	n/a	Van Waesberghe et al. ⁷⁵
T_1 time	0.61		Mottershead et al. ^{13†}
T_1 time	0.49	n/a	Schmierer et al. ¹⁴
T_1 time	0.50	n/a	Bot et al. ⁷⁶
$\langle D \rangle$	0.46		Schmierer et al. ^{99*}
$\langle D \rangle$	0.20	n/a	Mottershead et al. ¹³
Diffusion Anisotropy	0.62		Schmierer et al. ^{99*}
Diffusion Anisotropy	0.26	n/a	Mottershead et al. ¹³

$\langle D \rangle$, mean diffusivity; n/a, not available; NAWM, normal appearing white matter; PD, proton density.

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†Reprinted from Journal of Neurology, 250(11), Mottershead JP, Schmierer K, Clemence M et al., High field MRI correlates of myelin content and axonal density in multiple sclerosis—a post-mortem study of the spinal cord, pgs. 1293-1301, Figure 4, Copyright 2003 with kind permission of Springer Science and Business Media.

ing T_1 -weighted and T_2 -weighted images. On T_1 -weighted images, the WM of the newborn brain is hypointense compared with the GM, with the exception of a few regions (e.g., posterior internal capsule) that are hyperintense, presumably due to early myelination. During the next 8 months to 10 months, WM becomes completely hyperintense relative to GM.¹⁰⁴ On T_2 -weighted spin echo images, newborn WM is hyperintense com-

pared with GM, except, again for small regions such as the posterior internal capsules. During the next 30 months, the WM slowly becomes hypointense leading to the normal gray/white contrast observed in the adult brain.¹⁰⁴

In the developing brain, $\langle D \rangle$ was found to decrease in central WM, but not in the posterior internal capsules, even with ongoing myelination, suggesting that $\langle D \rangle$ is largely

TABLE 2. Comparison of Myelin Staining to T_2 Time, MTR, and MWF

MR Measure	R^2 With Myelin Stain	Plot	Reference
T_2 (4 echoes, mono-exponential)	0.59		Bot et al. ^{76*}
T_2 (2 echoes, mono-exponential)	0.32	n/a	Mottershead et al. ¹³
MTR	0.71		Schmierer et al. ^{14†}
MTR	0.20	n/a	Van Waesberghe et al. ⁷⁵
MTR	0.58	n/a	Bot et al. ⁷⁶
MTR	0.42	n/a	Mottershead et al. ¹³
MWF (2500 echoes, multi-exponential)	0.56		Webb et al. ^{61‡}
MWF (32 echoes, multi-exponential)	0.67		Laule et al. ^{78§}

HISIL, high-signal-intensity lesions; IMSIL, intermediate-signal-intensity lesions; MTR, magnetization transfer ratio; MWF, myelin water fraction; n/a, not available; NAWM, normal appearing white matter; WM, white matter.

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FIG. 4. (A) Proton density and (B) myelin water map from a normal control. (Courtesy of Field A, Wu Y, Samsonov A, and Alexander A, [Wisconsin]).

dependant on axonal growth.¹⁰⁵ Furthermore, $\langle D \rangle$ was found to drop by more than 25% during the first 3 months to 4 months of life and reached adult values by approximately 3 years of age,¹⁰⁶ even though the brain is known to continue myelinating for several decades after birth.^{100,101} In children greater than 1 year of age, the fractional anisotropy began increasing and continued increasing into the second decade of life.¹⁰⁷ The change in FA with age may reflect a combination of the compacting of neurons into fiber tracks, increased myelin content, and decreased WC, all of which lead to more restricted diffusion. It should also be noted that detectable FA in the posterior internal capsule was observed at 26 weeks of gestational age, even with no myelin present.¹⁰⁸ Prayer et al.¹⁰⁹ found in a study of premyelinated rat pup nerves that inhibiting sodium channel pumps caused a loss of diffusion anisotropy, suggesting yet another mechanism for anisotropy in axons. In a very recent study, Ashtari et al.¹¹⁰ examined two groups of late adolescent males and found no changes in $\lambda_{\perp}$, but they did find increases in FA and $\lambda_{\parallel}$ between the ages of 16 and 18.2 years. The authors hypothesize that normal brain development during late adolescence is more strongly influenced by increased axonal fiber organization and reduction of tortuosity toward more straightened fibers than axonal myelination. In the aging adult brain, FA has been found to decrease with age in WM.^{111–114} The reduction in FA was observed to be linear from approximately 20 years old, it was concentrated in the frontal WM areas,¹¹¹ and it was more dramatic for the genu compared to the splenium of the corpus callosum.¹¹² Ota et al.¹¹² also observed an increase in $\langle D \rangle$, as well as $\lambda_{\perp}$ with increasing age. Measures from DTI may represent different aspects of development because changes occurring in the brain structure at infancy are quite different from changes occurring in adulthood.

