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Professor Special Lecture: 73rd Annual Meeting of the Medical Society of Toho University

Review Article

Quantitative MRI of Myelin and Axon *in vivo*

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ABSTRACT: Limited neuronal bodies and dendrites are observed in the white matter, and approximately 60% of the white matter space is occupied by the neuronal fibers. Approximately 70%-95% of the nerve fibers are covered by a myelin sheath. However, sequences of routine clinical magnetic resonance imaging (MRI), such as T2- and T1-weighted imaging and fluid-attenuated inversion-recovery, only provide qualitative, non-specific, tissue contrast images. Therefore, numerous MRI methods have been introduced for *in vivo* myelin and axon quantification. Myelin water fraction is a relatively older MR technique for quantitative MRI of the myelin sheath. Another method for *in vivo* myelin estimation is the use of R1, R2, and proton density values and has shown to be promising in some neurological disorders. Diffusion tensor imaging is a good candidate for quantitative MRI of the axon; however, it has some limitations. Neurite orientation dispersion and density imaging is a model-based diffusion-weighted MRI technique; it yielded good results in clinical settings. Moreover, the MR g-ratio, which is calculated with the myelin volume fraction and axon volume fraction, using myelin- and diffusion-sensitive methods, respectively, showed promising results, providing new insights into *in vivo* microstructural imaging.

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KEYWORDS: magnetic resonance imaging, myelin volume fraction, axon volume fraction, diffusion-weighted imaging, magnetic resonance g-ratio

1. MRI of the Central Nervous System

The white matter in the central nervous system is made up of the following four main components: neurons, glial cells, extracellular space, and blood vessels. Neurons can be further subdivided into fibers, cell bodies, and dendrites. The white matter has limited neuronal bodies and dendrites, and approximately 60% of the space of the white matter is occupied by neuronal fibers. Up to 70%-95% of the nerve fibers are covered by a myelin sheath, so-called myelinated nerve fiber, which imparts its white appearance to the white matter.[1] Moreover, approximately 33% and 27% of the white matter is composed of axons and myelin sheaths, respectively.[1]

However, the routine clinical MRI sequences that are widely used, such as T2- and T1-weighted imaging, as well as fluid-attenuated inversion-recovery (FLAIR) imaging, provide non-quantitative, non-specific tissue contrast images. Conventional MRI has relatively low signal intensity. Moreover, the spatial limitations of MRI prevent its application in the microstructural investigation of the central nervous system *in vivo*. Therefore, another techni-

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cal approach is required for microstructural quantification. Numerous MRI methods have been introduced for *in vivo* myelin and axon quantification.

2. Quantitative MRI of Myelin

Myelin water fraction (MWF) is a relatively older MR technique which uses multi-echo T2-weighted imaging because multi-component T2 relaxation studies of the white matter have revealed the existence of at least two different water environments.[2,3] These environmental components include a short T2 component from water trapped in the myelin sheath and a longer T2 component emerging from the intra- and extracellular water. By measuring the amount of water with a short T2 relaxation time per voxel, it is possible to measure the MWF per voxel. In addition, assuming that myelin water constitutes 40% of the myelin sheath, estimating the myelin volume fraction (MVF) from MWF is possible.

Another method for *in vivo* myelin estimation is the use of R1, R2, and proton density (PD) values.[4] Quantification of tissue parameters, such as relaxation rates (R1 and R2) and PD, provides an absolute scale; however, these parameters have only been measured in research settings due to the required relatively long scanning time. Recently, a rapid quantification MRI technique, such as QRAPMASTER, with scan times of 5-7 min for full head coverage imaging, has been developed for clinical use.[5] The myelin quantification technique using QRAPMASTER is based on a model assumption of the following four brain compartments: the myelin partial volume (VMY), cellular partial volume, free water partial volume, and excess parenchymal water partial volume. Briefly, VMY contains the myelin water and myelin sheaths and are estimated by combining the R1m, R2, and PD values, according to the previously simulated database.

With regard to the clinical application, a recent study from Cincinnati Children's Hospital revealed that the developmental pattern of myelin visualized by this technique was comparable with that published previously.[6] Another study demonstrated that this technique provided the information of accelerated myelination in the damaged brain hemisphere of patients with Sturge-Weber syndrome, a rare neurocutaneous disorder, which causes facial cutaneous vascular malformation and ipsilateral leptomeningeal angiomatosis, most often involving the parietal and occipital lobes.[7,8] Another study reported that the quantitative myelin volume in the brain of patients with multiple sclerosis (MS) was different in the plaques (demyelinated lesion), periplaque white matter, and normal-appearing white matter.[9]

As reported previously, myelin quantification by MRI has showed promising results in clinical settings; moreover, the correlation between MWF and the actual myelin volume in these techniques including MVF and QRAPMASTER has been validated *in vitro* and by histopathological examination.[10-12] However, more validation is required to obtain clinically useful data.

