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REVIEW

An Invited Review for the Special 20th Anniversary Issue of MRMS

Advanced Diffusion MR Imaging for Multiple Sclerosis in the Brain and Spinal Cord

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Diffusion tensor imaging (DTI) has been established its usefulness in evaluating normal-appearing white matter (NAWM) and other lesions that are difficult to evaluate with routine clinical MRI in the evaluation of the brain and spinal cord lesions in multiple sclerosis (MS), a demyelinating disease. With the recent advances in the software and hardware of MRI systems, increasingly complex and sophisticated MRI and analysis methods, such as q-space imaging, diffusional kurtosis imaging, neurite orientation dispersion and density imaging, white matter tract integrity, and multiple diffusion encoding, referred to as advanced diffusion MRI, have been proposed. These are capable of capturing *in vivo* microstructural changes in the brain and spinal cord in normal and pathological states in greater detail than DTI.

This paper reviews the current status of recent advanced diffusion MRI for assessing MS *in vivo* as part of an issue celebrating two decades of magnetic resonance in medical sciences (MRMS), an official journal of the Japanese Society of Magnetic Resonance in Medicine.

Keywords: *diffusional kurtosis imaging, double diffusion encoding, multiple sclerosis, neurite orientation dispersion and density imaging, oscillating gradient spin-echo*

Introduction

Multiple sclerosis (MS) is a demyelinating disorder characterized by inflammatory demyelination accompanied by axonal degeneration that mainly affects young individuals. Some lesions undergo repair of injured myelin subsequently, while others may fail to repair and evolve into chronic plaques with variable degrees of chronic demyelination and axonal injury. Currently, there is no cure for MS, and the treatment focuses on hastening the recovery from the attacks, slowing the progression of the disease and managing the symptoms of MS. Corticosteroids, such as pulse steroid therapy and oral prednisone, reduce nerve inflammation during MS attacks. Several disease-modifying therapies modify disease progression. Interferon β, fingolimod, natalizumab, glatiramer acetate, and dimethyl fumarate are disease-modifying drugs approved for use in Japan.[1]

Conventional clinical MRI, including T1-, T2-, and fluid-attenuated inversion-recovery (FLAIR) imaging, has played an important role in the diagnosis and monitoring of the disease in clinical situations, as stated in the revised McDonald criteria.[2] However, the degree of disease progression in MS does not always coincide with the initial imaging findings.[3,4] This has been explained by the normal-appearing white matter (NAWM), which has ongoing microstructural damage in neural tissues but does not show abnormal intensity on conventional MRI.

Diffusion tensor imaging (DTI) is a technique sensitive to the motion of water molecules *in vivo* and has been reported to be a useful tool in detecting abnormalities in the brain and spinal cord in patients with MS. Quantitative metrics of DTI, such as mean diffusivity (MD), which shows the rotationally invariant magnitude of the water molecule diffusivity within a voxel, and fractional anisotropy (FA), which shows the directionality of water molecule diffusion, have been widely used as a quantitative assessment index for NAWM and MS

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plaques. Over 300 DTI papers have been published in the evaluation of MS to date.[5] For instance, DTI parameters are abnormal within MS lesions showing increased diffusivity and reduced anisotropy on comparing with NAWM.[6,7] These results are consistent with the increased water content, loss of myelin and axons, and the presence of gliosis. Moreover, abnormal DTI parameter values are frequently found in the NAWM of MS patients relative to age-matched controls, which contribute to the establishment of widespread white matter damage, even in the early phases. However, DTI metrics lack specificity as indicators of pathological changes. For instance, decreased FA is a common finding in the white matter of MS patients, but it is not specific, as it can be caused by a variety of factors, including the decreased density of neurites and decreased myelin. There are limitations in evaluating FA alone, and FA cannot distinguish between diseases characterized by pathological processes, such as edema, inflammation, demyelination, and leukoaraiosis.[8] Therefore, several advanced and complex diffusion MR imaging (dMRI) and analyses have been introduced in the last two decades to capture more specific pathological changes. There is a review that suggests that multiple advanced dMRI is a quantitative MRI method with high sensitivity and specificity for the evaluation of MS lesions and NAWM.[9]

In this review, we describe the recent advances in dMRI in assessing MS *in vivo*.

Q-Space Imaging

Q-space imaging (QSI) is an analytical method for diffusion MRI using high b-values. It can calculate the average distance traveled and the probability density map of water molecules in one voxel during a given diffusion time from the MRI data with multiple and high b-values (Fig. 1). QSI does not introduce the assumption of Gaussian diffusion in the calculation of quantitative values, which acts as an advantage, while DTI assumes Gaussian diffusion of water molecules. In DTI, the Einstein–Smoluchowski equation,

$$<x2>=2Dt$$

where <x2> = mean square displacement, D = the diffusion coefficient, t = the diffusion time, acts as the basis for the diffusion tensor image, and it is assumed that water molecules exhibit Gaussian diffusion. However, there is a discrepancy in the actual water movement in neuronal tissues *in vivo*. In a living organ, there is a 3D partition or compartmental structure composed mainly of cells and other structures, and water molecules collide with obstacles immediately after initial movement. Therefore, the assumption that diffusion is normally distributed is not true in most cases *in vivo*. However, compared to conventional DTI, QSI is not as widely used in clinical practice since it requires a large number of high b-values established by limited high-performance MRI systems. Moreover, it requires a long