The MTR and MTR histogram peak location were found to increase with age, predominantly in the first 2 years of life to a value approximately double those observed in infancy.^{115,116} The observed increase over time was fit to a single exponential and was region-dependent.¹¹⁶ In the aging adult brain, Silver et al.¹¹⁷ found a

weak inverse correlation between age and MTR ($R^2 = 0.09$). A similar trend was found by Armstrong et al.,¹¹⁸ but neither Rovaris et al.¹¹⁹ nor Mehta et al.¹²⁰ found a correlation between the MTR and age. In adult WM, some groups^{25,117,118,120} have found small regional differences in the MTR and size of the restricted pool (F), but others have not.^{121,122}

As neurons proliferate, N-acetyl-aspartate has been observed to increase and choline-containing compounds (Cho) to decrease in the developing brain.¹²³ The large amount of Cho present in early development is believed to be due to a large membrane turnover rate related to myelination.¹²⁴ As myelination slows down, the area of the Cho peak decreases¹²³ and much lower values of Cho are reported in the adult brain.¹²⁵ Although several studies have found no correlation between Cho and age in the adult brain,^{126,127} one study found an increase in Cho with increasing age.¹²⁸ Kreis et al.¹²⁹ found a significant correlation between age and metabolite T_1 and T_2 relaxation times in healthy WM. In particular, they found that the T_1 of both N-acetyl-aspartate and creatine decreased with age, whereas the T_2 of N-acetyl-aspartate significantly increased. This was the first study to demonstrate a correlation between metabolite relaxation times and age in the adult brain, and this was previously only observed in the developing brain.¹²³

In healthy controls, much larger MWFs have been observed in WM than GM, and MWF has also varied by more than a factor of 2 between different WM structures.^{30,35,48,122,130} The observed regional differences in MWF are hypothesized to be a result of differing regional myelin contents. Figure 4 shows an example of a myelin water map for a healthy control. A correlation between MWF of the frontal lobes and age (as well as years of education) has been observed in normals.¹³¹ Although MT has been cited as a measure for myelin, only a weak correlation exists between MWF and MTR.^{28,122} Figure 5 shows a comparison between F (data taken from reference 25), MTR, and MWF for various WM and GM structures. Note that MWF of GM is approximately 20% of WM, whereas MTR and F of GM are 87% and 53% of WM, respectively. Figure 6 shows the relationship between MTR (data taken from reference 120) and MWF¹³¹ with age in frontal WM.

A number of studies investigating myelin in the spinal cord have also been done. The imaging of the spinal cord provides challenges due to the small diameter of the cord, magnetic field inhomogeneities, and the presence of flow from CSF, which causes motion and artifacts. T_2 studies have shown the feasibility of measuring MWF in the spinal cord *in vivo*.^{47,132,133} The MWF has been found to be approximately 50% higher in spinal cord than normal brain WM and is reported to vary along the length of the cord.¹³² Several spectroscopy studies have also demonstrated the feasibility of using MRS to study the spinal cord,^{134–136}

FIG. 5. Studies investigating the semi-solid pool (F, triangles) (data from Sled et al.,²⁵ 2004), magnetization transfer ratio (MTR, squares) and myelin water fraction (MWF, circles) for various white matter (WM) (internal capsule [IC], splenium [SP], major forceps [MJ], genu [GU], minor forceps [MN]) and gray matter (GM) (thalamus [TH], cortical gray [CO], putamen [PU], insular cortex [IN], cingulate gyrus [CG], and head of the caudate [CA]) structures in human healthy brain. Note that MWF of gray matter (GM) is approximately 20% of WM, whereas MTR and F of GM are 87% and 53% of WM, respectively.

although normative studies have yet to be done. Both MTR^{137–140} and diffusion^{141–143} measures have also been examined in the normal spinal cord, although typically as a control for various disease studies and large normative studies that have not yet been completed.