3. Quantitative MRI of Axon

Diffusion MRI is widely used for estimating brain disorders, such as stroke, and is useful in clinical settings. The characteristic tissue contrast of diffusion MRI is that this technique enhances the visualization of restricted water molecules in neuronal tissues. Diffusion-weighted MRI is particularly well suited in the estimation of the axon and axon volume fraction (AVF). Although diffusion MRI is the modality of choice for imaging brain microstructures, it can only measure the displacement distribution of water molecules that are visible in a diffusion MRI experiment. This is limited to the water that is visible on images at the echo time of 50-100 ms; therefore, it excludes the water that is trapped between the myelin bilayers, which has a T2 on the order of 10 ms.[13] Therefore, the estimates provided by these models are of the intra-axonal volume fraction of the visible diffusion imaging information.

Recently, the usefulness of diffusion tensor imaging (DTI) to quantify axons has been investigated. DTI yielded good results in aligned white matter fibers; however, it failed to visualize complex area of fiber orientation, such as the region of crossing nerve fibers.[14]

Therefore, biophysically plausible models have been developed, which provides better description of the underlying tissue microstructure. Among them, the neurite orientation dispersion and density imaging (NODDI) is a model-based diffusion-weighted MRI technique that can quantify specific microstructural features directly related to neuronal morphology.[15] A key concept for NODDI is a neuronal tissue model made up of three compartments, a restricted intracellular compartment, a hindered extracellular compartment, and cerebrospinal fluid (Gaussian distribution of free water molecules), used to analyze data from diffusion MRI. Therefore, the intracellular volume fraction calculated from the NODDI analysis

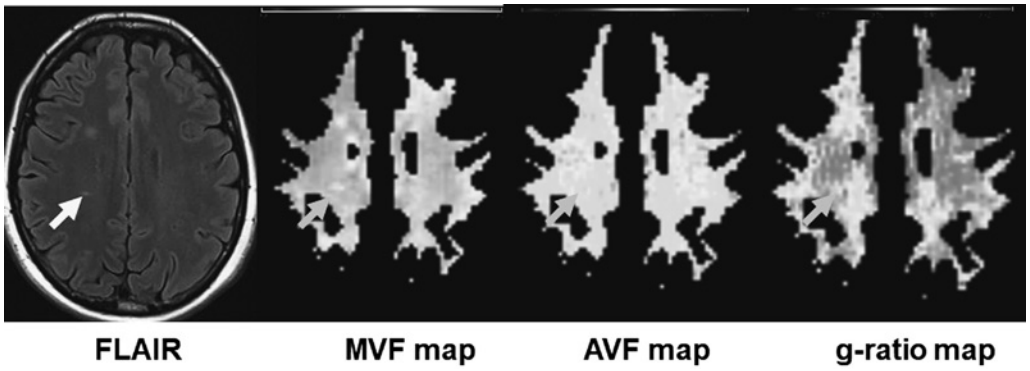

Fig. 1 Axial FLAIR image, corresponding MVF map, AVF map, and g-ratio map of a patient with multiple sclerosis. The degree of the damage in the demyelinated lesion was different on MVF, AVF, and g-ratio maps.
FLAIR, fluid-attenuated inversion-recovery; MVF, myelin volume fraction; AVF, axon volume fraction

in the brain seems to be the most realistic and precise metric for estimating AVF *in vivo*. In such condition, the AVF is estimated using the following equation:

$$AVF = (1 - MVF)(1 - viso)\,vic, \quad (1)$$

where viso and vic are the isotropic and restricted volume fractions from the NODDI analysis, respectively, and the MVF is obtained from one of many possible myelin mapping techniques.

The application of NODDI showed promising results in some neurological diseases *in vivo*. For example, retrograde degeneration of the nigrostriatal pathway in Parkinson's disease was observed by the NODDI and tract-profile analyses.[16] Moreover, in patients with Moyamoya disease, the NODDI analysis can visualize specific brain microstructural damage even without a known history of cerebral infarction.[17] Moreover, the correlation between normal-appearing brain parenchyma and neurocognitive dysfunction has been revealed by the NODDI analysis.[18] These *in vivo* microstructural changes in the brain cannot be evaluated using conventional MRI techniques.

Moreover, NODDI imaging can be performed in 5-10 min using clinical MR scanners, and the scanning time seems tolerable to patients. The NODDI analysis is easy and can be conducted freely using the NODDI Matlab toolbox (https://www.nitrc.org/projects/noddi_toolbox).

