Advanced Diffusion MRI in Neurological Diseases: The Multiple Sclerosis Model

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system and the most common cause of non-traumatic disability in young and middle-aged adults [1]. Pathologically, MS is characterized by areas of demyelinated plaques scattered throughout the central nervous system with a predilection for optic nerves, the spinal cord, periventricular white matter (WM), the corpus callosum, and cortical and sub-cortical grey matter (GM). MS lesions reveal a great heterogeneity with respect to the presence and extent of inflammation, demyelination, axonal injury, gliosis, and remyelination. Similar pathological features have been described, albeit to a lesser extent, in normal-appearing (NA) brain tissues: both white (NAWM) and grey matter (NAGM) [1]. Conventional MRI (including T2-weighted, pre- and post-contrast T1-weighted scans) has had a huge impact on MS by enabling earlier diagnosis, and by providing surrogate markers for monitoring response to current disease-modifying treatments and upcoming experimental agents. Despite its increasing role in the clinical management and scientific investigation of MS, conventional MRI is limited by low pathological specificity and low sensitivity to diffuse damage in NAWM and NAGM. In addition, conventional MRI shows only limited associations with clinical status.

Diffusion MRI (dMRI) is a powerful quantitative technique that probes information on the movement of water molecules within brain tissues [2] and can thus provide markers of different types of microstructural alterations. Since its introduction and with the establishment of multishell sequences, many microstructural models and signal representations have been proposed [3–5] and applied to study how different neurological diseases affect the integrity of brain tissues. The sensitivity of dMRI to the microscopic motion of water molecules allows to use this technique also to recover the principal directions of diffusion, which can be assumed to coincide with that of the underlying white matter fibers. This forms the basis for diffusion tractography [6], a method able to produce three-dimensional reconstructions of the major white matter pathways, thereby offering a reasonable representation of anatomy. Recently, the possibility to reconstruct WM connections using diffusion tractography has been combined with network analysis and graph theory to form connectomics, a branch of science aimed at mapping all neural connections within the central nervous system, i.e., the brain connectome [7].

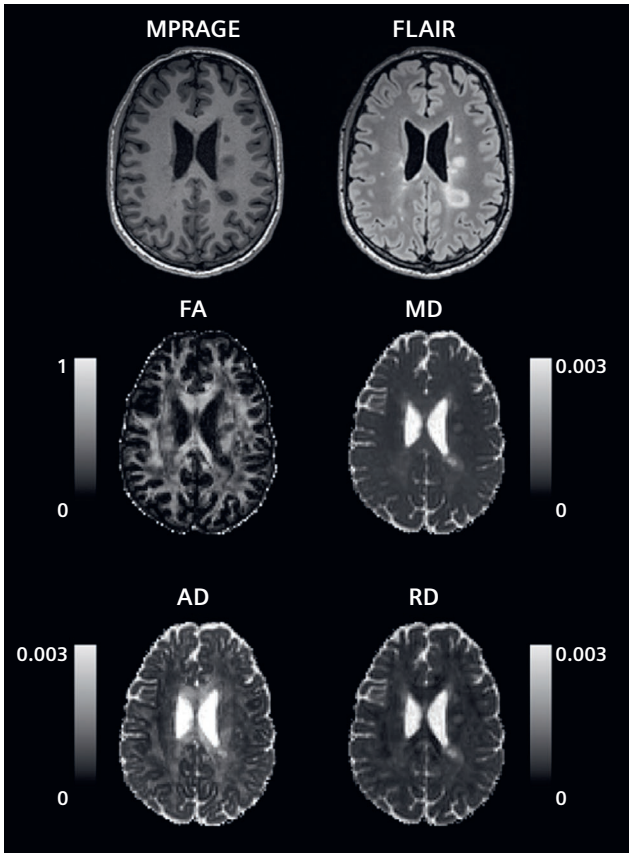
Here we summarize some applications of dMRI in the context of MS and illustrate some real-life acquisitions using MAGNETOM MRI scanners from Siemens Healthcare (3T and 7T).