DEMYELINATION

The ability to image myelin *in vivo* has widespread application in the study of neurodegenerative diseases, both from the aspect of gaining insight into disease processes, as well as monitoring clinical therapy. Demyelination refers to the loss or destruction of previously healthy myelin and a wide variety of existing demyelinating diseases and disorders. Filley¹⁴⁴ presents an excellent review of many such disorders in a recent text,

and here we will discuss two such diseases that include demyelination in their pathology.

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease of the CNS that is characterized by areas of focal, as well as diffuse, edema, inflammation, demyelination, and axonal loss.¹⁴⁵ However, the mechanisms underlying the clinical evolution and ultimate progression of MS and their relationship to these pathological features are still poorly understood. Much of the pioneering work in attempting to image myelin with MR has been carried out in the field of MS. The initial focus on imaging myelin in MS was on the study of lesions, which are clearly visible with conventional imaging (bright on T₂-weighted imaging, dark or gadolinium enhancing on T₁-weighted imaging).

FIG. 6. (A) Magnetization transfer ratio (MTR) (data from Mehta et al.,¹²⁰ 1995) and (B) myelin water fraction (MWF) (Flynn et al.,¹³¹ 2003, reprinted with permission from Macmillan Publishers Ltd: Molecular Psychiatry, Flynn SW, Lang DJ, Mackay AL, et al. Abnormalities of myelination in schizophrenia detected *in vivo* with MRI, and post-mortem with analysis of oligodendrocyte proteins. 2003;8:811–820, copyright 2003) in control frontal white matter *versus* age. The MWF shows a positive correlation with age ($R^2 = 0.22$; $p = 0.012$), whereas MTR does not. Rovaris et al.¹¹⁹ also did not find a correlation between whole brain MTR and age, but Silver et al.¹¹⁷ and Armstrong et al.¹¹⁸ did find a correlation.

Table 3. *Changes in MR Measures Influenced by Myelin Compared with Changes in Myelin as Measured by Histology**

	Myelin (histology)	T ₁	T ₂	MTR	F	FA	$\langle D \rangle$	$\lambda_{\perp}$	Lipid	Cho	MWF
Myelination											
<i>Development</i>	↑ ¹⁰⁰	↓ ^{103,104}	↓ ^{103,104}	↑ ^{115,116}	—	↑ ¹⁰⁷	↓ ^{105,106}	no change ¹¹⁰	—	↓ ¹²³	—
<i>Aging</i>	↑ ¹⁰¹	↓ ²⁷¹	↑ then (a/f 40 yr) ↓ ^{271,272}	↑ ^{117,118} or no change ^{119,120}	—	↓ ^{111–114}	↑ ¹¹²	↑ ¹¹²	—	↑ ¹²⁸ or no change ^{126,127}	↑ ¹³¹
Demyelination											
<i>MS (lesion)</i>	↓ ²⁷³	↑ ²⁷⁴	↑ ²⁷⁴	↓ ^{122,153–158}	↓ ^{26,164}	↓ ¹⁴⁶	↑ ^{147,148,150} or no change ¹⁴⁶	↑ ¹⁴⁶	↑ ^{166–168}	↑ ^{167–170}	↓ ^{46,122,130}
<i>MS (NAWM)</i>	↓ ¹⁷⁸	↑ ²⁷⁵	↑ ²⁷⁶	↓ ^{26,156,176,177}	↓ ^{46,165}	↓ ¹⁴⁹	↑ ¹⁴⁸	↑ ^{146,173}	↑ ¹⁶⁹	↑ ¹⁷⁵	↓ ^{47,130} or no change ⁴⁶
<i>Alzheimer's disease</i>	↓ ^{187,188}	—	↑ ^{189–192}	↓ ^{200,201}	—	↓ ^{193–196}	↑ ^{193,194,196}	↑ ¹⁹⁷	↑ ²⁷⁷	↑ ²⁷⁸ or no change ^{279,280}	—
Dysmyelination											
<i>Leukodystrophies</i>	↓ ²⁸¹	↑ ²⁸²	↑ ²⁸³	↓ ^{198,216}	—	↓ ^{18,217–219}	↑ or ↓ ^{18,217– 219}	↑ ^{23,95}	No change ²²⁸ except Zellweger ²²⁷	↑ ^{220–223} or ↓ ^{224–226}	—
<i>PKU</i>	↓ ²³³	—	↑ ²³⁵	—	—	↓ ²³⁹	↓ ^{217,235,238,240}	↓ ²⁴⁰	no change ²³⁴	↓ ^{235,236} or no change ^{237,240}	↓ ²³⁴
<i>Schizophrenia</i>	↓ ^{242,243}	↑ ²⁸⁴ or no change ²⁸⁵	↑ ^{256,285} or no change ²⁸⁴	↓ ^{252,257,258}	—	↓ ^{250–252}	↑ ^{253,254}	↑ ²⁵⁵	↑ ^{246,247}	no change ^{248,249}	↓ ¹³¹
Remyelination	↑ ²⁷³	—	↓ ^{85,86,159,265}	↑ ^{65,159}	—	—	—	↓ ^{90,92}	↓ ^{169,266}	↓ ^{169,266}	↑ ^{61,267}