Therefore, *in vivo* axon quantification employing NODDI seems to be a promising MR method for estimating brain abnormality in patients with neurological disorders, which is difficult when conventional MRI and mapping techniques are used.

4. Future Directions

In recent years, Stikov et al. proposed an approach for measuring the area-weighted g-ratio for voxels using MRI,[14,19] which is termed the MR g-ratio and is calculated with the MVF and AVF using myelin- and diffusion-sensitive methods, respectively. These parameters can sufficiently compute the g-ratio for each voxel as an aggregate g-ratio.

Originally, the g-ratio of a myelinated axon was directly visualized and measured *via* electron microscopy. This method helps obtain the diameters of axons and myelinated axons in an immunohistochemically processed specimen. The g-ratio determines the neuron conduction velocity,[20,21] which influences normal brain functions.

The MR g-ratio mapping helps derive the fiber density from the g-ratio to achieve a more complete and specific picture of the *in vivo* microstructural detail of the nerve fibers.[13]

With regard to the clinical applications, several studies have investigated the *in vivo* g-ratio imaging in MS.[14] It has the potential to help in the assessment of disease progression and monitoring of treatment response, as well as in the development of new therapies for remyelination. By using the MR g-ratio, demyelination, remyelination, and axon damage can be separately estimated (Fig. 1), which is difficult when conventional routine MRI is used.

Moreover, the MR g-ratio technique has the potential to accurately estimate *in vivo* nerve fibers. Kamagata et al.

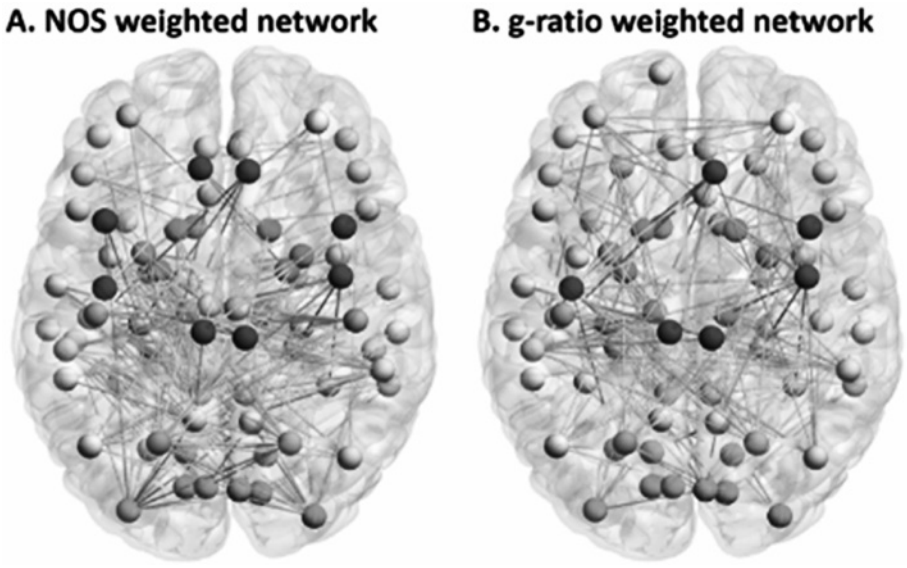

Fig. 2 Connectome maps on the number of streamlines and MR g-ratio. These maps show the subnetworks with significantly high connectivity in each network. The results are different, and the subnetwork alteration can be confirmed more accurately using the MR g-ratio-based connectome analysis (This image has been adopted from the article, Kamagata et al. Sci Rep 9, 13522 (2019) (https://doi.org/10.1038/s41598-019-50025-2), and this image is licensed under a Creative Commons Attribution 4.0 International License).
MR, magnetic resonance

reported the use of the MR g-ratio technique for structural brain network analysis in patients with MS.[22] They demonstrated subnetwork alteration in patients with MS, predominantly in the motor, somatosensory, visual, and limbic areas. Moreover, significant positive correlations were observed between the EDSS scores and MR g-ratio-weighted nodal strength in motor, visual, and limbic brain regions. This study demonstrated that the structural MR network can be analyzed more accurately using the MR g-ratio technique (Fig. 2). However, only few studies have used the MR g-ratio technique for *in vivo* assessment. Therefore, further investigation is required to establish the significance of the MR g-ratio in other diseases.

Conflicts of interest: None declared.