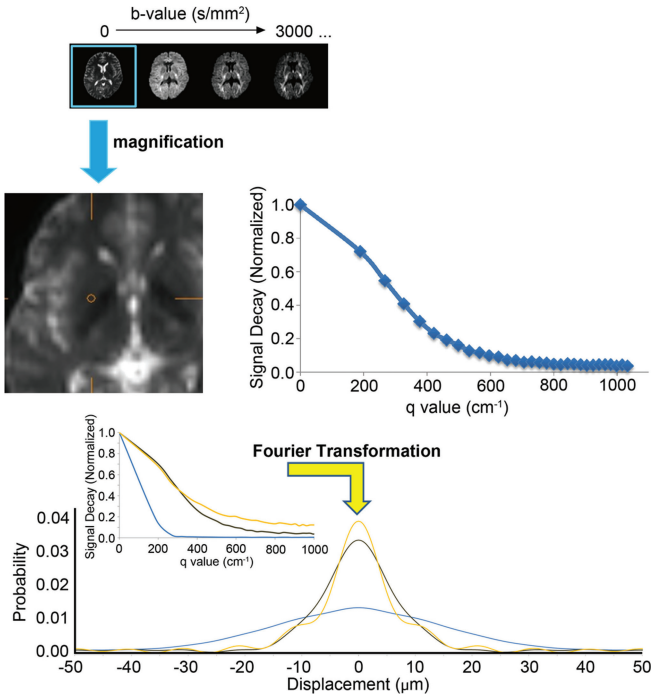

Fig. 1 The process of QSI metrics from DWI data set. First, a DWI dataset with multiple b- (q-) values of up to approximately 10000 s/mm^2 is acquired. A q-value signal intensity curve is obtained for each pixel. After the Fourier transformation of the signal decay with respect to q producin a non-Gaussian displacement distribution profile for each pixel, probability density function curves are calculated. The mean displacement (calculated from the full width at half height) and the probability for zero displacement (given by the height of the profile at zero displacement) are important indices. The yellow line indicates white matter, the gray line indicates gray matter, and the blue line indicates cerebrospinal fluid (adapted from Fig. 1 of reference #17). DWI, diffusion-weighted imaging; QSI, q-space imaging.

imaging time. In addition, its application in humans is relatively older than that of DKI, which was introduced later and reported on by Assaf et al.[10] and Cohen et al.[11] in 2002. The maximum b-value in these studies was 14000 s/mm^2. In these early reports, QSI was found to be very sensitive to MS lesions compared with conventional MRI, especially in the NAWM of the brains with MS. A more detailed study showed that QSI correlated with N-acetylaspartate levels measured by MRS and was useful in detecting abnormalities in NAWM in MS.[12] One QSI study using a maximum b-value of 6400 s/mm^2 showed the potential to assess different cerebral water components and plaques of different degrees of demyelination showed different features in MS patients.[13] In spinal cord MS lesions, Farrell et al.[14] showed the usefulness of QSI analysis as a feasibility study. The mean displacement of water molecules, one of the metrics of QSI analysis, similar to the apparent diffusion coefficient (ADC) of the diffusion tensor analysis, showed higher values in NAWM and MS plaques (Fig. 2).[15,16] In general, the

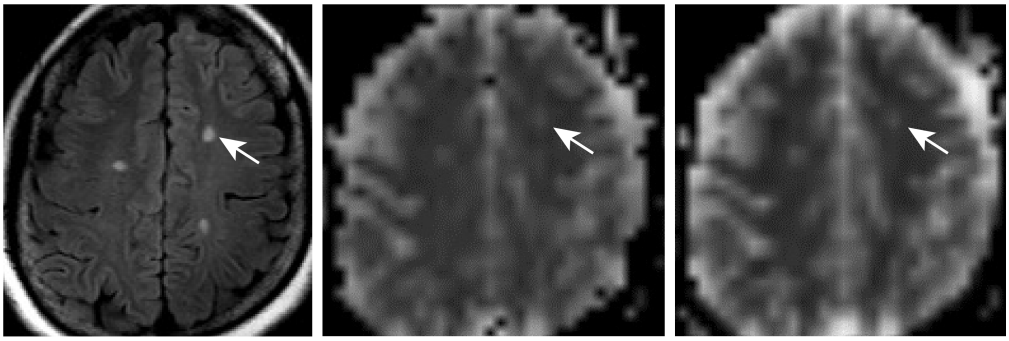

Fig. 2 Images from a patient with MS. FLAIR image shows the demyelinated lesions as abnormal hyperintensity spots. The corresponding map of ADC from a DTI analysis and a mean displacement map from a QSI analysis show the lesions as abnormally high values compared with surrounding white matter. ADC, apparent diffusion coefficient; DTI, diffusion tensor imaging; FLAIR, fluid-attenuated inversion recovery; QSI, q-space imaging.

advantage of QSI compared to DTI is its ability to detect pathologic conditions with higher sensitivity.[17,18] Moreover, QSI-based myelin imaging was introduced to monitor demyelination and remyelination in MS patients.[19–22] It is important to note that advanced diffusion analysis in the spinal cord and brain has been performed *in vivo*,[23–25] demonstrating that it is possible to observe microstructural changes in the spinal cord in patients with MS.

Diffusional Kurtosis Imaging

Diffusional kurtosis imaging (DKI) is closely related to QSI. QSI methods have been employed to estimate diffusional kurtosis as a metric derived from QSI analyses.[13] DKI was established by Jensen et al.[26] as a method to quantify the deviation from a Gaussian distribution. According to this report, the relationship between diffusivity (D), diffusional kurtosis (K), and the signal in the diffusion-weighted image is expressed using the following equation:

$$\ln[S(b)/S0] = -bD + \frac{1}{6}b^2D^2K$$

where b = b value (s/mm2), S(b) is the signal intensity at b, and S0 is the signal intensity at b value of 0. This formula is an expansion of the DTI (Fig. 3).

