Neurite Orientation Dispersion and Density Imaging Color Maps to Characterize Brain Diffusion in Neurologic Disorders

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ABSTRACT

PURPOSE: Neurite orientation dispersion and density imaging (NODDI) has recently been developed to overcome diffusion technique limitations in modeling biological systems. This manuscript reports a preliminary investigation into the use of a single color-coded map to represent NODDI-derived information.

MATERIALS AND METHODS: An optimized diffusion-weighted imaging protocol was acquired in several clinical neurological contexts including demyelinating disease, neoplastic process, stroke, and toxic/metabolic disease.
The NODDI model was fitted to the diffusion datasets. NODDI is based on a three-compartment diffusion model and provides maps that quantify the contributions to the total diffusion signal in each voxel. The NODDI compartment maps were combined into a single 4-dimensional volume visualized as RGB image (red for anisotropic Gaussian diffusion, green for non-Gaussian anisotropic diffusion, and blue for isotropic Gaussian diffusion), in which the relative contributions of the different microstructural compartments can be easily appreciated.

RESULTS: The NODDI color maps better describe the heterogeneity of neoplastic as well inflammatory lesions by identifying different tissue components within areas apparently homogeneous on conventional imaging. Moreover, NODDI color maps seem to be useful for identifying vasogenic edema differently from tumor-infiltrated edema.
In multiple sclerosis, the NODDI color maps enable a visual assessment of the underlying microstructural changes, possibly highlighting an increased inflammatory component, within lesions and potentially in normal-appearing white matter.

CONCLUSION: The NODDI color maps could make this technique valuable in a clinical setting, providing comprehensive and accessible information in normal and pathological brain tissues in different neurological pathologies.

Keywords: NODDI, diffusion, neurite, color map, glioma.

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Introduction

Diffusion imaging represents a noninvasive magnetic resonance imaging (MRI) technique that allows for a quantitative assessment of microstructural changes in the brain. In recent years, diffusion imaging has largely been applied in the clinical setting and for research purposes to describe pathological as well as normal appearing brain tissue. Diffusion tensor imaging (DTI)[1] is the most used diffusion imaging technique worldwide; nevertheless, its metrics (eg, mean diffusivity, fractional anisotropy) lack specificity in measuring microstructural tissue changes due to neurological pathologies.[2–6] The main assumption in DTI is that water diffusion in each voxel can be described by a Gaussian displacement in a single compartment. However, the tensor model is increasingly recognized as inadequate for modeling biological systems. To overcome the aforementioned intrinsic limitation of the model, diffusion MRI research has recently switched towards in vivo quantification of microstructural tissue features and neurite morphology by developing advanced models that can measure multiple diffusion compartments.[7] The clinical application of these new diffusion methods has been limited by significant acquisition time. Recently, an advanced diffusion MRI model, neurite orientation dispersion and density imaging (NODDI), has been developed to overcome DTI limitations with a clinically feasible acquisition protocol.[8] The increasing application of the NODDI model has been favored by the open-source nature of the processing software (http://mig.cs.ucl.ac.uk/Tutorial.NODDImatlab).

NODDI provides a quantification of the relative contribution of three diffusion compartments to the total diffusion signal in each voxel for a richer description of tissue microstructural properties. The compartments identified are cerebrospinal-fluid-like, extraneurite and intraneurite, which are charactherized by isotropic, anisotropic Gaussian, and anisotropic non-Gaussian diffusion, respectively (Fig 1).[8] The multiple NODDI processing output maps are very useful for this quantitative assessment; however, the interpretation of these gray-scale images is not straightforward. The output maps depicting the contribution of each compartment to the total diffusion signal represent

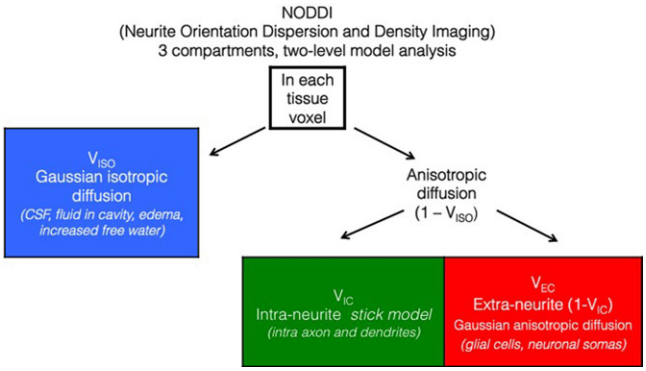

Fig 1. NODDI two-level model analysis. Scheme of the NODDI two-level model analysis is shown. V_{ISO} = isotropic volume fraction; V_{IC} = intracellular volume fraction or Neurite density; V_{EC} = extra-neurite volume fraction.