Lesions and normal-appearing white matter microstructure

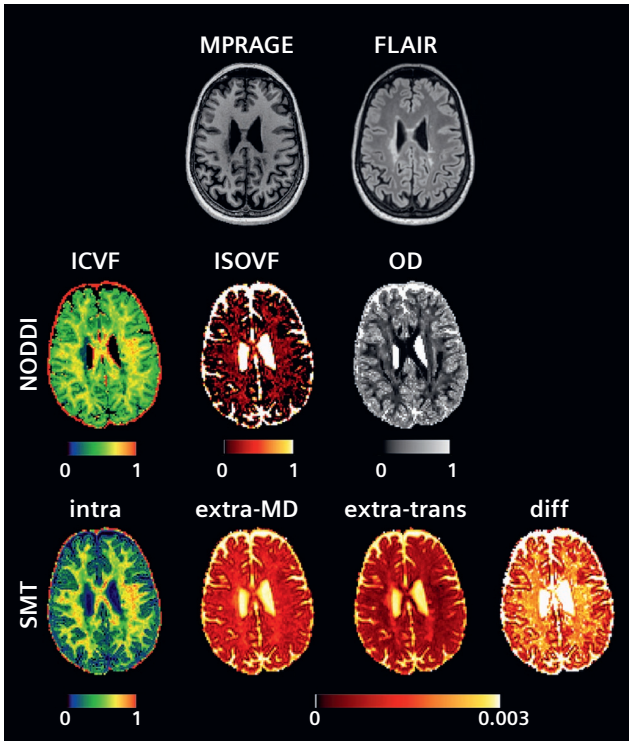
MS was among the first neurological diseases to be investigated with dMRI. Indeed, ever since the introduction of diffusion tensor imaging (DTI), the scalar indices derived from the tensor, such as the axial, radial, and mean diffusivity (AD, RD, and MD, respectively), which quantify the magnitude of principal, radial, and average diffusion within a voxel, and the fractional anisotropy (FA), which measures the directionality of diffusion, have been applied to study MS alone or compare its microstructural alterations with those caused by other neurological pathologies [8–11]. DTI has proven to be a valuable tool for investigating the variety of pathological features of T2-visible lesions. Increased MD and RD, and decreased FA are always more pronounced in lesions than in NAWM; however, their values are highly heterogeneous, indicating the variable degrees of tissue damage occurring within MS lesions [9]. Examples of DTI indices obtained with a 3T MAGNETOM Prisma scanner (Siemens Healthcare, Erlangen, Germany) in a patient with MS are shown in Figure 1. These results are consistent with increased water content, loss of myelin and axons, and the presence of gliosis. More interestingly,

abnormal DTI parameter values are typically found in the NAWM of patients relative to age-matched healthy controls, consistent with subtle but widespread damage known to occur in MS. These initial findings have contributed to the knowledge that white matter damage is widespread in MS, even in the early phases, although they did not provide a clear definition of the substrate underpinning these abnormalities [8–12].

Although DTI has been proven to have good sensitivity to disease changes over time, it has low pathological specificity, which does not allow to discriminate between the different pathological processes underlying MS pathogenesis [13]. To overcome these issues, multishell dMRI sequences and many multicompartment microstructural models and signal representations have been proposed [3–5]. Two very popular examples that can be obtained using a clinically feasible two-shell sequence are the Neurite Orientation Dispersion and Density Imaging (NODDI) [14] model and the multicompartment Spherical Mean Technique (SMT) [15] model, both of which have also been proven to be sensitive to MS [16]. Briefly, NODDI distinguishes between three microstructural environments: intracellular (or intra-axonal), extracellular (or extra-axonal), and cerebrospinal fluid compartments. All these compartments have fixed diffusivities (with a relationship between the external axial and radial diffusivities), and geometrical assumptions that affect diffusion in a unique way, resulting in three separate dMRI signals. Similarly, the multicompartment SMT estimates microscopic features specific to the intra- and extra-neurite compartments in the WM. The use of the spherical mean average in the fitting allows minimization of the confounding effects derived from axonal fiber crossings, curving, and orientation dispersion. Moreover, compared to NODDI, although it can only indirectly capture the potential presence of free water, it does not fix any values for the intra- and extra-neurite axial diffusivities, allowing to estimate them from the measured signal. In Figure 2 we show the microstructural maps of NODDI and SMT estimated on the same subject using the same multishell dMRI sequence. An example of using these two microstructural models in MS can be found in [17], where the authors



1 DTI microstructural metrics extracted for one patient affected by MS. On the top row, we show MPRAGE and FLAIR axial views in which T1 and T2 lesions are clearly visible. Below, we show fractional anisotropy (FA), mean, axial, and radial diffusivities (MD, AD, RD) in approximately the same position. Diffusivities are reported in mm^2/s.