The merit of DKI compared to QSI is that it can be calculated with lesser MRI data than QSI and is easier to apply in clinical situations. In a minimal DKI protocol, an image dataset consisting of two b-values (such as b = 1000 and 2000 s/mm^2) is often used in addition to the b = 0 image. Numerous motion probing gradient axes (usually 15 or more axes) are required for DKI than for DTI, but a realistic imaging time is possible for clinical application. However, in early reports of DKI, some studies did not cover the whole brain as the imaging range,[27] and a reasonable imaging time could be achieved by methods such as the simultaneous multislice technique that shortens the imaging time.[28–30] The advantage of DKI compared to DTI is that white matter damage in MS patients, especially hidden microstructural abnormalities in NAWM, can be detected with greater sensitivity by quantitative values obtained from DKI, such as the mean kurtosis.[31,32] Moreover, the mean kurtosis obtained from DKI has the advantage of being less susceptible to crossing fibers, unlike FA (Fig. 4). Therefore, an accurate evaluation of NAWM in the whole brain can be expected using DKI. In addition to the brain, the usefulness of DKI has also been shown in the spinal cord in patients with MS.[17,33] However, Martin et al.[34] described some skepticism regarding the usefulness of DKI in the spinal cord. It is difficult to argue that the most robust diffusion MRI technique for assessing past spinal abnormalities is the FA calculated from DTI. The number of studies evaluating the spinal cord using DKI at this stage is small, and more studies with a larger number of patients are needed to establish a base of evidence. Furthermore, studies on the brain have reported abnormalities in MS patients, such as microstructural changes in images, and correlated various clinical indices with metrics calculated from DKI. Bester et al.[35] showed that decreased cortical mean kurtosis was correlated with poor performance on cognitive tasks. A notable aspect of this study is that DKI was used to assess gray matter rather than white matter. Takemura et al.[36] found that the lateral geniculate nucleus may compensate for unilateral damage in the pregeniculate optic pathway via neural plasticity by using DKI and visual-evoked potentials. Spampinato et al.[37] showed that radial kurtosis of the corticospinal tract, which is kurtosis perpendicular to the main nerve fiber direction in the voxel, may be associated with neurological disability in MS patients.

DKI is also being applied in neuromyelitis optica (NMO), a clinically similar disease often misdiagnosed as MS on conventional MRI.[38,39] Technically, the study of MS patients