relative and not absolute values. Furthermore, NODDI is characterized by two main steps: (1) identification of the relative contribution of the isotropic water diffusion compartment out of the total signal (V_{ISO}); (2) calculating the relative contribution of the intra-axonal volume fraction (V_{IC} neurite density) out of the remaining anisotropic compartment (Fig 1). No map for the Gaussian extraneurite component (V_{EC}) is provided as output of the NODDI toolbox. The coherence of neurite direction is also characterized by the NODDI model and reported as orientation dispersion index (ODI).[8] In this work, we present the use of a single color-coded map (the NODDI color map) to represent the information derived with NODDI in normal and pathological brain tissue in different diseases.

Materials and Methods

This study was approved by each local Committee on Human Research and Research Ethics Board.

Since June 2014 to July 2015, a two-shell NODDI protocol was implemented on 3T Siemens Skyra scanners at University of California, San Francisco (United States) and at St. Michael's Hospital in Toronto (Canada) (30 directions at b = 700 s/mm^2 with TR/TE = 6,425/80 ms and 64 directions at b = 2,000 s/mm^2 with TR/TE = 6,425/80 ms, 2.2 mm^3 isotropic voxel, 50 axial slices) and on a 3T Philips Achieva at IRCCS San Raffaele Scientific Institute in Milan (Italy) (35 directions at b = 711 s/mm^2 with TR/TE 5,729/74 ms, and 60 directions at b = 3,000 s/mm^2 with TR/TE 11,548/74 ms; voxel size 1.875 × 1.875 × 2.5 mm^3, 50 axial slices). The NODDI protocol was added to the conventional clinical acquisitions (eg, standard 3D-T1-weighted and fluid-attenuated inversion recovery [FLAIR]) performed at each site.

This MRI protocol was applied in several clinical neurological contexts: demyelinating disease (eg, multiple sclerosis), tumor (eg, low- and high-grade gliomas, lymphoma, and metastasis), and stroke and toxic/metabolic disease (eg, hyperosmolarity injury). We retrospectively processed and reviewed the data. The NODDI model was fitted to the diffusion datasets in MATLAB (http://mig.cs.ucl.ac.uk/Tutorial.NODDImatlab). The NODDI toolbox decomposes the signal of a voxel into the three aforementioned compartments (Fig 1) but outputs only the isotropic and intraneurite compartments and on different scales. The two output maps were used to derive the extraneurite compartment signal and convert the anisotropic signal maps to match the scale of the isotropic compartment map. Using the fslmerge tool from the FSL pipeline (FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl), the compartment maps were then combined into a single RGB image (red for extraneurite (V_{EC}), green for intraneurite (V_{IC}), and blue for isotropic Gaussian diffusion (V_{ISO})), in which the relative contributions (summing up to 1) of the different microstructural compartments could be easily appreciated. Since the NODDI nomenclature was originally formulated for healthy tissues, in the description of pathological conditions, we will instead refer to the three compartments only according to their diffusion characteristic: Gaussian anisotropic diffusion (V_{EC}), non-Gaussian anisotropic diffusion (V_{IC}), and isotropic Gaussian diffusion (V_{ISO}).

Results

At the University of California, San Francisco, the protocol was dedicated to the study of multiple sclerosis and 20 subjects were studied. At St. Michael's Hospital in Toronto, the protocol was applied in several clinical cases including toxoplasmosis, B-cell lymphoma, osmotic injury (secondary to diabetic ketoacidosis), traumatic brain injury, renal cell carcinoma metastasized, arteriovenous malformation, stroke, suspect brain sarcoidosis, and in a suspect progressive multifocal leukoencephalopathy. At IRCCS San Raffaele Scientific Institute in Milan, the NODDI protocol was implemented to study brain tumor patients: 13 subjects with diffuse low-grade WHO II, 13 intermediate-grade WHO III, and one glioblastoma were studied.

The NODDI color maps of one healthy subject and several clinical cases (with corresponding routine clinical imaging) are reported in Figures 2 to 4. In Figure 3, cases of low- and high-grade gliomas as well as B-cell lymphoma and brain metastasis from renal carcinoma are shown. The NODDI color map better visualizes the heterogeneity of the lesions by identifying different tissue components within apparently homogeneous lesions on conventional imaging. Moreover, the NODDI color map seems to be useful for identifying vasogenic edema (eg, metastasis, lymphoma, and toxoplasmosis; see Figs 3 and 4), characterized by a marked increase of the V_{ISO} (blue), differently from tumor-infiltrated edema, characterized by an associated increase of the V_{EC} (red) (eg, high-grade glioma, see Fig 3).

