

Bringing Advanced Brain Microstructure into the Clinics: How I do it

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Introduction

Diffusion magnetic resonance imaging (dMRI) provides a unique window into tissue organization by probing the microscopic displacement of water molecules. In clinical imaging, diffusion-derived measures such as the apparent diffusion coefficient (ADC) and diffusion tensor imaging (DTI) metrics are widely used because they provide quantitative information that is not directly accessible from conventional anatomical MRI.

However, the diffusion signal contains substantially more information than can be described by a single apparent diffusion coefficient or diffusion tensor. Biological tissues contain multiple microscopic environments, including cellular bodies, neuronal processes, extracellular spaces, and freely diffusing water. Changes in the relative contribution and organization of these compartments can accompany pathological processes even when conventional image contrast remains relatively unspecific.

Over the last two decades, advanced dMRI has therefore progressively moved from phenomenological signal descriptions toward biophysical models of tissue microstructure. These approaches aim to associate the measured diffusion signal with specific features of the underlying tissue and provide quantitative maps that can complement conventional morphological imaging.

Two representative examples are Neurite Orientation Dispersion and Density Imaging (NODDI) [1] and Soma And Neurite Density Imaging (SANDI) [3]. NODDI characterizes the density and geometrical organization of neurites.

SANDI extends microstructural modeling by explicitly accounting for signal contributions associated with cell bodies in addition to neurites and the extracellular environment.

Despite the potential of these approaches, adopting them in the clinical imaging environment has remained challenging. Multicompartment models typically require dedicated diffusion acquisitions, specialized software, expertise in dMRI processing, and computationally demanding model fitting. Data are commonly exported from the clinical environment to dedicated workstations, processed using research pipelines, and subsequently imported into separate visualization software.

MRmicro (DICEtech, Verona, Italy) was developed to bridge this translational gap. The MRmicro NODDI and SANDI applications that are available through *syngo.via* Frontier¹ integrate the processing of multishell dMRI directly into the *syngo.via* environment. This enables quantitative microstructural maps to be generated without the need to construct an external research-processing pipeline.

The workflow is designed to require minimal interaction. Once a compatible diffusion acquisition is available along with a structural image (typically a 3D T1-weighted or 3D T2-weighted FLAIR image), MRmicro processing can be run with one click. Alternatively, the entire workflow can be automated, so that MRmicro recognizes a compatible acquisition and automatically initiates the appropriate processing pipeline.

¹ *syngo.via* Frontier research applications are for research only. Not for clinical use.

This article describes the information provided by NODDI and SANDI, the MRmicro processing workflow, and practical considerations for their use. Two examples from the University of Pavia and Humanitas Research Hospital illustrate different levels of application of the MRmicro workflow. NODDI is presented as a feasibility example in multiple sclerosis, where it demonstrates the generation and visualization of microstructural maps in a clinical research dataset. SANDI is examined in greater detail through a neuro-oncological case to explore the spatial relationship between model-derived microstructural information and conventional MRI findings.

From diffusion contrast to tissue microstructure

Diffusion MRI is sensitive to the microscopic displacement of water molecules, which is shaped by tissue architecture and cellular organization. Conventional DTI captures this information through metrics such as fractional anisotropy and mean, axial, and radial diffusivity. While highly sensitive to tissue alterations, these measures have limited biological specificity, as similar changes can arise from different microstructural processes.

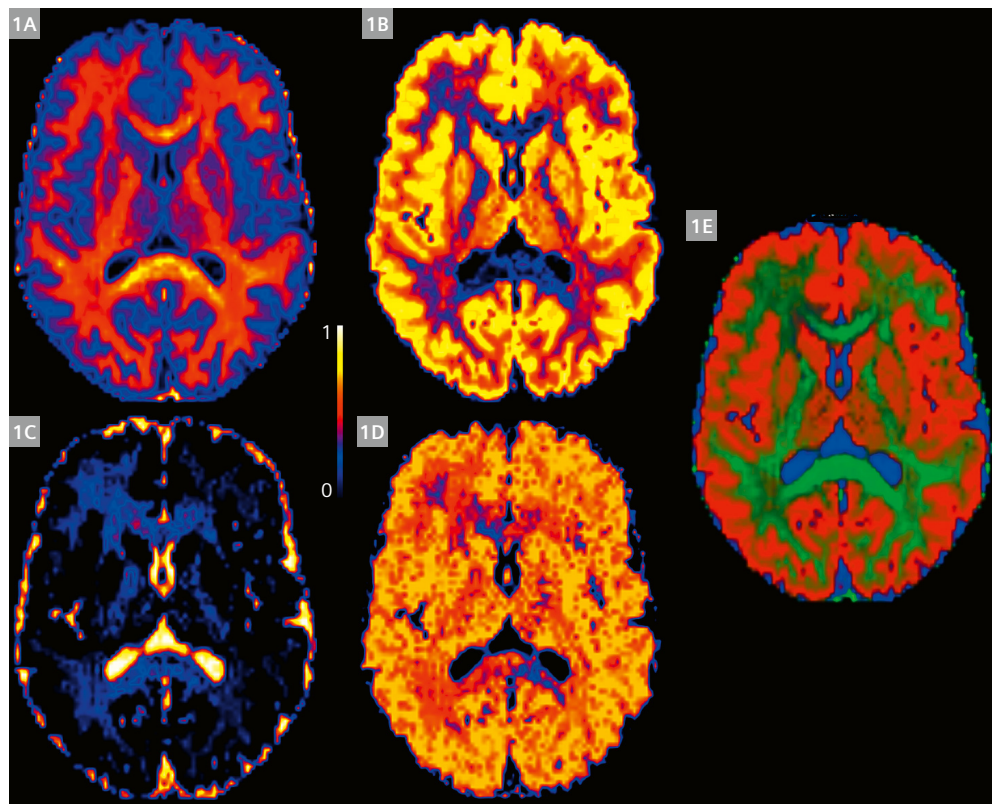
Multicompartment models address this limitation by describing the diffusion signal as the combination of signals generated by distinct microscopic environments. Acquisition of multiple diffusion weightings, or *b*-value shells, disentangles how water signal decays across different microscopic geometric constraints and makes it possible to estimate parameters associated with these compartments.