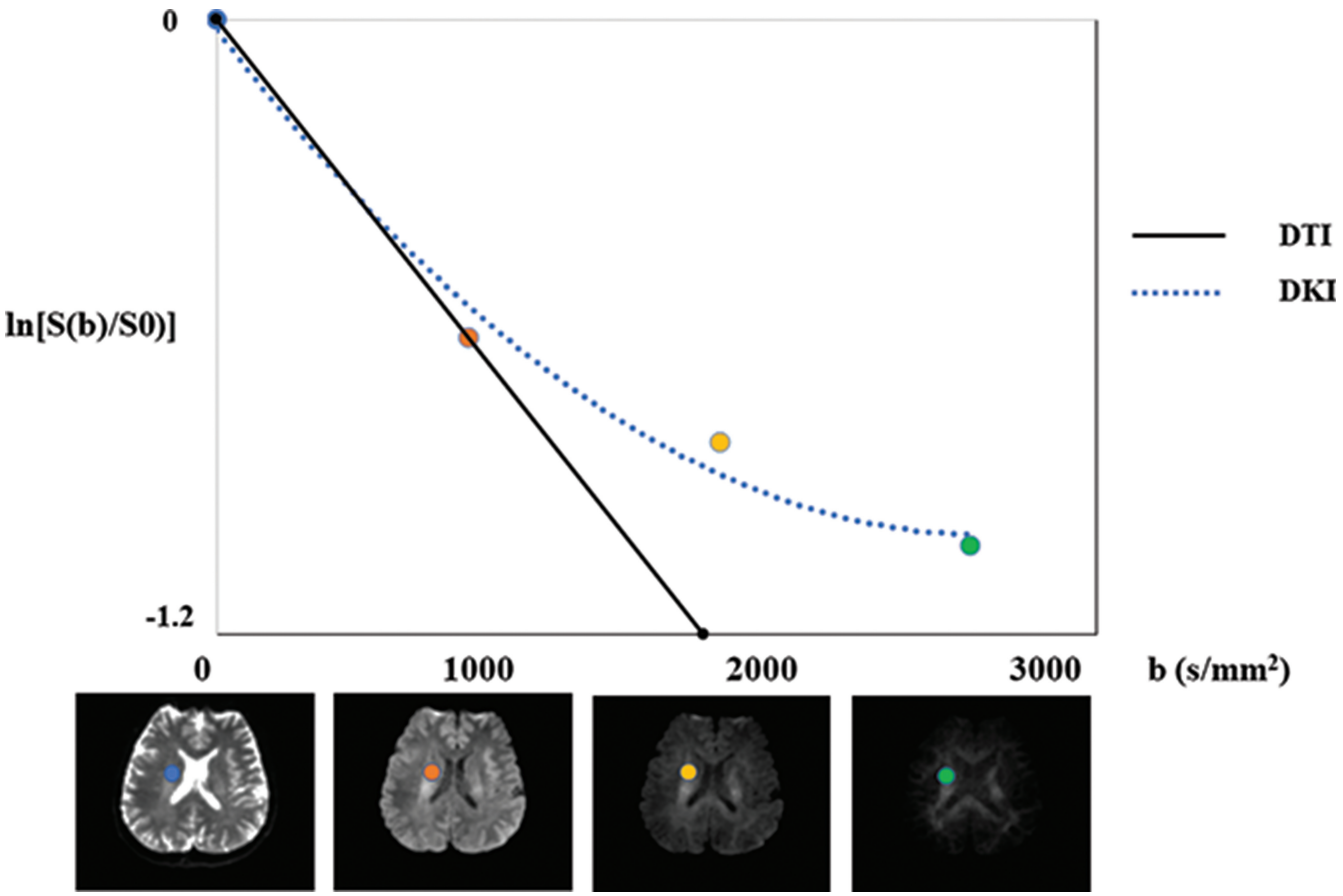

Fig. 3 Brief description of DKI and DTI signal fitting. The logarithm of normalized signal intensity of DWI (color dots) at b values of 0 and 1000 s/mm^2 is fitted to a black line for DTI. The logarithm of normalized signal intensity of DWI at multiple b-values is fitted to parabola for DKI. DKI, diffusional kurtosis imaging; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging.

in 7T MRI systems, which are expected to be widely used in the future, has already begun.[40] In addition, the usefulness of DKI with an imaging time of less than 3 minutes that utilizes a particular data collection method has been reported, although further reductions in the imaging time of DKI may be necessary for widespread use in clinical practice.[41] One caveat regarding DKI is that kurtosis indicates the degree of deviation from the Gaussian distribution, and the value of kurtosis in diffusion MRI is thought to reflect the complexity of biological tissues to some extent; however, the interpretation of the value itself should be done carefully, and data from a large number of cases should be studied to establish its clinical usefulness. In addition, values such as mean kurtosis are not specific.

Neurite Orientation Dispersion and Density Imaging

From the viewpoint of modeling,[42] DTI and DKI can be considered as numerical representations that aim to summarize or compress the information contained in the data without detailed knowledge regarding the substrate itself. In contrast, NODDI[42] belongs to the category of biophysical models[43] that aim to infer specific microstructural properties of biological tissue (e.g., neurite density).[44] Among several models proposed thus far, neurite orientation dispersion and density imaging (NODDI) is arguably the most popular model in clinical research at present.[45] NODDI assumes three compartments: intraneurite, extraneurite, and cerebrospinal fluid (CSF) (free water). The respective fractions for each of these were calculated as quantitative values. In addition, orientation dispersion, a measure that indicates the orientation of structures (such as axons and dendritic spines) in a voxel, was also calculated. The dMRI data required for the analysis of NODDI are approximately the same as those of DKI and less than those of QSI. In addition, it is possible to analyze both DKI and NODDI from the same data. Several studies on patients with MS have evaluated MS lesions and NAWM using NODDI.[46–56] Moreover, NODDI has also been applied to spinal cord evaluation.[57,58] A common finding in these studies is the reduction in intraneurite volume fraction (INVF) in the plaques of MS patients. In addition, there