In multiple sclerosis, the NODDI color map enables a visual assessment of the underlying microstructural changes within lesions, possibly highlighting lesions with increased inflammatory component as well as in normal-appearing white matter, such as in the genu of the corpus callosum in Figure 4.

Hindered water molecule diffusion in cases of acute ischemic (left middle cerebral artery stroke) and hyperosmolarity injury (hypernatriemia) shows characteristic patterns of diffusion redistribution on the NODDI color map with increased V_{IC} in areas of high-diffusion directionality, such as the splenium of the corpus callosum (hypernatriemia) or the superior longitudinal fascicle (eg, stroke).

Discussion

In this multicenter work, we have addressed the issue of representing the NODDI analysis results in a unique map, presenting a color-coded visualization that provides a simple and effective way to visualize the relative weight of each diffusion compartment. By itself, the map provides immediate

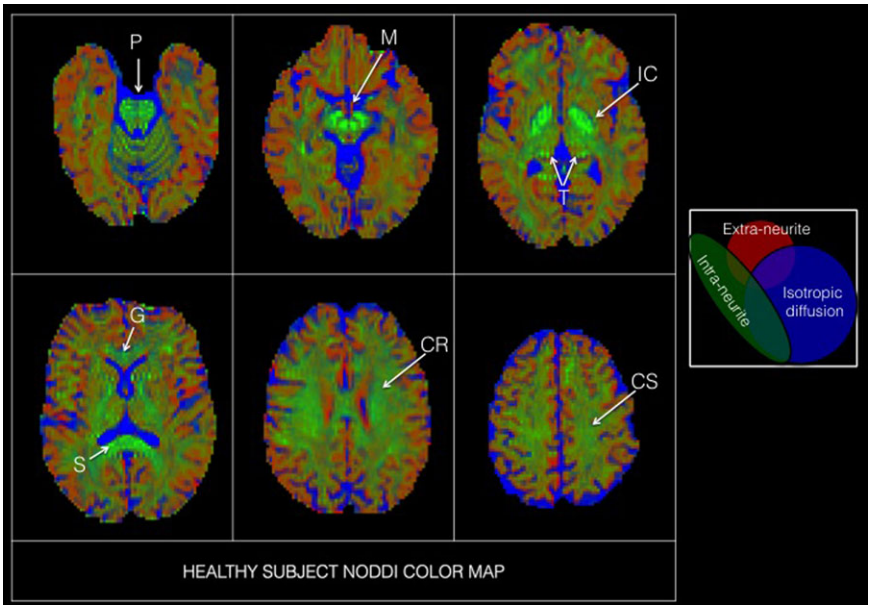

Fig 2. NODDI color map of healthy subject. NODDI color map of a healthy subject is shown at the level of the pons (P), midbrain (M), internal capsule (IC) and thalamus (T), genu (G)/splenium (S) of the corpus callosum, left corona radiata (CR), and left centrum semiovale (CS). Relative contributions of the different microstructural compartments are reported into RGB image: red for anisotropic Gaussian diffusion (V_{EC}), green for non-Gaussian anisotropic diffusion (V_{IC}), and blue for isotropic Gaussian diffusion (V_{ISO}). NODDI = neurite orientation dispersion and density imaging.