The resulting maps represent model-derived quantitative indices of tissue microstructure that can be displayed voxel by voxel and compared with anatomical and conventional diffusion images.

NODDI: Characterizing neurite density and orientation

NODDI was introduced by Zhang et al. [1] as a multicompartment framework for characterizing neurite architecture in vivo. The model separates the diffusion signal into three principal environments:

- An intra-neurite compartment representing water associated with axons and dendrites
- An extra-neurite compartment representing water surrounding the neurites
- An isotropic compartment describing freely diffusing water



1 Representative axial slices showing the quantitative outputs generated by MRmicro-NODDI, including NDI (1A), ECVF (1B), ODI (1C), and fISO/FWF (1D) compartment contribution. The RGB composite map provides an additional visualization of the three principal tissue compartments, with the extra-neurite anisotropic, intra-neurite, and isotropic contributions encoded in the red, green, and blue channels, respectively (1E).

The model relies on simplifying assumptions about tissue geometry and diffusion. Neurites are represented as highly restricted cylindrical structures, the extra-neurite compartment as anisotropic diffusion, and the isotropic compartment as freely diffusing water. Compartment diffusivities are constrained according to the original NODDI formulation [1]. The resulting parameters should therefore be interpreted as model-derived indices of tissue microstructure rather than direct histological measurements.

MRmicro generates the main NODDI parameters as separate voxel-wise quantitative maps: the Neurite Density Index (NDI), reflecting the relative intra-neurite contribution; the Orientation Dispersion Index (ODI), describing the degree of neurite orientation dispersion; the isotropic/free-water fraction (fISO/FWF); and the extra-cellular volume fraction (ECVF). These individual maps constitute the primary quantitative outputs of the NODDI analysis.

As an additional visualization, MRmicro also provides a composite RGB map based on the approach proposed by Caverzasi et al. [2]. The extra-neurite anisotropic, intra-neurite, and isotropic contributions are encoded in the red, green, and blue channels, respectively, allowing their relative contribution to be appreciated simultaneously within each voxel. The RGB representation provides a convenient visual summary of tissue composition, while the individual NODDI maps remain available for quantitative assessment.

SANDI: Probing cell bodies and neurites

Many diffusion microstructure models were originally developed primarily around white matter architecture, with a strong focus on elongated structures such as axons. This makes them unsuitable when studying gray matter, tumors, and other tissues in which cellular bodies may make an important contribution to the microscopic environment.

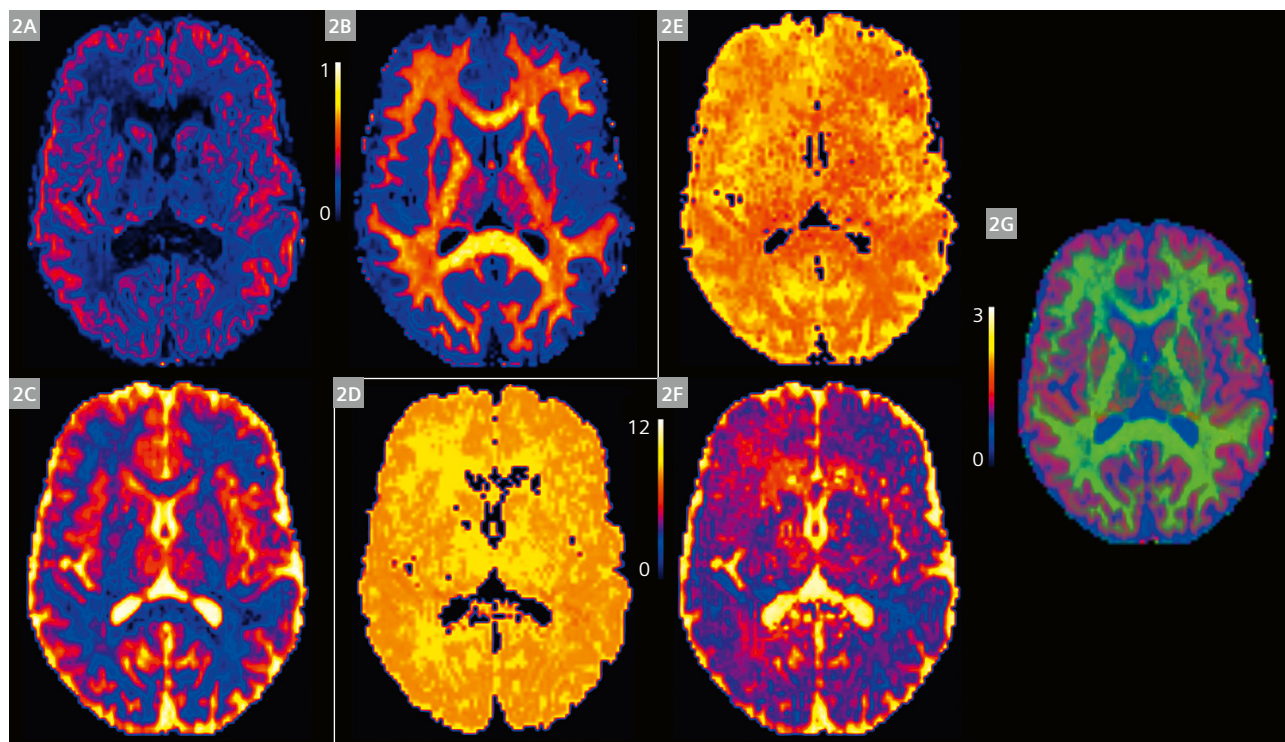
SANDI was introduced by Palombo et al. [3] to provide sensitivity to both soma and neurite compartments. The model assumes that soma and neurites can be approximated as non-exchanging spherical and zero-radius cylindrical ("stick") compartments, respectively, together with an extracellular compartment.