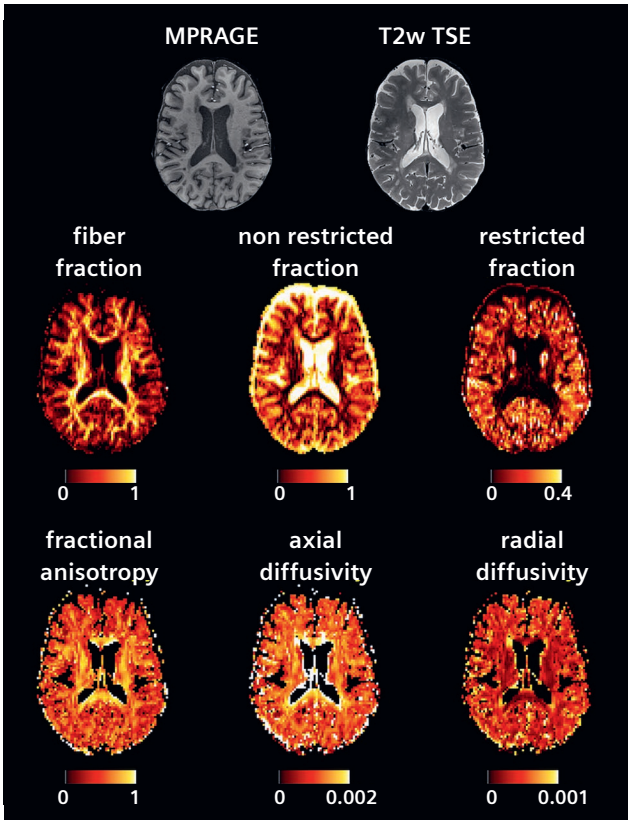
2 Microstructural maps derived from NODDI and SMT models on the same MS patient. The top row shows axial views of FLAIR and MPRAGE sequences in which T2 and T1 lesions are visible. The middle row shows axial views of intra-axonal and isotropic signal fractions (ICVF and ISOVF) and the orientation dispersion index (OD) derived from NODDI. The bottom row shows axial views of intra-axonal signal fraction (intra), extra- mean and transversal diffusivities (extra-MD and extra-trans) and axial diffusivity (diff) derived from SMT. Diffusivities are reported in mm^2/s.
ICVF: Intracellular volume fraction, ISOVF: Isotropic volume fraction

used a MAGNETOM Prisma 3T scanner to acquire a multi-shell diffusion (TR / TE / resolution = 4.5 s / 75 ms / 1.8 × 1.8 × 1.8 mm^3 isotropic with b-values 0 / 700 / 1000 / 2000 / 3000 s/mm^2 with 12 / 6 / 20 / 45 / 66 measurements, respectively, per shell) and a non-diffusion weighted acquisition with 12 measurements of b-value 0 s/mm^2 with reversed phase encoding to quantify the axonal damage among different lesion types, in NAWM, and across MS clinical subtypes and healthy controls (HCs). Comparing diffusion metrics reflecting axonal integrity with MRI-derived myelin maps, the authors found that myelin and axonal pathology in MS is extensive in both lesions and normal-appearing tissue; certain types of lesions exhibit more damage to myelin and axons than others; and myelin and axonal pathology in lesions is related to disability in patients with clinical deficits and global measures of neuroaxonal damage.