MTR, magnetization transfer ratio; F, the fraction of protons in nonaqueous tissue; FA, fractional anisotropy; $\langle D \rangle$, mean diffusivity; $\lambda_{\perp}$, radial diffusivity; Cho, choline; MWF, myelin water fraction; MS, multiple sclerosis; MS NAWM, multiple sclerosis normal appearing white matter; PKU, phenylketonuria.

*The references quoted herein are purely representative examples and the summarized results are not an exhaustive search.

FIG. 7. (A) Proton density weighted image, (B) myelin water fraction map, (C) magnetization transfer ratio map, (D) $\lambda_{\perp}$ map, and (E) fractional anisotropy map for a patient with multiple sclerosis.

The MWF has been shown to be variably decreased in MS lesions,^{29,46,122,130} likely reflecting the different lesion pathology. A recent DTI study by Lin et al.¹⁴⁶ examining lesions in the pyramidal tract found increased $\lambda_{\perp}$ and lower FA, but no abnormalities in $\lambda_{\parallel}$ or $\langle D \rangle$ when compared to NAWM consistent with the removal of barriers perpendicular to the axon. In the brain^{147–150} and spinal cord,^{151,152} the less myelin-specific diffusion metrics, FA and $\langle D \rangle$, were also observed to be abnormal in MS lesions. The MTR has consistently been observed to be reduced by varying degrees in MS lesions.^{153–158} The T_1 hypointense lesions, representing lesions with more severe tissue damage and axonal loss than T_1 isointense lesions on postmortem studies,¹⁵⁹ were found to have a greater reduction in MTR than T_1 isointense lesions.¹⁶⁰ Reductions in MTR have also been described to antedate the appearance of lesions on conventional MR,^{158,161–163} although whether these MTR changes arose from demyelination, inflammation, or a combination of both is still unclear. Quantitative MT (qMT) studies investigating F, which is partially made up of myelin, and the MT rate (k_{for}), have found both measures to be decreased in MS lesions,^{26,46,164,165} attributed to changes in myelination. Magnetic resonance spectroscopy has detected a strong lipid peak in acute lesions attributed to myelin breakdown product during demyelination.^{166–168} Increases in Cho have also been seen in lesions^{167–170} and have been described to antedate lesion appearance on conventional MR.¹⁷¹ Such increases in choline may be related to in-

creased turnover of choline-containing myelin membrane phospholipids and cellular inflammation.

In recent years, much effort has also been put into studying the normal-appearing WM in MS. The MWF of NAWM was found to be diffusely reduced in both the brain (by 16%)¹³⁰ and the spinal cord (by $\sim 25\%$)⁴⁷ when compared to healthy controls. Fractional anisotropy was also reduced (by 4%–11%) and $\langle D \rangle$ increased (by 2%–3% in all cases except for 13% in reference 146) in NAWM,^{146,148,149,172} and recently an increased $\lambda_{\perp}$ was observed in NAWM^{146,173,174} by 4% to 20%. Magnetic resonance spectroscopy of NAWM has found abnormalities that could be associated with myelin pathology. In NAWM, Narayana et al.¹⁶⁹ observed the presence of lipid peaks, and increased myoinositol and choline have also been described in NAWM.¹⁷⁵ Reductions in NAWM MTR (by 1.2%–5.5%) have been reported by many groups,^{26,156,158,176,177} as well as reductions in F using qMT^{46,165} by 11% to 14%. All these findings are consistent with a decrease in the amount of myelin in MS normal-appearing WM.