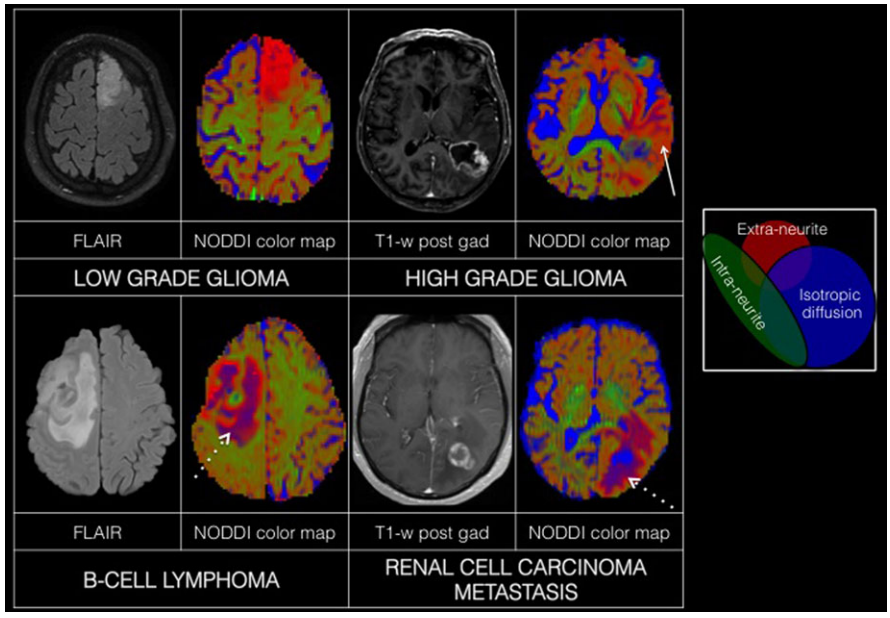

Fig 3. NODDI color map in neoplastic pathology. NODDI color maps and corresponding conventional imaging of clinical cases are shown. Specifically: a case of low-grade glioma (oligodendroglioma WHO II); high-grade glioma (glioblastoma WHO IV); B-cell lymphoma; and renal cell carcinoma brain metastasis. Areas of vasogenic edema observed around the metastatic lesion/lymphoma and tumor-infiltrated edema in a glioblastoma are indicated by a dotted and continuous arrows, respectively. RGB image: red for anisotropic Gaussian diffusion (V_{EC}), green for non-Gaussian anisotropic diffusion (V_{IC}), and blue for isotropic Gaussian diffusion (V_{ISO}). NODDI = neurite orientation dispersion and density imaging; FLAIR = fluid-attenuated inversion recovery; DWI = diffusion-weighted imaging; T1-w post gad = T1-weighted image after gadolinium administration; ADC = apparent diffusion coefficient.

information about the NODDI results, which can be further enriched by weighting the results with other metrics such as DTI ones.

In brain gliomas (Fig 3), the NODDI color map describes the tumor extension and the different tissue components within lesions that appear to be homogeneous on corresponding FLAIR images. Areas of increased V_{ISO} (blue) and V_{EC} (red) diffusion components are likely to correspond to cystic/necrotic and infiltrative tumor components, respectively. The visualization of the underlying microstructural tissue heterogeneity might be helpful to guide biopsy sampling and treatment planning. Moreover, the NODDI color map appears to be useful in identifying vasogenic edema (eg, metastasis, lymphoma, and toxoplasmosis; see Figs 3 and 4), characterized by an increase in the