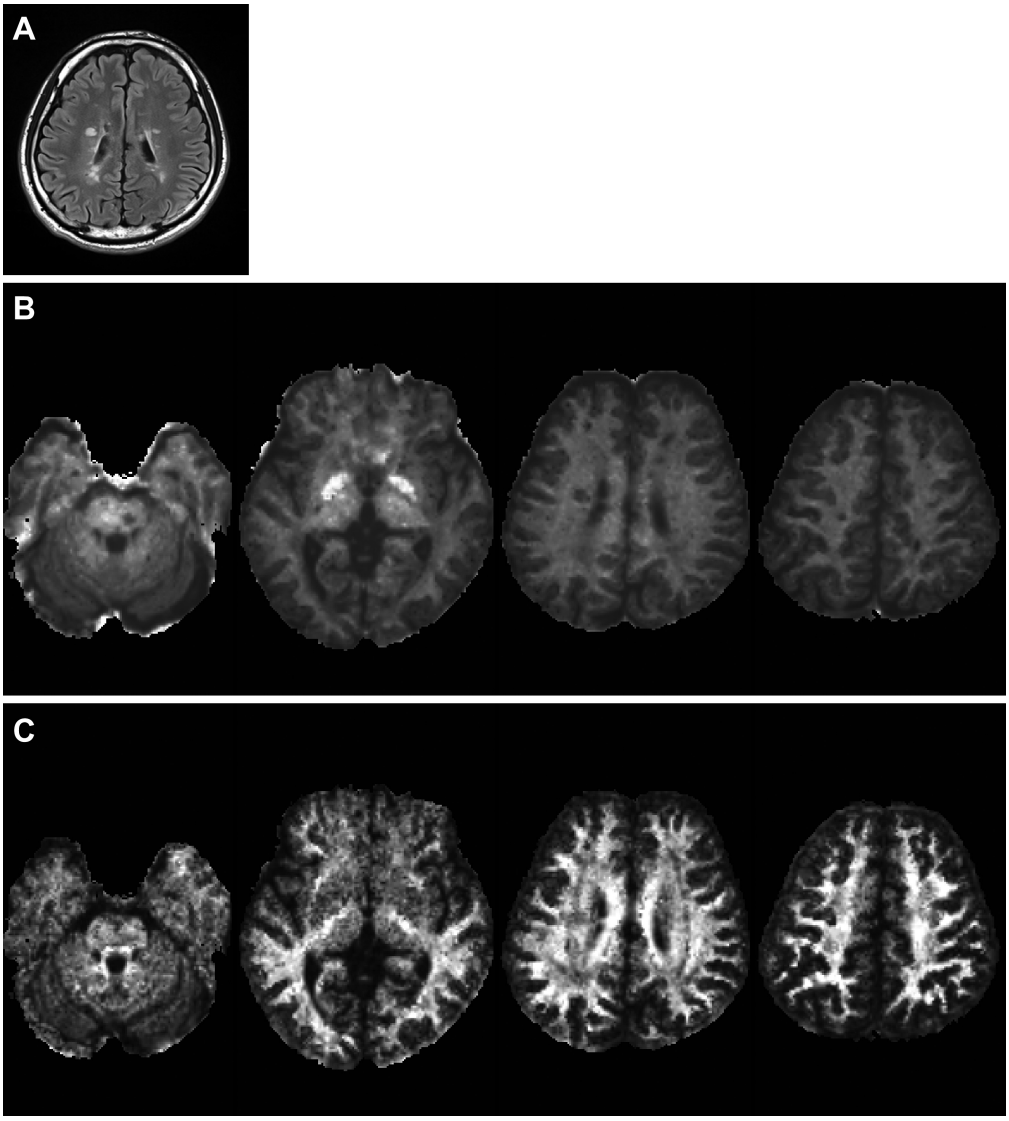

Fig. 4 FLAIR image (**a**) shows hyperintense lesions in deep white matter, indicating MS plaques. Mean kurtosis maps (**b**) and FA maps (**c**) show the plaques as hypointense lesions. Note that, in the mean kurtosis map, white matter can be assessed without the influence of crossing fibers. FA, fractional anisotropy; FLAIR, fluid-attenuated inversion recovery.

was a decrease in INVF in the NAWM, though not as much as in the above demyelinated foci. These changes captured by NODDI are more widespread than those observed by DTI and conventional MRI techniques, suggesting that NODDI is an excellent method for evaluating microstructural changes. Pathologically, a decrease in INVF in NODDI suggests neurite degeneration and decreased density associated with chronic or progressive nerve demyelination in MS. However, it should be noted that the results with orientation dispersion (OD), one of the indices calculated from NODDI, have not been consistent in MS patients. Grussu et al.[59] showed decreased OD in MS lesions and excellent agreement between the orientation dispersion index and its histological counterpart in a postmortem spinal cord study. However, there are some caveats regarding the use of NODDIs in clinical research. The analysis of diffusion MRI using a model such as NODDI may not always fit correctly in tissues under pathological conditions.[45] Further studies with more clinical cases and comparisons with histopathology, clinical symptoms, and prognosis are needed to confirm this. In addition, the quantitative metrics calculated by NODDI vary depending on the imaging conditions, although clinicians are not particularly aware of it.[60] Diffusion time dependence and TE dependence on diffusion MRI exist and affect the quantitative values, which is not limited to NODDI.[61–65] Therefore, the above validity should be confirmed when the parameters calculated using NODDI are used as biomarkers in actual clinical cases.

White Matter Tract Integrity

White matter tract integrity (WMTI)[64] is another popular biophysical model that can be applied to the same data acquired for DKI and NODDI. WMTI is a two-compartment model (intra- and extra-axonal compartments) and is based on an analytical solution that directly links the kurtosis tensor to the model parameters (intra- and extra-axonal compartmental diffusion tensors and the axonal water fraction [AWF]). Subsequently, this analytical solution was extended to general situations (arbitrary fiber orientation distribution and the existence of a free water compartment) to elucidate the acquisition requirements for solving the general model. Enthusiastic readers are referred to previous publications on this topic.[66,67] WMTI has been applied in clinical studies of MS,[68–71] and these studies suggested that a decrease in AWF in the white matter correlates with clinical disability, presumably reflecting chronic axonal loss. In animal models, WMTI has been shown to be capable of distinguishing different tissue pathologies in demyelinating lesions and tracking their longitudinal courses. Specifically, extra-axonal radial diffusivity is related to the g-ratio,[72] while AWF is linked to the axonal fraction derived from electron microscopy, which is in agreement with computer simulations of diffusing molecules.[73] In a cuprizone mouse model, intra-axonal axial diffusivity was observed in the acute phase, presumably reflecting axonal swelling or beading.[74] While NODDI and WMTI have their pros and cons, a distinguishing feature between the two is the estimation of compartmental diffusivities. Robust estimation of compartmental diffusivities has been a long-desired goal[66,75] and is not yet possible in clinical situations, which is partly because the compartmental diffusivities affect the dMRI signal only marginally under the condition that SNR values and b-values are within the clinically available range. A common approach is to fix such parameters to reasonable values for the stable estimation of the others. Nonetheless, the compartmental diffusivities and their dependence on diffusion time would yield indispensable information regarding axon morphologies and demyelination,[76–78] and extend the parameter space of dMRI biophysical models (multiple diffusion encoding, diffusion relaxation, and diffusion time), as discussed in the following paragraphs, which are promising avenues for future research.