These observed MR changes in NAWM are supported by histopathologic studies finding demyelination,¹⁷⁸ as well as decreased myelin-associated glycoprotein immunostaining in WM that appeared normal with Luxol fast blue.¹⁷⁹ An early study suggested that since myelin is rich in lipid, and makes up the majority of all lipid found in WM, total lipid determination could be used as a simple indicator for myelin.¹⁸⁰ The NAWM showed a 15.5% reduction in total

lipid when compared to control WM, suggesting a similar decrease in NAWM myelin. Several other studies have examined galactolipids, including cerebroside, which are believed to be more directly related to myelin content and have found galactolipid decreases in NAWM of 13.5%¹⁸¹ and 17%¹⁸² when compared to control WM. The reduction in these biochemical markers of myelin has, in the past, been attributed to the inclusion of small plaques in the NAWM assayed.¹⁸³ However, MR data, such as the aforementioned studies, would suggest that such findings might also be due to a more diffuse reduction of nonlesional myelin in NAWM. This diffuse myelin loss could be due to concomitant loss of axons in Wallerian degeneration as reported in NAWM.^{184–186} Table 3 summarizes myelin-related MR changes observed in MS and Figure 7 shows an example of a PD-weighted image, myelin map, MTR map, FA map, and $\lambda_{\perp}$ map for an MS subject.

Because MS is a complex disease characterized by many different types of pathology, it is important to consider other possible sources for changes in MR markers claiming to be specific for myelin. Changes in WC arising from inflammation or edema can strongly influence diffusion parameters and MTR. The MWF is also influenced by WC, as this measure is a ratio of the myelin water signal to the total signal from all water; hence decreases in MWF could arise from increases in WC. However, a recent model showed that the observed increases in WC in MS should only result in a small decrease in MWF. If the MWF decreases observed in lesions and NAWM were to have occurred purely due to increases in WC, the volume increases would be larger than 15% making this scenario unrealistic.¹³⁰ Nevertheless, small changes in MWF can certainly, at least in part, arise from an increase in WC. Similarly, MRS metabolites would also be diluted by an increase in WC.

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, typically affecting the elderly, and it is characterized by short-term memory loss, confusion, emotional instability, and progressive loss of mental ability. Alzheimer's disease is a neurodegenerative disorder that results in loss of neurons and subsequent loss of axons and myelin. In AD, histological studies have demonstrated a widespread decrease in myelin that has been observed in NAWM, as well as more severe myelin loss in focal regions.^{187,188} Numerous studies have measured the T_2 (either 2^{189–191} or 7 echoes¹⁹²) in patients with AD and have found increases in some WM areas compared to controls. Iron, which decreases T_2 , is found in oligodendrocytes, and therefore the increase in T_2 has been attributed to a lower iron concentration due to a loss of oligodendrocytes and consequently myelin.¹⁹² Using diffusion tensor imaging, $\langle D \rangle$ was found to be increased, and fractional anisotropy decreased in AD.^{193–196} The

$\lambda_{\perp}$ was also observed to be increased in AD frontal WM, attributed to a decrease in myelin.¹⁹⁷ No difference was found between AD patients and controls when measuring global brain MTR^{198,199}; however a decrease in AD WM MTR was observed.^{200,201} Using MTR histograms, the peak height, but not position, was found to be lower in subjects with AD than controls.^{199,202,203} All of the observed reductions in MTR could potentially arise from reductions in myelin. Table 3 summarizes myelin-related MR changes observed in AD.

Wallerian degeneration

When an axon is transected, the remaining portion of the axon will degenerate back to the cell body. The myelin was believed to be immediately removed, but more recent experiments by Trapp et al.²⁰⁴ have shown that myelin debris can remain for several months before being taken away by macrophages. This myelin debris, although not in the form of intact myelin, may still contribute to the MWF signal.⁶¹ Eventually, the myelin is removed and changes in MR parameters consistent with demyelination can be measured. Wallerian degeneration can be found in ischemia due to stroke,^{205–207} WM changes in AD,^{193,208,209} amyotrophic lateral sclerosis,²¹⁰ diffuse damage measured in MS NAWM,^{184–186} spinal cord^{211,212} injury, and many other neurodegenerative diseases affecting the integrity of axons. As an interesting note, after spinal cord injury, regeneration of the axons has been shown to be inhibited by the presence of myelin,^{213,214} highlighting the deep association between axons and myelin.