Within this framework, SANDI therefore estimates three principal signal fractions:

- The neurite signal fraction (f_{neurite});
- The soma signal fraction (f_{soma});
- The extracellular signal fraction (f_{extra}).

Additional parameters, including the apparent soma radius (R_{soma}) and compartment diffusivities such as neurite axial diffusivity (D_{in}) and extra-cellular mean diffusivity (D_{extra}), can also be estimated depending on the model configuration.

The explicit inclusion of a soma compartment provides an additional dimension for studying tissues in which differences in cellular composition may be biologically



2 Representative axial slices showing the quantitative outputs generated by MRmicro-SANDI. The maps include f_{soma} (2A), f_{neurite} (2B), and f_{extra} (2C) signal fractions, together with R_{soma} (2D), D_{in} (2E), and D_{extra} (2F). The RGB composite map provides a compact visualization of the three compartment fractions, with soma, neurite, and extracellular contributions encoded in the red, green, and blue channels, respectively (2G).

relevant. These parameters should nevertheless be interpreted as model-derived apparent microstructural indices rather than direct histological measurements of cell number or cellular dimensions.

As for NODDI, MRmicro provides the individual SANDI fraction maps together with a composite RGB map in which neurite, soma, and extra fractions are encoded simultaneously in the three-color channels. The resulting image provides an immediate visualization of the balance between soma-like, neurite-like, and extracellular diffusion signal contributions.

This can be particularly useful in spatially heterogeneous tissue. Instead of examining three separate maps independently, different combinations of the three compartments appear as different colors, allowing regional variations in tissue composition to be identified visually and subsequently investigated quantitatively on the individual parameter maps.

SANDI requires short diffusion times with stronger diffusion weighting than conventional clinical diffusion imaging to achieve sufficient sensitivity to the restricted signal originating from cellular bodies. Previous work has nevertheless demonstrated that suitable acquisitions can be implemented on clinical 3T MRI systems.

For example, a previous MAGNETOM Flash article described a whole-brain SANDI protocol performed on a 3T MAGNETOM Prisma with a 64-channel receive coil. A multishell spin-echo EPI acquisition with $2 \times 2 \times 2 \text{ mm}^3$ isotropic resolution and b -values ranging from 0 to 6000 s/mm^2 was acquired in approximately 10 minutes [4]. The study demonstrated the feasibility of estimating SANDI parameters on a clinical MRI scanner, and illustrated its sensitivity to microstructural differences not evident from

conventional anatomical contrast alone. The advent of new high-performance gradient systems makes it even easier to fulfill SANDI's technical requirements.

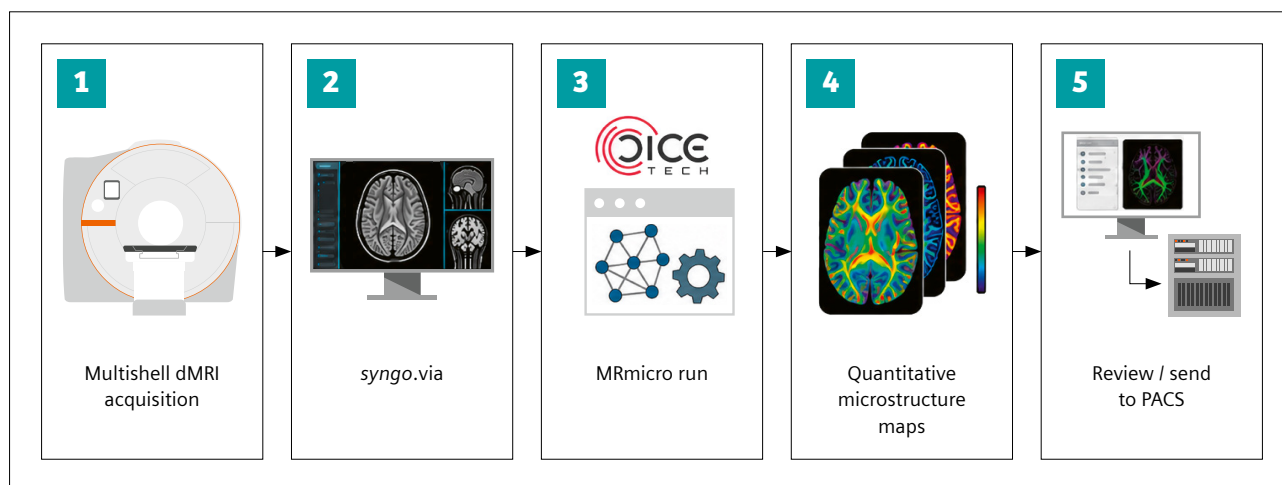
Bringing advanced microstructure imaging into syngo.via Frontier

The acquisition itself is only one component of advanced diffusion microstructure imaging. Historically, a substantial part of the complexity has occurred after scanning.

A typical research workflow requires transferring DICOM data from the scanner or PACS, converting them into a research format, extracting diffusion gradient information, preparing the model configuration, executing the fitting software, converting the resulting maps into a suitable image format, and finally loading the maps into a visualization environment.