Another multicompartment model that was proposed to resolve multiple tensor-like populations of water that may arise not only in healthy tissue but also from axonal injury, inflammation, and demyelination is Diffusion Basis Spectrum Imaging (DBSI) [18, 19]. Briefly, DBSI models diffusion as a combination of multiple discrete anisotropic tensors and a spectrum of isotropic diffusion tensors. The discrete anisotropic tensors are intended to represent myelinated and unmyelinated axons oriented in varying directions. The isotropic tensors, then, represent the integration of multiple pools of water, typically separated into the restricted spectrum which may reflect cellularity. The non-restricted isotropic diffusion spectrum reflects extracellular edema and cerebrospinal fluid. Thus, in DBSI, the diffusion signal is modeled as a summation of many diffusion tensors and an integration of free water with varying diffusivities. DBSI involves complex signal fitting of many free variables. By applying this model, in each voxel we obtain measures of fiber fraction (reflecting fiber density), non-restricted fraction (reflecting tissue destruction), restricted fraction (reflecting cellularity), axial and radial diffusivities (DBSI AD and DBSI RD, reflecting fiber integrity and demyelination), and fractional anisotropy (DBSI FA, reflecting intact fiber integrity). This model can be used to perform non-invasive quantification of inflammation, axonal, and myelin injury in MS. An example can be found in [20], where a MAGNETOM 7T scanner (Siemens Healthcare, Erlangen, Germany) was used with a 32-channel head coil to acquire a diffusion-weighted spin-echo imaging sequence with a 99-encoding-directions scheme selected as prescribed in DBSI of the human brain [21] (acquired with both anterior-posterior and posterior-anterior phase encoding directions) and maximum b-value = 2000 s/mm^2 (TR / TE: 4000 / 62 ms, resolution 2 × 2 × 2 mm^3) to compare the microstructural differences of different lesions and NAWM in MS patients and HCs.

The results obtained in that study confirmed the role of DBSI-derived metrics in the characterization of lesions and NAWM tissue at different stages of the disease. This also demonstrated the metrics' clinical relevance, suggesting that DBSI is a promising tool for investigating MS pathophysiology and monitoring disease progression and treatment response. Moreover, this type of protocol can be easily adapted to 3T scanners.

Finally, another clinically feasible example is Diffusion Kurtosis Imaging (DKI) [22]. DKI can be obtained using a standard spin-echo EPI sequence with two shells at b = 1000 s/mm^2 and b = 2000 s/mm^2, and multiple gradient directions in addition to at least one b = 0 s/mm^2 image. This type of acquisition makes it possible to model tissue microstructure using a white matter tract integrity (WMTI) model to quantify in each voxel the intra- (D_{axon}) and extra-axonal diffusivities (both radial and axial; De_{radial} and De_{axial}, respectively), the axonal water fraction (AWF), and the tortuosity of the extra-axonal space. In contrast to all the previously mentioned models, the



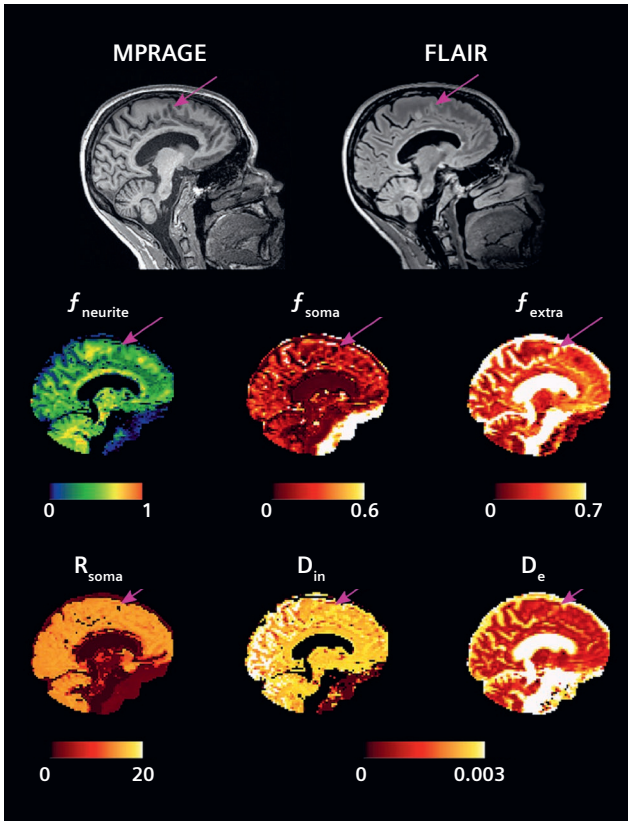
3 Microstructural map metrics estimated using the DBSI model for one MS patient. The top row shows axial views of MPRAGE and T2 sequences in which T1 and T2 lesions are visible. The other rows show all the DBSI microstructural metrics obtained in approximately the same position in diffusion space. Diffusivities are reported in mm^2/s.