References

1) Duval T, Stikov N, Cohen-Adad J. Modeling white matter microstructure. Funct Neurol. 2016; 31: 217-28.
2) Mackay A, Whittall K, Adler J, Li D, Paty D, Graeb D. In vivo visualization of myelin water in brain by magnetic resonance. Magn Reson Med. 1994; 31: 673-7.
3) MacKay AL, Laule C. Magnetic Resonance of Myelin Water: An in vivo Marker for Myelin. Brain Plast. 2016; 2: 71-91.
4) Warntjes M, Engstrom M, Tisell A, Lundberg P. Modeling the presence of myelin and edema in the brain based on multiparametric quantitative MRI. Front Neurol. 2016; 7: 16.
5) Hagiwara A, Warntjes M, Hori M, Andica C, Nakazawa M, Kumamaru KK, et al. SyMRI of the Brain: Rapid quantification of relaxation rates and proton density, with synthetic MRI, automatic brain segmentation, and myelin measurement. Invest Radiol. 2017; 52: 647-57.
6) McAllister A, Leach J, West H, Jones B, Zhang B, Serai S. Quantitative synthetic MRI in children: Normative intracranial tissue segmentation values during development. Am J Neuroradiol. 2017; 38: 2364-72.
7) Andica C, Hagiwara A, Nakazawa M, Tsuruta K, Takano N, Hori M, et al. The advantage of synthetic MRI for the visualization of early white matter change in an infant with Sturge-Weber syndrome. Magn Reson Med Sci. 2016; 15: 347-8.
8) Hagiwara A, Andica C, Hori M, Aoki S. Synthetic MRI showed increased myelin partial volume in the white matter of a patient with Sturge-Weber syndrome. Neuroradiology. 2017; 59: 1065-6.
9) Hagiwara A, Hori M, Yokoyama K, Takemura MY, Andica C, Kumamaru KK, et al. Utility of a multiparametric quantitative MRI model that assesses myelin and edema for evaluating plaques, periplaque white matter, and normal-appearing white matter in patients with multiple sclerosis: A feasibility study. Am J Neuroradiol. 2017; 38: 237-42.
10) Laule C, Yung A, Pavolva V, Bohnet B, Kozlowski P, Hashimoto SA, et al. High-resolution myelin water imaging in post-mortem

multiple sclerosis spinal cord: A case report. Mult Scler. 2016; 22: 1485-9.
11) Moore GR, Leung E, MacKay AL, Vavasour IM, Whittall KP, Cover KS, et al. A pathology-MRI study of the short-T2 component in formalin-fixed multiple sclerosis brain. Neurology. 2000; 55: 1506-10.
12) Warntjes JBM, Persson A, Berge J, Zech W. Myelin detection using rapid quantitative MR imaging correlated to macroscopically registered luxol fast blue-stained brain specimens. Am J Neuroradiol. 2017; 38: 1096-102.
13) Campbell JSW, Leppert IR, Narayanan S, Boudreau M, Duval T, Cohen-Adad J, et al. Promise and pitfalls of g-ratio estimation with MRI. Neuroimage. 2018; 182: 80-96.
14) Stikov N, Campbell JS, Stroh T, Lavelee M, Frey S, Novek J, et al. In vivo histology of the myelin g-ratio with magnetic resonance imaging. Neuroimage. 2015; 118: 397-405.
15) Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage. 2012; 61: 1000-16.
16) Andica C, Kamagata K, Hatano T, Okuzumi A, Saito A, Nakazawa M, et al. Neurite orientation dispersion and density imaging of the nigrostriatal pathway in Parkinson's disease: Retrograde degeneration observed by tract-profile analysis. Parkinsonism Relat Disord. 2018; 51: 55-60.
17) Hara S, Hori M, Ueda R, Hayashi S, Inaji M, Tanaka Y, et al. Unraveling specific brain microstructural damage in moyamoya disease using diffusion magnetic resonance imaging and positron emission tomography. J Stroke Cerebrovasc Dis. 2019; 28: 1113-25.
18) Hara S, Hori M, Murata S, Ueda R, Tanaka Y, Inaji M, et al. Microstructural damage in normal-appearing brain parenchyma and neurocognitive dysfunction in adult Moyamoya disease. Stroke. 2018; 49: 2504-7.
19) Stikov N, Campbell JS, Stroh T, Lavelee M, Frey S, Novek J, et al. Quantitative analysis of the myelin g-ratio from electron microscopy images of the macaque corpus callosum. Data Brief. 2015; 4: 368-73.
20) Rushton WA. A theory of the effects of fibre size in medullated nerve. J Physiol. 1951; 115: 101-22.
21) Waxman SG. Determinants of conduction velocity in myelinated nerve fibers. Muscle Nerve. 1980; 3: 141-50.
22) Kamagata K, Zalesky A, Yokoyama K, Andica C, Hagiwara A, Shimoji K, et al. MR g-ratio-weighted connectome analysis in patients with multiple sclerosis. Sci Rep. 2019; 9: 13522.

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