For researchers with extensive dMRI expertise, this procedure is manageable. For broader adoption, however, it creates substantial technical overhead and makes standardization between centers more difficult.

The MRmicro applications on syngo.via Frontier substantially reduce this operational burden by embedding the complete NODDI and SANDI processing workflow directly into the imaging environment, delivering reference-registered microstructural maps in less than 2 minutes. In addition to model fitting, MRmicro performs the required preprocessing steps, including Rician noise correction, bias-field correction, and motion correction. When desired, the resulting microstructural maps can also be registered to a user-selected reference image, such as a FLAIR or other structural MRI acquisition, facilitating direct comparison with conventional imaging.



3 Schematic representation of the MRmicro workflow. A compatible multishell dMRI acquisition is transferred to syngo.via, where MRmicro can be launched manually or configured to run automatically when a compatible acquisition is detected. MRmicro performs the required preprocessing, optional registration to a selected reference image, and NODDI or SANDI model fitting, generating quantitative microstructure maps that can be reviewed within the imaging environment or sent to PACS.

This integration enables two levels of workflow automation:

- **One-click execution:** The user selects a compatible multishell dMRI series and launches MRmicro. Preprocessing, optional registration to the selected reference image, model fitting, and map generation are then performed automatically in the background.
- **Fully automated pipeline:** Alternatively, *syngo.via* can be configured with trigger rules based on, for example, DICOM information such as protocol name, series description, or study description. When a compatible multishell dMRI acquisition is received, *syngo.via* automatically triggers MRmicro, which performs preprocessing, model fitting, and microstructural map generation without manual user intervention.

In both configurations, the underlying processing complexity is largely transparent to the user. The objective is to transform what would traditionally be a multistep research pipeline into a workflow that behaves much more like a conventional image-processing application.

Practical acquisition considerations

NODDI and SANDI obtain their additional microstructural information from the variation of the diffusion signal across different diffusion weightings. A suitable multishell acquisition is therefore fundamental.

The exact protocol can be optimized according to the MRI system, gradient performance, available scan time, and research question. The acquisition requirements of NODDI and SANDI are not identical.

For SANDI in particular, high diffusion weighting is required to increase sensitivity to slowly decaying restricted signal components. The previously reported 3T protocol with a maximum b -value of 6000 s/mm² provides one example of a clinically feasible research acquisition [4].

Acquisition design remains a compromise between microstructural sensitivity, spatial resolution, signal-to-noise

ratio, and examination time. Increasing the maximum b -value does not by itself guarantee better parameter estimation if the resulting images have insufficient signal-to-noise ratio. Likewise, the number and distribution of diffusion directions across shells affect model stability.

For this reason, acquisition and analysis should be considered together when establishing a local research protocol.

NODDI feasibility example: Multiple sclerosis

Here, we use a representative patient with multiple sclerosis as a proof-of-concept example to demonstrate the feasibility of generating and reviewing NODDI-derived maps within the integrated MRmicro workflow. The example is intended primarily to illustrate map generation and visualization, rather than to provide a quantitative characterization of lesion microstructure.

Multiple sclerosis is a particularly interesting application for NODDI because microstructural abnormalities may extend beyond lesions visible on conventional MRI and involve both normal-appearing white matter and gray matter from the earliest stages of disease. The NODDI composite color map can provide an intuitive visualization of the relative contribution of the different diffusion compartments, helping to characterize tissue heterogeneity within multiple sclerosis (MS) lesions and potentially revealing abnormalities in normal-appearing white matter that are inconspicuous on conventional FLAIR imaging. Earlier experience with NODDI color maps suggested that different lesion patterns may be associated with different compartment contributions, with a larger extra-neurite component in more active-appearing lesions, and a larger isotropic/free-water contribution in more chronic tissue damage. However, these changes should be interpreted as model-derived microstructural patterns rather than direct histological measurements.