assumptions involved in WMTI mean that it cannot be used to characterize lesions. However, it is very sensitive to NAWM alterations. In [23], the authors used a MAGNETOM Trio, A Tim System MRI scanner (Siemens Healthcare, Erlangen, Germany) to acquire a twice-refocused spin-echo EPI sequence for DKI with b-values of 1000 and 2000 s/mm^2 and 30 directions each (repeated twice), in addition to 11 b = 0 s/mm^2 images (TR/TE: 3700/96 ms, FOV 222 × 222 mm^2, matrix 82 × 82, 28 axial 2.7 mm thick slices) to compare 32 relapsing-remitting patients and 19 age- and sex-matched healthy controls (HC) in terms of WMTI metrics. The authors showed that WMTI metrics were sensitive to changes in the NAWM of MS patients and related to different clinical scores, which suggests that they provide a more pathologically specific, clinically meaningful, and practical complement to standard DTI-derived metrics.

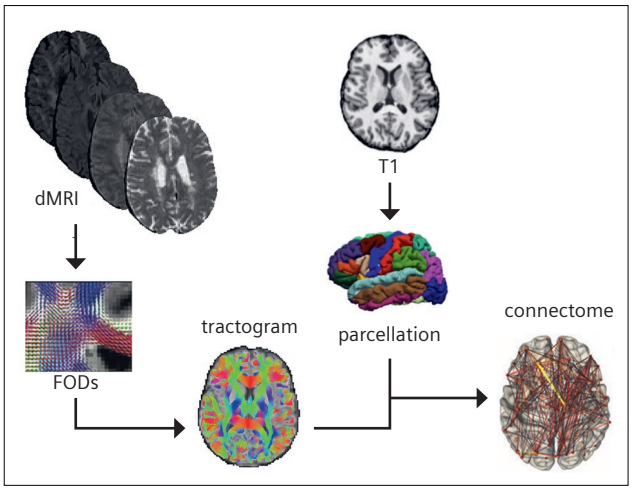
Lesions and normal-appearing grey matter microstructure

Although results on WM lesions and NAWM microstructural alterations have been proven to be highly correlated with clinical deficit, the chronic inflammatory process in MS also involves the cortical and deep GM. Thus, the possible effect of the presence of both WM and GM lesions/alteration must be considered when determining their role in causing clinical deficit [24]. However, although some of the previously mentioned dMRI models (DTI, DKI, NODDI, and SMT) have also been applied to capture tissue modifications in GM caused by MS [9, 11, 12], they are based on assumptions that are specific to WM. When applied to study GM, the results must be interpreted with particular care. Very recently, the Soma And Neurite Density Imaging (SANDI) [25] model has been proposed to noninvasively estimate MRI indices of apparent neurite and soma density in the brain. This model assumes that soma (neuronal and glial cell bodies) and neurites (axons, dendrites, and glial processes) can be approximated as two non-exchanging compartments, modelled as a sphere of certain size and cylinders of zero radius ("sticks"), respectively. Under these assumptions, it is possible to recover the neurite, soma, and extracellular signal fractions ($f_{neurite}$, f_{soma}, and f_{extra}), apparent soma radius (R_{soma}) and the intra-neurite and extra-cellular diffusivities (D_{in} and D_e, respectively). Although this model requires multishell dMRI acquisitions including b-values that are at least six times higher than those used in clinical practice, a recent work [26] demonstrated that measures of f_{soma}, $f_{neurite}$, and R_{soma} from SANDI were highly reliable across multiple GM regions using images acquired on a Connectom scanner (based on a MAGNETOM Skyra 3T system, Siemens Healthcare, Erlangen, Germany) with maximum b-value = 6000 s/mm^2.