DYSMYELINATION

Whereas demyelination is the destruction or loss of previously healthy myelin, dysmyelination is the defective formation of myelin during development, often involving biochemical abnormalities. Because a reduction of myelin is the outcome of both conditions, no MR technique related to myelination can differentiate between demyelination and dysmyelination. A wide range of dysmyelinating disorders exists, also nicely presented by Filley.¹⁴⁴

Leukodystrophies

In childhood, congenital defects (usually metabolic in origin), which interfere with the normal development of myelin fall within the category of leukodystrophies. Pattern recognition on conventional T_1 -weighted and T_2 -weighted images can be quite useful in diagnosing some of these metabolic disorders,²¹⁵ and in recent years, newer MR techniques such as MTR and diffusion have also been used to learn more about leukodystrophies. The MTR of WM in leukodystrophy patients was found to be lower than that of controls.^{198,216} The $\langle D \rangle$ was found to be either decreased (e.g., with inflammatory changes seen in adrenoleukodystrophy) or increased (e.g., with

abnormal myelin formation in metachromatic leukodystrophy), depending on the origin of the disorder, but anisotropy tended to decrease in all cases.^{18,217–219} Observed increases in $\langle D \rangle$ in some dysmyelinating disorders may be understood by examining animal models of dysmyelination, which have found increases in $\lambda_{\perp}$,^{23,95} and either increases⁹⁵ or no change²³ in $\lambda_{\parallel}$, relative to controls. Spectroscopy has also shown changes in the spectrum of affected individuals with increases in choline and myoinositol in both Krabbe and Alexander disease^{220–223} attributed to loss of myelin. Magnetic resonance spectroscopy of dysmyelination disorders such as metachromatic leukodystrophy²²⁴ and Canavan's disease^{225,226} have shown decreases in the choline peak. All these changes have been attributed to the lower myelin content of dysmyelinated WM. Magnetic resonance spectroscopy of Zellweger syndrome has shown the presence of a lipid peak,^{227,228} whereas other leukodystrophies do not tend to exhibit any lipid signal.²²⁸ Groenendaal et al.²²⁷ hypothesize the lipid observed in Zellweger could potentially arise from the breakdown of myelin, but may also be due to abnormal storage of neutral fat in astrocytes and phagocytes. Table 3 summarizes myelin-related MR changes observed in leukodystrophies.

Phenylketonuria

Phenylketonuria (PKU) is an inborn error of phenylalanine metabolism that causes severe mental retardation in most affected individuals who are not treated with a diet restricted in PHE. A number of studies have observed myelin abnormalities in the brain and spinal cord of subjects with PKU.^{229–232} Early work by Shah et al.²³³ comparing the lipid composition of cerebral WM and myelin in subjects with PKU to controls found the total lipid content to be lower and the ratio of cholesterol to galactolipid to be higher in subjects with PKU. Furthermore, the amount of myelin recovered from the brains of PKU patients was on average 40% lower than from controls. The authors suggest that the observed deficiency of myelin may reflect an early arrest of myelination. A very recent study by Sirrs et al.²³⁴ found the MWF to be reduced by up to 56% in normal-appearing WM of subjects with PKU; a reduction in MWF was also observed in diffuse WM lesions. Choline has been observed to be decreased in PKU lesions in some,^{235,236} but not all studies.²³⁷ Like the inflammatory type of leukodystrophies, diffusion studies found decreased FA and $\langle D \rangle$ in WM,^{238,239} and reduced $\langle D \rangle$ in diffusion-weighted imaging hyperintense areas in PKU.^{235,240} Table 3 summarizes myelin-related MR changes observed in PKU.

Schizophrenia

Myelination in the frontal brain regions continues well into the second decade of life. Schizophrenia often develops during this late period of brain maturation and is characterized by disorganized thinking, delusions, hallu-