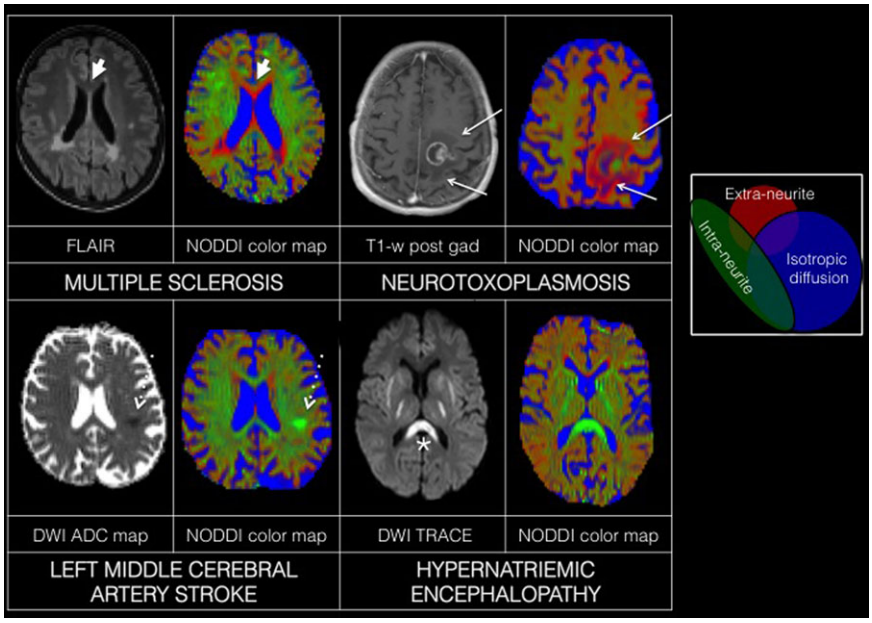

Fig 4. NODDI color map in nonneoplastic pathologies. NODDI color maps and corresponding conventional imaging of clinical cases are shown. Specifically: multiple sclerosis; toxoplasmosis; left middle cerebral artery stroke; and hypernatremia osmotic injury in a patient with diabetic ketoacidosis. A white arrowhead points the signal abnormality within the genu on the NODDI color map of a subject with multiple sclerosis; the genu is otherwise normal-appearing on conventional FLAIR. Areas of vasogenic edema around the nodular enhancing lesion in a case of neurotoxoplasmosis are indicated by a continuous arrow. Dotted arrows point to area of acute ischemic injury in the deep white matter of the left hemisphere. Area of hyperosmolarity injury (hypernatriemia) in the splenium of the corpus callosum is indicated by a white asterisk. RGB image: red for anisotropic Gaussian diffusion (V_{EC}), green for non-Gaussian anisotropic diffusion (V_{IC}), and blue for isotropic Gaussian diffusion (V_{ISO}). NODDI = neurite orientation dispersion and density imaging; FLAIR = fluid-attenuated inversion recovery; T1-w post gad = T1-weighted image after gadolinium administration.

isotropic diffusion (blue) component, differently from tumor-infiltrated edema, characterized by an associated increase of V_{EC} (anisotropic diffusion, red) (Fig 3). In multiple sclerosis, the NODDI color map may enable a better characterization of the underlying microstructural changes both within pathological white matter as well as in normal-appearing white matter. An increase in the V_{EC} might represent a more active lesion, whereas more "chronic" lesions are likely to show an increased isotropic diffusion (blue) component. The NODDI color map also helps to characterize specific patterns of diffusion redistribution in the non-Gaussian anisotropic diffusion compartment (V_{IC}) in case of acute ischemic stroke or hyperosmolarity injury (eg, hypernatriemia; see Fig 4). The surprising increase in the V_{IC} signal might be related to astrocytic swelling, causing a reduction in extracellular water component via abnormal transmembrane diffusion movements. This occurs in favor of an "astrocytic" rather than neurite intracellular component. The observed increase in the "green component," in fact, was not characterized by a concomitant preservation of the orientation dispersion index (which was instead increased; not shown), as one would expect if the phenomena were related to a purely intra-axonal component increase.

The NODDI technique has been successfully applied to study the tau pathology model of Alzheimer's disease,[9] age-related changes,[10] preterm born development,[11] neurofibromatosis type 1,[12] cortical dysplasia, and temporal epilepsy.[13] Further multicompartment diffusion studies using quantitative assessment and correlation with histopathology are needed to determine the specific meaning of the NODDI results. In fact, NODDI was originally developed to model the normal brain white matter; therefore, the parameters and constraints used to characterize human healthy brain may perform differently in pathological brain tissues across diseases, and thus the quantitative values of the estimated volume fractions should be carefully considered and interpreted in view of the disease-specific underlying histopathological changes. Nevertheless, the information and visualization of the NODDI results might still be of interest when comparing different brain regions in order to characterize the heterogeneity, extension, and maybe the type of lesion.

The feasible application of NODDI at high MRI field strengths[14] and future development of disease-specific models[15] will address these general issues, along with a possible tailoring of the NODDI model parameters, which could then be adjusted to study different pathologies.

Regarding the multicenter nature of our data, it is worth mentioning that the acquisition protocols were prepared by adapting protocols already implemented in each center. This was achieved by matching as much as possible the "P13" and "P14" protocols in the original NODDI paper.[8] Based on Zhang and colleagues' simulations, very small differences (almost negligible) might be expected in the NODDI metrics obtained with the two protocols, particularly for visualization purposes.[8] Testing multiscanner and multiprotocol reliability of NODDI was beyond the aims of this qualitative work about NODDI color maps; however, a rigorous evaluation of the effect of acquisition protocol differences represents an interesting extension of this work.

In conclusion, the NODDI color map summarizes the compartmentalization of diffusion signals into a single image and is obtained using a clinically feasible acquisition. We showed the successful application of these maps in several brain diseases.

This color-coded map is a promising tool that can visualize the microstructural complexity of brain tissue. The NODDI color map is a simple and comprehensive approach that can foster the application of this technique in a clinical setting, providing useful, accessible information in normal brain tissue and in neurological pathologies. Future studies will explore the NODDI color maps weighting by other MRI contrasts/metrics such as T1/T2 relaxation time, mean diffusivity, and orientation dispersion index. Further tuning of the NODDI model in different pathologies might also be required to achieve an accurate quantification and histopathological specificity.

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