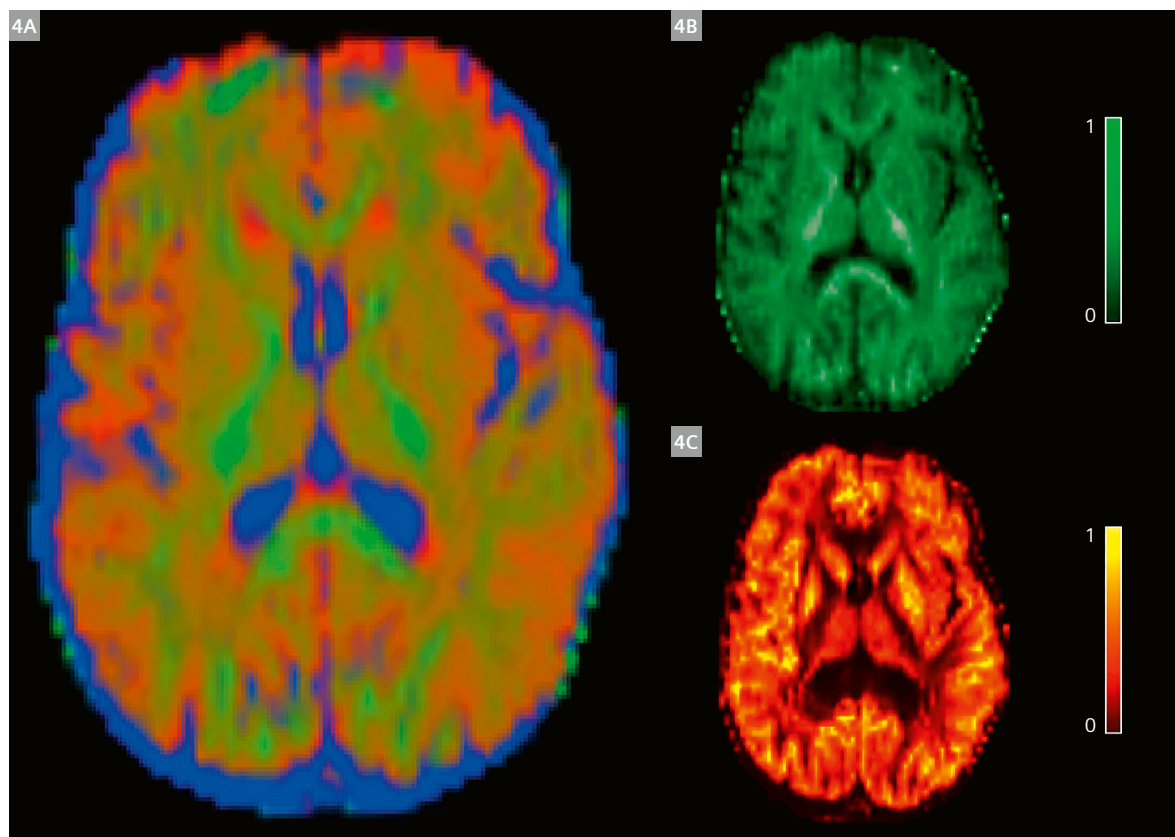
	NODDI	SANDI
Principal target	Neurite density and orientation dispersion	Apparent soma, neurite, and extracellular compartments
Acquisition	Multishell dMRI	Multishell dMRI including high b -values
Fraction maps	NDI, free-water fraction	Neurite, soma, and extracellular compartments
Additional outputs	Orientation dispersion	Apparent soma radius and compartment diffusivities
Composite output	Three-compartment RGB map	Three-compartment RGB map
Main practical consideration	Adequate angular sampling across multiple shells	Sufficient high b -signal and SNR, and low diffusion time

Beyond focal lesions, quantitative NODDI also offers the possibility of exploring the spatial distribution of tissue injury across the brain. White matter can, for example, be analyzed according to its proximity to cerebrospinal fluid (CSF) spaces, distinguishing periventricular, deep, and juxtacortical regions and allowing investigation of whether microstructural abnormalities follow a CSF-related gradient. This approach may be particularly relevant when combined with imaging markers of neuroinflammation, such as choroid plexus volume, given the potential relationship between inflammatory activity at CSF–brain interfaces and tissue injury adjacent to the ventricular system. A similar strategy can be extended to cortical and deep gray matter, where NODDI-derived measures may provide information on microstructural involvement before or during measurable tissue loss. Integrating white- and gray-matter microstructural metrics with conventional

lesion assessment, volumetry, choroid plexus imaging, and inflammatory biomarkers could therefore provide a more comprehensive picture of early MS-related tissue involvement and help explore how neuroinflammatory processes relate to the spatial pattern of brain damage.

SANDI clinical application: Exploring tumor microstructure in gliomas

To illustrate the potential application of SANDI in a clinical research setting, we present a patient with high-grade brain glioma who underwent preoperative MRI for neuro-navigation. SANDI was added to the imaging protocol to explore whether compartment-based diffusion imaging could provide complementary information on tumor microstructure beyond conventional anatomical and diffusion-weighted imaging.



4 Representative NODDI-derived maps in multiple sclerosis.

Representative axial images from a 38-year-old man with relapsing-remitting multiple sclerosis showing **(4A)** the RGB composite NODDI map with the extra-neurite anisotropic, intra-neurite, and isotropic/free-water components encoded in red, green, and blue, respectively; **(4B)** the neurite density index (NDI), reflecting the relative intra-neurite signal contribution; and **(4C)** the orientation dispersion index (ODI), reflecting the degree of neurite orientation dispersion. Together, these maps provide complementary visualization of tissue microstructure and may help characterize abnormalities within focal lesions and normal-appearing brain tissue.

MRI acquisition

MRI was performed on a 3T MAGNETOM Cima.X system using a 32-channel head receive coil. The clinical neuro-navigation protocol included high-resolution three-dimensional anatomical imaging, including 3D T1-weighted imaging before/after contrast administration and 3D T2-weighted FLAIR, together with the additional multishell diffusion acquisition required for SANDI.

Diffusion-weighted images were acquired using a multishell diffusion research sequence with freely adjustable gradient timing based on the spin-echo EPI sequence with $2 \times 2 \times 2 \text{ mm}^3$ isotropic spatial resolution and whole-brain coverage. The protocol included diffusion weightings of $b = 0, 500, 1000, 2000, 3000, 4000, 6000 \text{ s/mm}^2$, and 16, 6, 32, 40, 40, 40, 40 diffusion-encoding directions for the respective shells. The main acquisition parameters were $\text{TR} = 3600 \text{ ms}$, $\text{TE} = 58 \text{ ms}$, diffusion gradient timing $\delta = 17.7 \text{ ms}$, $\Delta = 24.0 \text{ ms}$, diffusion time $\text{TD} = 18.1 \text{ ms}$, parallel imaging factor = 2, and simultaneous multislice factor = 2. Total acquisition time was approximately 13 min 30 s.