Double Diffusion Encoding

The dMRI methods described above are all single diffusion encoding methods, despite the differences in b-values and the number of motion probing gradient (MPG) axes,[79,80] which apply only one MPG in one direction and one size per encoding. The double diffusion encoding (DDE) pulse sequence,[81,82] a method that applies two MPGs per encoding, has recently become available as a part of multiple encoding technique. DDE allows the anisotropy to be measured in a single voxel and the microstructure of the individual elements comprising the voxel, which is quantified by the microscopic fractional anisotropy (μFA) metric. DDE makes it possible to observe tissue microstructure *in vivo*, which differs from FA obtained by conventional DTI analysis and is expected to be clinically useful in the future. The first method proposed for the application of DDE in humans was quite long.[83] Subsequently, Yang et al.[84] proposed an imaging protocol for DDE that can be performed in 5 minutes in a clinical setting using data thinning during imaging. They showed that the μFA maps showed improved delineation of MS lesions in the brain compared with conventional fractional anisotropy derived from DTI. Notably, the lesions displayed focal hypointensities on the μFA map but not on the T2-FLAIR images in one patient. This was a feasibility study with a small patient number; however, the μFA derived from DDE showed the potential to be a promising tool in the evaluation of MS *in vivo*. Further extension of diffusion encoding methods includes triple diffusion encoding[85] and more flexible arbitrary gradient waveforms.[86] Such arbitrary waveforms enable a more time-efficient protocol than DDE (under the assumption of multiple Gaussian compartments), and promising results have been reported in a recent clinical study of MS.[87]

Combination of MR Myelin Imaging and Advanced dMRI

Various methods of myelin imaging using MRI have been proposed[88–90] and are expected to be clinically useful in MS, a demyelinating disease, and correlate with a variety of clinical indices. However, the details of myelin imaging are beyond the scope of this study.

Recently, MR fiber g-ratio (the ratio of the diameter of the axon to the diameter of the neuronal fiber) mapping was introduced for the brain[91–93] and spinal cord.[94,95] For MR fiber g-ratio mapping, two quantitative MR measurements, quantitative myelin mapping for the myelin volume fraction (MVF) and quantitative axon mapping, which are usually metrics derived from dMRI for the axon volume fraction (AVF), were used to calculate the aggregate g-ratio in a voxel. The MR g-ratio is expected to be a promising method for the quantitative evaluation of the degree of myelination or axonal damage *in vivo*, which is difficult to evaluate with conventional MRI. The g-ratio was directly visualized and measured using electron microscopy.[96] A previous autopsy study of brains reported dynamic g-ratio changes in demyelinating diseases, such as MS.[97] The g-ratio is related to the neuron conduction velocity.[98] Lesions with pure demyelination have an increased g-ratio. In contrast, lesions with concomitant myelin and axonal loss demonstrate an unchanged or increased g-ratio. We analyzed MVF, AVF, and MR g-ratio values in MS patients and showed that myelin is more damaged than axons in plaques and periplaque white matter

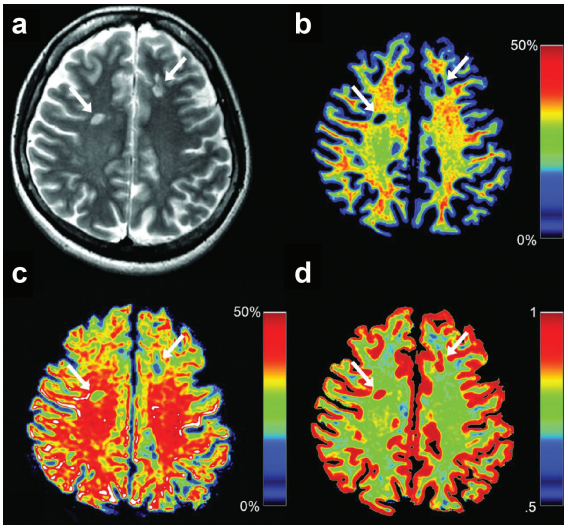

Fig. 5 Representative images from a patient with MS. Synthetic T2WI (**a**) and maps of myelin volume fraction (**b**), axon volume fraction (**c**), and g-ratio (**d**) are shown. Two plaques are designated by arrows in these images. The myelin is severely damaged in these plaques (**b**, 5.53% and 7.23%); however, the degrees of axon damage are milder (**c**, 31.30% and 22.95%). Since the myelin is severely damaged in these plaques, the corresponding g-ratios are close to 1.00 (**d**, 0.94 and 0.91) (adapted from Fig. 1 of reference #48). T2WI, T2-weighted imaging.