cinations, changes in emotions, and changes in behavior. Despite effective treatments for psychotic symptoms, the mechanisms that account for disability are poorly understood. There is growing evidence for neuronal and oligodendrocyte-related abnormalities being associated with schizophrenia. Hakak et al.²⁴¹ found an abnormal expression of myelin-related genes in schizophrenia and using electron microscopy, Uranova et al.²⁴² observed damage to the myelin sheath due to the formation of concentric lamellar bodies and decreased volume density of mitochondria in oligodendrocytes in the postmortem brain.²⁴² Tkachev et al.²⁴³ also observed myelin and fatty-acid biosynthesis dysfunction in schizophrenia based on postmortem brain studies. Magnetic resonance imaging of schizophrenia has also provided evidence of myelin abnormalities within the WM. Flynn et al.¹³¹ found a mean 12% decrease in MWF in the WM of schizophrenia subjects when compared to controls. Furthermore, in healthy subjects, MWF of frontal WM and total WM increased with age and years of education, whereas this relationship was not observed in schizophrenia. Bartzokis et al.²⁴⁴ also demonstrated a relationship between WM and GM ratio and age in controls, which was not observed in subjects with schizophrenia. These findings suggest that the normal WM development and myelination is dysregulated in schizophrenia.²⁴⁵ Some studies have found elevated phosphodiesterases in schizophrenia, implying increased membrane breakdown products,^{246,247} although choline has been reported as normal in several studies.^{248,249} Studies in diffusion have also observed WM abnormalities, such as decreases in fractional anisotropy^{250–252} and increases in $\langle D \rangle$.^{253,254} Kitamura et al.²⁵⁵ observed decreased FA in schizophrenia WM, but found this reduction could be accounted for by the observed increase in $\lambda_{\perp}$. Using a 2-echo fast-spin-echo experiment, Pfefferbaum et al.²⁵⁶ showed subjects with schizophrenia had significantly longer WM T_2 . A number of studies have observed decreased MTR in schizophrenia WM.^{252,257,258} All these findings are consistent with a decrease in the myelination state for schizophrenia WM. Table 3 summarizes myelin-related MR changes observed in schizophrenia.

REMYELINATION

The brain has a limited capacity to repair itself after damage. Myelinating oligodendrocytes may be recruited in areas of damage and reform myelin, although the internode distance is shorter and the myelin thickness is decreased compared with normal myelin.²⁵⁹ With myelin staining, areas of remyelination may show a pallor and are referred to as "shadow plaques."²⁶⁰ The ability to measure remyelination *in vivo* would be extremely useful in monitoring drug therapies as well as giving new insight into progression of disease.

Conventional MR can not differentiate remyelination from other pathologies; however, newer techniques show more promise. A number of studies investigating remyelination in animal models have been completed. From an animal model of demyelination, a predicted remyelination at 6 weeks after cuprizone treatment was detected using the texture analysis parameter, horizontal gray level nonuniformity, on T_2 -weighted images.²⁶¹ In several other studies involving cuprizone diet in mice, measurement of $\lambda_{\perp}$ was found to increase with demyelination and subsequently decrease with remyelination. However, $\lambda_{\perp}$ did not return to pretreatment values.^{90,92} In another study, again examining a cuprizone mouse model, Merkler et al.²⁶² were able to classify regions with 95% accuracy into normal, demyelinated, or remyelinated WM using discriminate function analysis of T_1 , T_2 , and MTR. In a study of injured rat sciatic nerve, Webb et al.⁶¹ demonstrated that MWF reflected myelin loss and remyelination due to Wallerian degeneration and regeneration. Deloire-Grassin et al.⁶⁵ induced demyelinating lesions in rats and examined MTR at varying stages of demyelination and remyelination in comparison to histology. The profile of MTR correlated well with the course of demyelination and remyelination. Schwann cells and olfactory ensheathing cells have been shown to promote remyelination after transplantation.²⁶³ These cells can be labeled with a superparamagnetic iron oxide that allows them to be visualized with MR. Recently, these transplanted cells were shown to promote remyelination in rat spinal cord and could be followed with T_2 -weighted imaging.²⁶⁴

Some work studying remyelination in humans has also been completed. In biopsy and postmortem studies of the MS brain, lesion hypointensity on T_1 -weighted images increased with increasing demyelination, and subsequently decreased with remyelination, with some lesions returning to isointensity compared to the surrounding WM.^{85,86,159,265} In two MRS studies, MS lesions showed a decrease in choline and lipid signals, which could be attributed to remyelination, but also to a decrease in edema and inflammation.^{169,266} In a serial MS study, several large lesions showed dramatic decreases in MWF at first appearance, presumably due to demyelination. A subset of these lesions then exhibited a subsequent increase in MWF, indicating possible remyelination.²⁶⁷ Comparing postmortem MTR to histopathology in the MS brain, Barkhof et al.¹⁵⁹ found that although remyelinated lesions showed a higher MTR than demyelinated lesions, they were still below NAWM values. Measuring the inhomogeneity of MTR in lesions was used to determine whether regions would show subsequent increases or decreases in MTR. Voxels with a low MTR in regions of high MTR inhomogeneity showed increases in MTR after 2 months. These MTR increases were attributed to

remyelination.²⁶⁸ Table 3 summarizes myelin-related MR changes observed in remyelination.