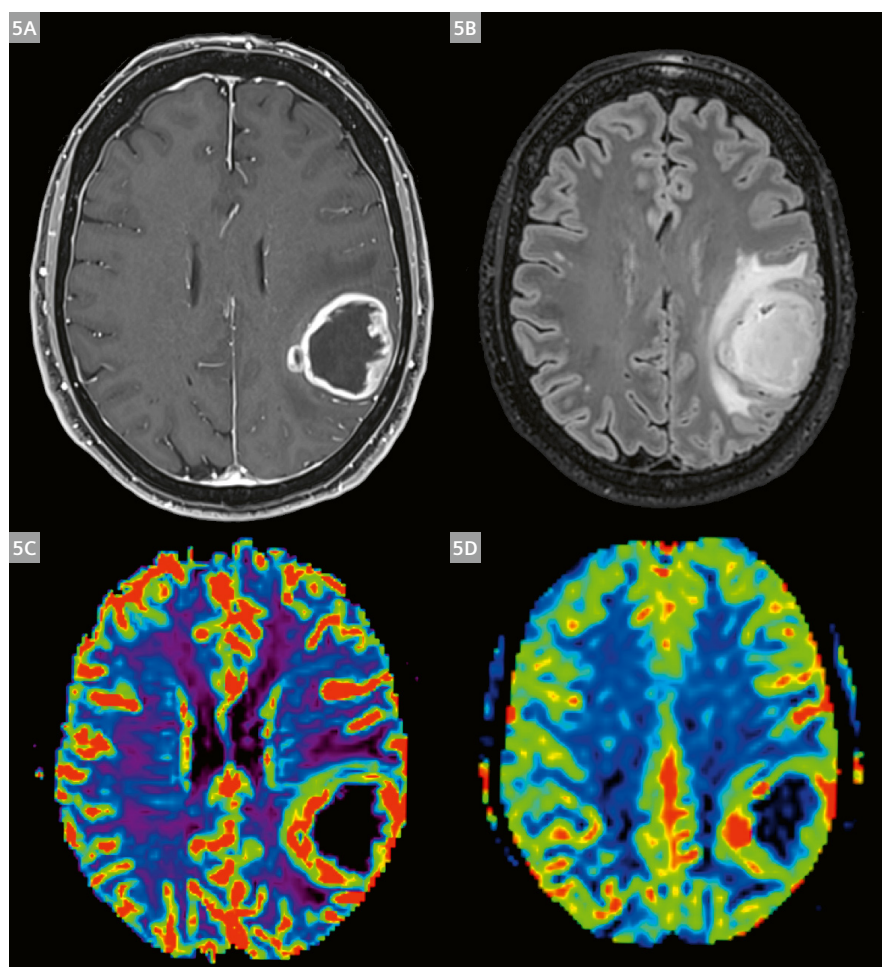
The protocol was designed to combine sufficiently strong diffusion weighting with a short diffusion time,

taking advantage of the gradient performance of the MAGNETOM Cima.X system to retain sensitivity to the restricted signal contribution associated with the soma-like compartment.

The diffusion dataset was processed using the MRmicro SANDI application on *syngo.via* Frontier, generating the neurite signal fraction (f_{neurite}), soma signal fraction (f_{soma}), and extracellular signal fraction (f_{extra}), together with the SANDI RGB composite map. The maps were reviewed alongside the anatomical images used for neuronavigation.

SANDI characterization of intratumoral heterogeneity

A 58-year-old woman with histologically confirmed IDH-wildtype glioblastoma underwent preoperative MRI for neuronavigation. Conventional MRI demonstrated a left parietal lesion characterized by an irregular peripheral component showing intense contrast enhancement, central necrosis, and surrounding FLAIR hyperintensity. The lesion showed marked spatial heterogeneity on conventional imaging. Perfusion imaging demonstrated elevated rCBV, rCBF, Vp, and K^{trans} values along the lesion margin (Fig. 5).



5 Conventional and perfusion MRI findings.

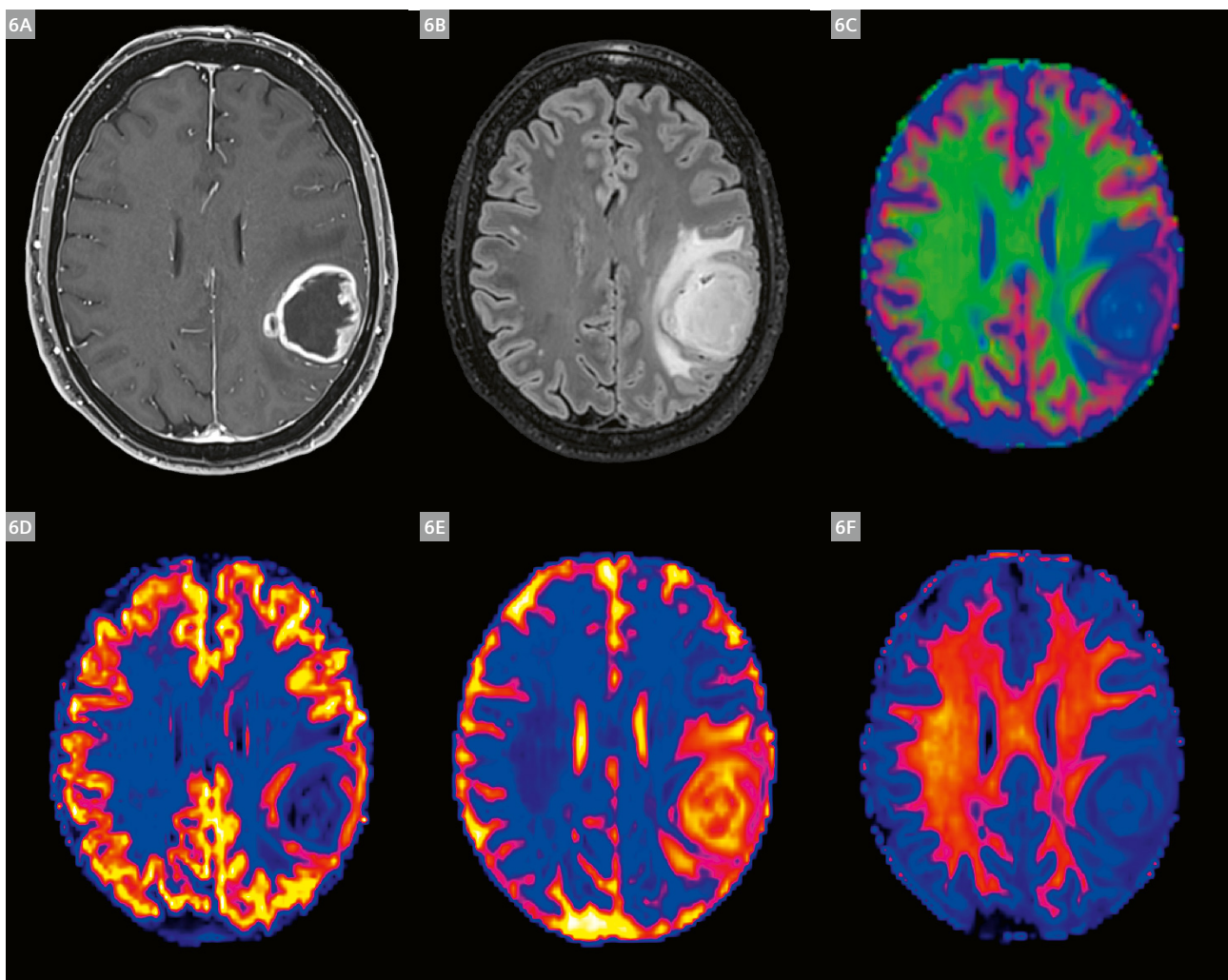
Contrast-enhanced T1-weighted image (5A), FLAIR image (5B), corrected relative cerebral blood volume (rCBV) map derived from dynamic susceptibility contrast (DSC) perfusion MRI (5C), and relative cerebral blood flow (rCBF) map derived from arterial spin labeling (ASL) (5D). The lesion shows an irregular contrast-enhancing peripheral component surrounding a central necrotic core, with associated FLAIR hyperintensity. A focal hyperperfused region is evident along the medial margin of the lesion, with particularly elevated rCBF corresponding to the small nodular component.