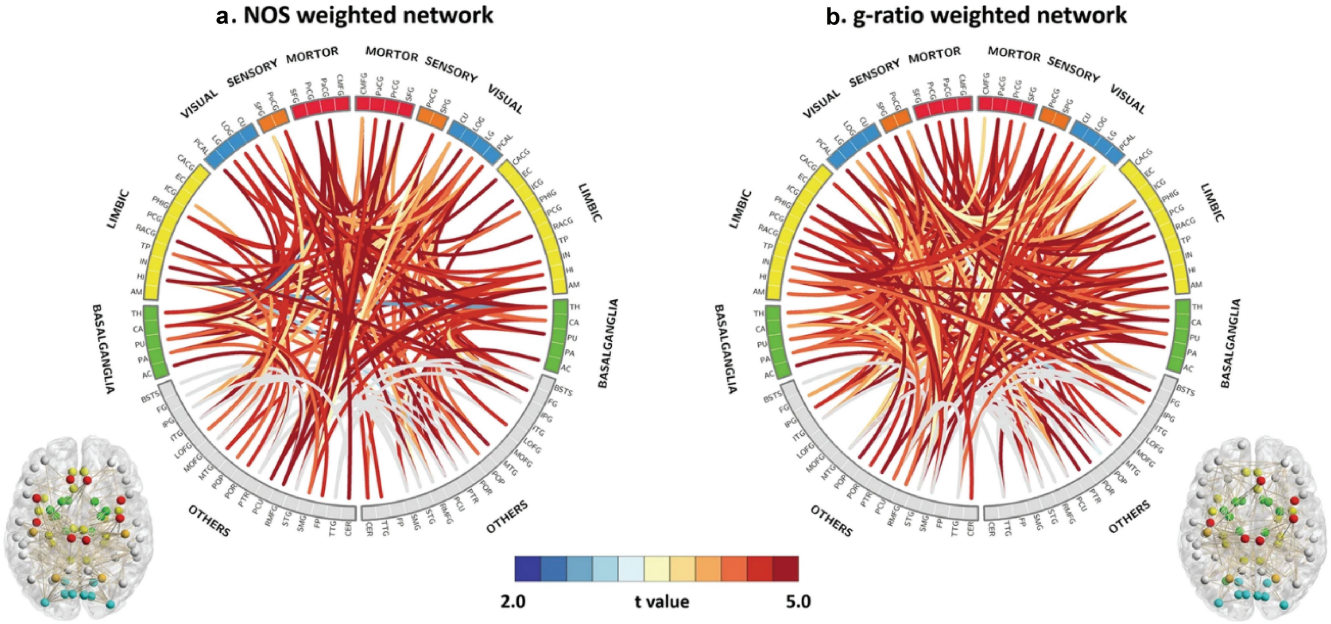

Fig. 6 Comparison of subnetworks with significantly altered connectivity in each network. (**a**) Subnetworks with significantly decreased NOS-weighted connectivity in patients with MS versus controls. (**b**) Subnetworks with significantly increased g-ratio-weighted connectivity in patients with MS versus controls (see correspondence of abbreviations with anatomical regions in Supplementary Table S5 of reference #99) (adapted from Fig. 2 of reference #99). MS, multiple sclerosis; NOS, number of streamlines.

of patients with MS.[48] Thus, these imaging methods could be used as a measure of myelination, demyelination, and remyelination, which cannot be discriminated using conventional MRI in demyelinating diseases, such as MS (Fig. 5). An advanced study involved the application of the MR g-ratio to structural connectome analysis.[99] In this study, Kamagata et al.[99] compared the network topology of the brain in MS patients using MR g-ratio-weighted analyses and normal network analyses. The authors found that the g-ratio-weighted nodal strength in the motor, visual, and limbic regions significantly correlated with interindividual variation in measures of disease severity (Fig. 6). The g-ratio determines the neuron conduction velocity[98,100] and influences normal brain functions;[101] therefore, network analysis using the MR g-ratio could be a potential biomarker that more accurately reflects the state of the brain network.

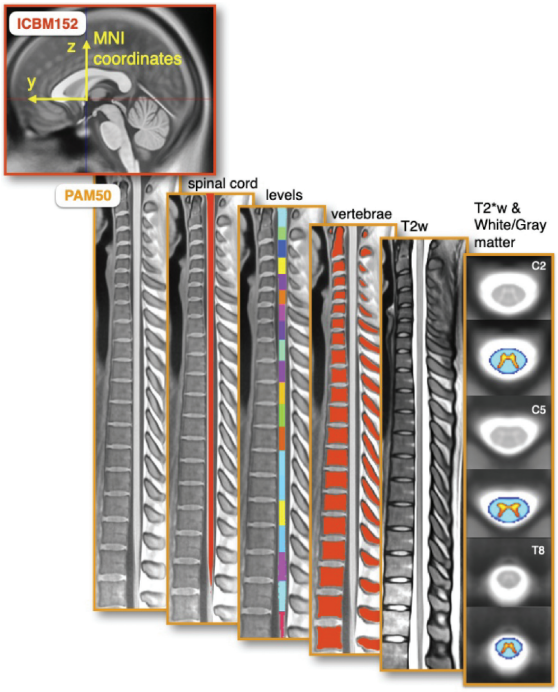

Fig. 7 PAM50 MRI template of the full spinal cord and brainstem. The PAM50 template is compatible with the ICBM152 brain template (the MNI template), allowing researchers to conduct simultaneous brain/spine studies within the same coordinate system. The PAM50 template includes atlases of white matter pathways, gray matter subregions, and probabilistic spinal levels (adapted from https://spinalcordtoolbox.com, with permission).

Notes for Spinal Cord Imaging Analysis

Advanced dMRI has recently been applied and studied *in vivo* in the brain and spinal cord. However, a problem with MRI studies of the spinal cord in the past was that, unlike the brain, there was no standardized method or software for analyzing any quantitative maps. As a result, quantitative values in past MRI studies of the spinal cord were often created by ROIs, and arbitrariness could not be completely eliminated. Currently, well-known and objective tools for quantitative evaluation, such as statistical parametric mapping software (SPM, www.fil.ion.ucl.ac.uk/spm/software/) and the FMRIB software library (FSL, www.fmrib.ox.ac.uk/fsl/index.html), are widely used for advanced dMRI of the brain, and many templates can automatically set up anatomical ROIs in standard space.[102,103] Thus, the recent release of the Spinal Cord Toolbox (SCT)[104] (this software can be downloaded and installed free of charge from the following link: https://spinalcordtoolbox.com), for objective measurement and evaluation in the spinal cord, is considered to be of great significance. The functions of SCT include spinal cord segmentation in the image, motion correction of diffusion MRI of the spinal cord, and registration to the template[105] (Fig. 7). This template of normal white matter and gray matter enables objective analyses. For instance, if the study investigated the spatial distribution of MS lesions in MRI images of the spinal cord from multiple centers with different imaging protocols, the problem of differences in protocols between centers (i.e., differences in spatial resolution and slice thickness) can be resolved by aligning the MRI images on this template.