CONCLUSIONS

In this review we have reported on the extensive literature that uses MR to image myelin. We close with a brief critical assessment of the relative merits of the different MR approaches used.

MR techniques for monitoring myelin

It is clear that myelination affects the values of most MR parameters. Hence, we find a very large number of different approaches to monitoring myelination in the literature. In this review we reported seven approaches, but we focused on the five most common techniques. We provide a critical summary on each of these techniques below:

Conventional T_1 -weighted and T_2 -weighted imaging approaches have seen the largest application in the study of children under the age of 2 years, because by far the greatest changes in relaxation time weighting occur in this age range. Two cautions come to mind with this approach: 1) given that T_1 and T_2 are heavily influenced by WC, the observed changes in brain development are not necessarily specific to myelination; and 2) there is a large amount of literature on the influence of iron on T_1 and T_2 in the brain (reviewed elsewhere in this volume by Stankiewicz et al.²⁶⁹). Consequently, for older subjects, the use of conventional relaxation time weighting as a myelin measure is not appropriate. For this reason, we caution researchers to reserve this qualitative approach to subjects under the age of 2 years.

With MRS, the presence of neutral lipid, assuming it can be isolated from lactate, is most likely a result of active demyelination. However, proton MRS is not capable of assessing the content of intact myelin, and currently, it has a limited resolution.

The research community is largely in agreement about the relationship between DTI parameters and myelin, due to a series of elegant studies on animal models of human disease. To summarize, measurements of changes in radial diffusivity, $\lambda_{\perp}$, give information on changes in myelination, but the absolute value of $\lambda_{\perp}$ also depends on the degree of fiber tract orientational order within the imaging voxel. Also, small changes in $\lambda_{\perp}$ may only be detectable in regions of high anisotropy and not in areas of low anisotropy, such as regions of crossing fibers or gray/WM interfaces.¹⁷⁴

It is well established that MTR is a robust and very sensitive indicator of tissue integrity; hence this parameter has great value for monitoring CNS pathology. However, there continues to be controversy about the relationship between MTR and myelin. Models for magnetization transfer in CNS tissue (e.g., Stanisiz et al.,³⁴ 1999) suggest that MTR is influenced by changes in WC

and T_1 , as well as changes in myelin. Also the MTR value includes magnetization transfer and direct saturation effects, both of which depend critically on the pulse sequence parameters.^{34,270} The degree of direct saturation can differ between tissues and water compartments in a manner that again depends on the nature of the pulse sequence.³² Most magnetization transfer models assume a two-pool system (i.e., water and nonaqueous tissue), although WM is known to be more complicated. The magnetization transfer effect depends not only on the presence of two (or more) proton pools, but also on the exchange rate between the pools, which itself may vary with pH, temperature, and pathology.⁷¹ The ratio of GM-measured to WM-measured values of MTR and F^{25} are typically 50% or higher, whereas histological measures of myelination in CNS tissue indicate that GM has on average about 10% to 20% as much myelin as WM (Tables 1 and 2). The current understanding of magnetization transfer contrast in CNS tissue is an area of active research; improved modeling for this may result in a robust technique for measuring myelination. However, although there is a great deal of evidence to indicate that myelination plays a role in determining the MTR value, it is inappropriate to associate changes in MTR solely with changes in myelin content.

In the opinion of the authors of this review, the short T_2 component from water in myelin provides the most specific measure of CNS myelination available today. This is best demonstrated from the perusal of Tables 1 and 2, which show plots of MWF *versus* a histological measure of myelination. The plots from Webb et al.,⁶¹ 2003 (PNS) and Laule et al.,⁷⁸ 2006 (CNS) show linear relations (with near zero intercept) across the entire range of data acquired, and for the CNS data, GM, lesions and WM points fit the same line. When compared to the other plots in Tables 1 and 2, these show the most promise for a robust linear relationship between MR myelin marker and myelin content. A key point here is that plots of measured relationships are more informative than R^2 values.

Concluding remark

In conclusion, we continue to learn a great deal about myelin from MR studies. Many researchers have played a key role in understanding myelin development in neonates and young children, as well as in the maturing adult. Most neurodegenerative diseases have a myelination component that can be elucidated by MR. We believe that in the future there will be a greater understanding in the research community regarding the optimal MR approach or approaches for imaging myelin with continued research, advancements in high-field imaging, and further discussion.

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