SANDI provided an additional representation of this intratumoral heterogeneity. A high soma signal fraction was observed within the contrast-enhancing region and immediately beyond its medial enhancing margin, in correspondence with and adjacent to the small nodular component. The surrounding FLAIR-hyperintense region was itself heterogeneous, comprising areas with relatively high soma, extracellular, or neurite signal fractions. In contrast, the central necrotic core was characterized by a predominantly high extracellular signal fraction. These spatial differences were immediately appreciable on the SANDI RGB map and could subsequently be examined on the individual quantitative fraction maps (Figs. 6, 7).

Importantly, the SANDI parameters should not be interpreted as direct measurements of cellular density or cell size. Rather, they provide a model-based description of differences in the diffusion signal originating from distinct microscopic environments within the heterogeneous tumor volume.

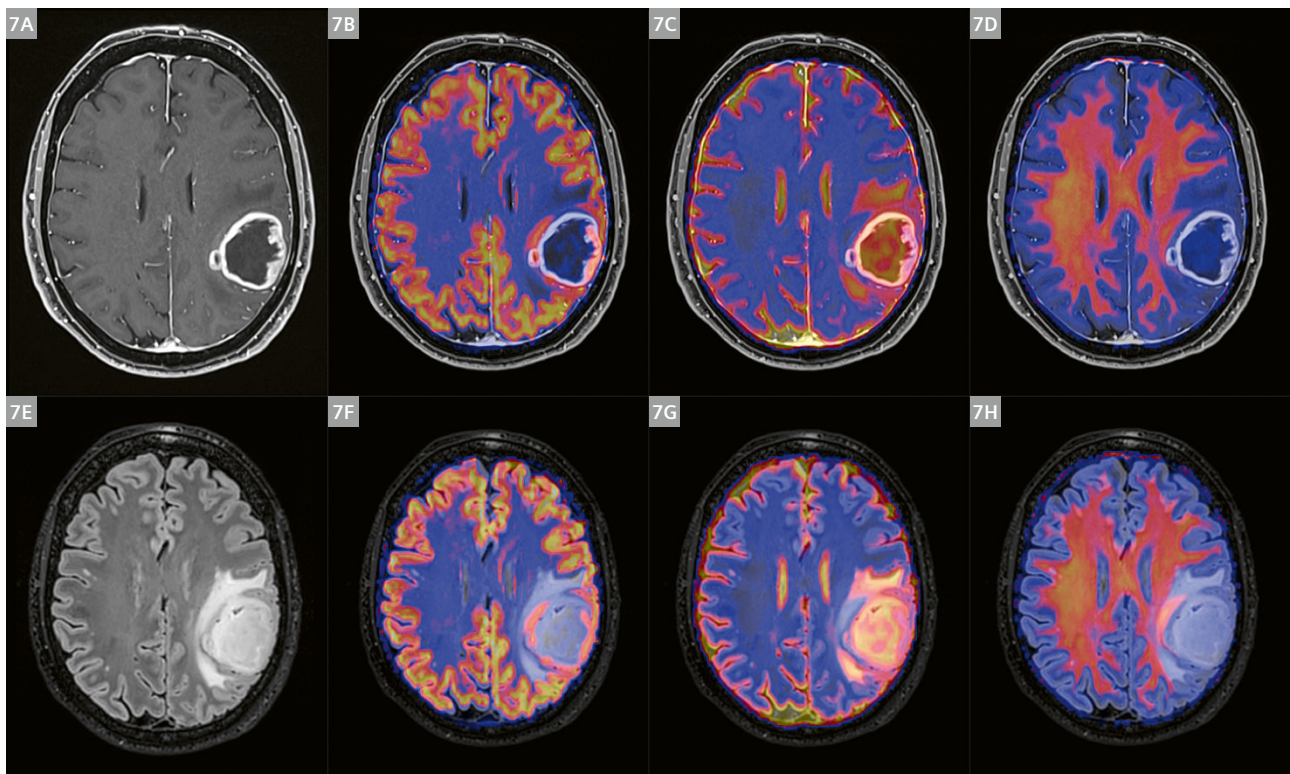
Potential role in neuro-oncological imaging