We have recently proposed a 10-minute protocol based on a spin-echo EPI sequence [27–29] for multishell dMRI acquisition on a 3T MAGNETOM Prisma equipped with a 64-channel receive coil with the following parameters: TR/TE = 2600/80 ms, resolution 2 × 2 × 2 mm^3, GRAPPA 2, SMS factor 4, with b-values 0/500/1000/2000/3000/4000/6000 s/mm^2 with 15/6/32/40/40/40/40 measurements per shell in anterior-posterior phase encoding, as well as one b-value = 0 s/mm^2 with reversed phase encoding. Using this sequence, we showed that we could reliably assess GM and WM microstructures according to the SANDI model on a clinical scanner. Moreover, we showed the potential clinical impact of simultaneously studying GM and WM, by demonstrating the sensitivity to GM microstructural changes due to lesions (Fig. 4) and the potential discrimination of lesions that appear to have similar contrast in FLAIR and MPRAGE but are actually different in their microstructure.



4 Microstructural metrics estimated using the SANDI model for one MS patient. The top row reports sagittal views of MPRAGE and FLAIR, with the purple arrows indicating the location of a GM lesion. Below, we show approximately the same sagittal views of neurite, soma, and extra-cellular signal fractions ($f_{neurite}$, f_{soma}, and f_{extra}), average soma radius (R_{soma}), as well as intra- and extra-neurite diffusivities (D_{in}, D_e). In correspondence to the lesion, we observe a decrease in $f_{neurite}$, f_{soma}, and R_{soma}, and an increase in f_{extra} and De. Diffusivities are reported in mm^2/s, R_{soma} in µm.



5 Example of a structural connectivity pipeline. Starting from multishell dMRI data, fiber orientation distribution (FOD) functions are estimated to reconstruct the major pathways, followed by the axons in the brain (streamlines), to create the tractogram. Using T1 images, the grey matter is parcellated to obtain regions of interests that, when combined with the tractogram, create the connectome: A graph representing all the connections found in the brain and their strengths.

Tractography and structural connectivity

Beyond microstructural estimation, dMRI also allows to estimate the principal trajectories followed by the axons in the brain and thus investigate structural connectivity (Fig. 5). Recent developments in the tractography algorithm have allowed users to perform tract reconstruction in the presence of WM lesions using the most common multishell acquisitions [30]. These advancements have permitted the study of potential disconnections caused by MS, not only via indirect quantification of fiber loss expressed as area, volume, thickness, or average voxel-wise microstructural damage of specific regions of interest, but also by using subject-specific bundle reconstructions. Using tractography, we can then either segment specific tracts of interest and study only their properties (number of reconstructed streamlines, average of microstructural parameters from dMRI, and/or other quantitative sequences, volumes, etc.) or analyze global structural connectivity disruptions via graph theory [7]. Examples of this can be found in [31, 32, and 33], where the same data from a multishell dMRI sequence performed on a 3T MAGNETOM Prisma scanner were used to

1. investigate different degrees of disconnection for each portion of the corpus callosum via streamline density;
2. characterize sensory motor alterations in MS patients versus HCs via graph theory applied to quantitative connectomes obtained via microstructure-informed tractography;
3. classify MS patients by applying a robust feature selection procedure to quantitative structural connectomes.

Moreover, in all these studies, when comparing dMRI-derived features with clinical scales, strong relationships were identified. This indicates that these types of analyse are useful for understanding the mechanisms underlying the manifestation of disability in MS.

Another example can be found in [34], where researchers used data from the same multishell dMRI sequence performed on the 3T MAGNETOM Prisma scanner in [17] to investigate differences in global network metrics among MS patients and HCs and their sensitivity, and the sensitivity to MS of diffusion-based microstructural maps used to build the connectomes were assessed via correlation with clinical scores. Results indicated that graph metrics extracted from connectomes weighted by intra-axonal microstructural components were most sensitive to MS pathology and most related to clinical disability. In contrast, measures of network segregation extracted from the connectomes weighted by maps describing extracellular diffusivity were most related to serum concentration of neurofilament light chain.

Conclusions

DMRI can play an essential role in better understanding the pathophysiology of MS and in monitoring the disease course and, possibly, response to treatments. Here we provided examples of the research applications and the potential clinical impact of this technique that has not been fully exploited to date. The use of multishell sequences coupled with advanced microstructural models and quantitative tractography might really help to investigate multiple sclerosis pathophysiology and monitor structural connectivity changes.

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