The spinal cord has the same white matter and gray matter structures as the brain, but there is some debate as to whether it is appropriate to apply the same dMRI analysis methods used in the brain to the spinal cord. In humans imaged using current MRI systems, only the cranio-caudal direction nerve fibers can be depicted, taking into account the spatial resolution and other various conditions. In addition, it is difficult to obtain good image quality since spinal cord imaging is more easily affected by surrounding structures, such as bone and air, and physiological movements (breathing, etc.). Therefore, taking these factors into consideration, a dMRI imaging and analysis method that is more suitable and specific to the spinal cord is desired in the future.

Future Perspective for Advanced dMRI

Recently, an oscillating gradient spin-echo (OGSE) sequence has become available in clinical MRI scanners.[106–109] OGSE can shorten the diffusion time by replacing the long diffusion-sensitizing gradients used in pulsed gradient spin-echo (PGSE) sequences with rapidly oscillating gradients. DWI with OGSE sequence enables short diffusion times and allows us to explore time dependencies that are not accessible to the PGSE sequence. OGSE sequences are expected to provide insight into the internal structures of pathologic lesions based on the analysis of changes in ADC values with different diffusion times. Clinically, acute ischemic stroke,[110]

intracranial epidermoid cysts,[111] transient splenial lesions,[112] head and neck tumors,[113] breast tumors,[114] and prostate cancer[115] have been analyzed using DWI with OGSE sequence. OGSE sequences may be useful in evaluating the internal structure of lesions and differentiating between benign and malignant tumors. No studies have evaluated the brain and spinal cord of MS patients using OGSE sequences, but there is a preliminary study that evaluated the spinal cord of two MS patients using an OGSE sequence.[116] OGSE sequences may be used to evaluate the microstructure of the brain and spinal cord of MS patients and may provide us with new insights. In addition, an important key concept with OGSE is the diffusion time dependence. In dMRI using SDE in conventional MRI systems, TE and diffusion time are almost automatically set once the b-value is determined. Preclinical studies have reported that the differences in the diffusion-weighted images and the quantitative values obtained from the dMRI data due to the diffusion time provide various types of new information on the microstructure of the body. For instance, a correlation with abnormal mitochondria in MS has been reported in human studies.

Other future advances in diffusion MRI include the development of more complex models and analysis methods. For instance, a compartment-based model for noninvasive apparent soma and neurite imaging by diffusion MRI (SANDI) is a model analysis method for diffusion that assumes the existence of a cell body in the neural tissue called soma in addition to NODDI.[117] Estimation of the soma fraction, if possible, is expected to yield more insights into the activities within the tissue affected by MS, such as the loss of cortical neurons and/or microglial activation.

Currently, SANDI is possible only with MRI systems equipped with exceptionally strong gradients and is dependent on some model assumptions that might not be generally valid, especially in diseased brains.

The immediate disadvantage of more advanced dMRI is that the amount of data required for analysis is much larger than that of DTI, although it is true that the more data there are, the more accurate the analysis can be. SANDI is not commonly used in 3T MRI scanners, which are currently used frequently in clinical practice, since only a limited number of models are capable of performing high b-values and short diffusion times. However, there is a possibility that it will become more widespread in the future with the optimization of the imaging technique and advancements in the imaging technique. In any case, ADCs and FAs in DTI currently used in clinical practice are robust and can be imaged and calculated with any clinical MRI system, although they are not specific enough for any disease or condition; therefore, it is necessary to develop advanced diffusion MRI analysis and apply these methods in clinical practice.

Moreover, the combined analysis of several advanced dMRI techniques may provide a more detailed assessment of the pathogenesis of MS than is possible with conventional MRI. In addition, advanced dMRI may become a marker for assessing disease severity and determining treatment efficacy in patients with MS. Moreover, dMRI may be useful in differentiating demyelinating diseases, such as MS, from other brain diseases. In particular, differentiation between tumefactive MS and brain tumors is clinically important. Thus, further research on advanced dMRI is necessary in the future.

Conclusion

Several studies have reported that DTI is superior to conventional MRI in the evaluation of NAWM in MS patients; however, advanced dMRI techniques, as described in this review, are more sensitive and have the potential to show specific pathological changes in the microstructure *in vivo*. Clinically, advanced dMRI has been reported to be more sensitive in detecting microstructural changes in the brain that correlate with patient disability[118] and in tracking disease progression in NAWM over time, even before clinical symptoms occur.[119] In addition, several reports have shown the usefulness of advanced dMRI in NAWM and demyelinating foci. For instance, it is useful in differentiating plaque activity.[41,120] This indicates that advanced dMRI has clinical promise as an objective and highly sensitive indicator for more accurate staging and subsequent monitoring.

Currently, such advanced dMRI is not possible with any installed MRI system and is not a clinically relevant tool due to hardware and software limitations, complexity, and, in some cases, the need for long analysis times. In addition, most studies on MS patients using advanced dMRI are not sufficient in terms of number and quality to establish evidence. Nevertheless, we believe that dMRI is a promising technique that can noninvasively capture microstructural changes in lesions in the brain and spinal cord and that it will become more clinically useful with the further development of MRI technology.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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