This case provides an example of how advanced diffusion microstructure imaging can be incorporated into an MRI examination that is already performed for surgical planning. Gliomas are spatially heterogeneous lesions in which cellular, extracellular, and infiltrative tissue components



6 SANDI-derived compartment fraction maps and RGB representation.

A (6A) contrast-enhanced T1-weighted image, (6B) FLAIR image, and (6C) SANDI RGB map are shown from left to right in the top row. The corresponding (6D) SANDI-derived soma, (6E) extracellular, and (6F) neurite signal fraction maps are shown from left to right in the bottom row. For visualization, the extracellular and neurite fraction maps were displayed with window width (W) = 1000 and center (C) = 500, whereas the soma fraction map was displayed with W = 500 and C = 250. In the RGB map, the soma fraction was assigned to the red channel and multiplied by a factor of 1.2. The neurite and extracellular fractions were assigned to the green and blue channels, respectively, with a multiplication factor of 1. The RGB representation provides an immediate visual overview of the spatially varying microstructural heterogeneity within the lesion by simultaneously displaying the relative contributions of the three SANDI-derived compartments.



7 Spatial relationship between SANDI-derived compartment fractions and conventional MRI abnormalities.

The top row shows (7A) the contrast-enhanced T1-weighted image alone, followed by overlays of (7B) the soma, (7C) extracellular, and (7D) neurite signal fraction maps, from left to right. The bottom row shows (7E) the FLAIR image alone, followed by overlays of (7F–7H) the same SANDI-derived maps in the corresponding order. For all overlays, the conventional MRI background (contrast-enhanced T1-weighted or FLAIR image) was displayed with 70% opacity, and the SANDI map with 30% opacity. The same window width and center settings used in Figure 6 were applied to the SANDI maps: $W = 500$ and $C = 250$ for the soma fraction map, and $W = 1000$ and $C = 500$ for the extracellular and neurite fraction maps. These overlays illustrate the spatial relationship between SANDI-derived microstructural heterogeneity, contrast enhancement, and FLAIR hyperintensity.

may coexist within the same imaging-defined abnormality. A model explicitly accounting for soma-like, neurite-like, and extracellular signal contributions therefore provides an interesting framework for investigating this heterogeneity *in vivo*.

For preoperative imaging in particular, the possibility of displaying SANDI maps together with the structural datasets used for neuronavigation creates opportunities for future studies investigating the relationship between local microstructural imaging characteristics and spatially matched surgical or histopathological samples. Such validation will be essential to determine the biological meaning and potential clinical value of SANDI-derived parameters in brain tumors.

At present, SANDI should therefore be regarded as a research tool that is complementary to conventional neuro-oncological MRI, rather than as a replacement for established imaging biomarkers. Integrating SANDI into

the clinical imaging environment nevertheless makes it possible to investigate these questions prospectively without relying on a separate diffusion-processing pipeline.

Lowering the barrier between development and application

Advanced diffusion microstructure imaging has been widely adopted in research, with NODDI introduced more than a decade ago and SANDI more recently, extending dMRI toward the simultaneous characterization of soma and neurite compartments. The remaining challenge is increasingly one of translation and accessibility.

For many advanced imaging techniques, the difference between a promising research method and one that can be systematically evaluated in a hospital is not determined by the underlying model alone. Acquisition requirements, processing time, software installation, data

transfer, workflow integration, visualization, and reproducibility all influence whether a technique can move beyond specialized dMRI laboratories.

MRmicro addresses many of these barriers by integrating NODDI and SANDI processing directly into the *syngo.via* Frontier environment. The resulting quantitative maps can then be reviewed within the same imaging environment as the rest of the examination. Individual parameter maps provide detailed information about the model compartments, while the RGB representation offers an additional, compact visualization of their relative contributions.

By reducing the technical and operational burden associated with advanced microstructure analysis, MRmicro makes these techniques easier to deploy, standardize, and evaluate in clinical research settings.

Conclusion

Diffusion MRI contains information about tissue architecture that extends considerably beyond conventional diffusion-weighted imaging and DTI metrics. Multicompartment techniques such as NODDI and SANDI provide complementary quantitative descriptions of the microscopic environments contributing to the measured diffusion signal.

Previous studies have demonstrated the scientific potential of these approaches and shown that advanced microstructure imaging can be performed on clinical MRI systems. A key next step is to make the corresponding analysis sufficiently accessible, reproducible, and integrated into the imaging workflow to enable broader clinical research.

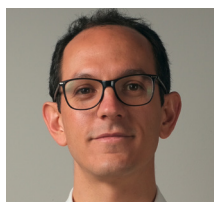
The release of the MRmicro NODDI and SANDI applications on *syngo.via* Frontier provides an integrated workflow from multishell diffusion acquisition to quantitative microstructural maps. By enabling one-click or fully automated processing, MRmicro reduces the need for dedicated external pipelines and specialized processing expertise, bringing advanced diffusion microstructure imaging closer to routine clinical research workflows.

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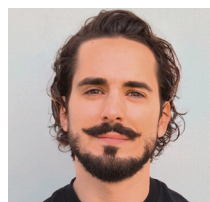
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