Sensitivity of multi-shell NODDI to multiple sclerosis white matter changes: a pilot study

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Summary

Diffusion tensor imaging (DTI) is sensitive to white matter (WM) damage in multiple sclerosis (MS), not only in focal lesions but also in the normal-appearing WM (NAWM). However, DTI indices can also be affected by natural spatial variation in WM, as seen in crossing and dispersing white matter fibers. Neurite orientation dispersion and density imaging (NODDI) is an advanced diffusion-weighted imaging technique that provides distinct indices of fiber density and dispersion.
We performed NODDI of lesion tissue and NAWM in five MS patients and five controls, comparing the technique with traditional DTI. Both DTI and NODDI identified tissue damage in NAWM and in lesions. NODDI was able to detect additional changes and it provided better contrast in MS-NAWM microstructure, because it distinguished orientation dispersion and fiber density better than DTI.
We showed that NODDI is viable in MS patients and that it offers, compared with DTI parameters, improved sensitivity and possibly greater specificity to microstructure features such as neurite orientation.

KEY WORDS: diffusion, multiple sclerosis, NODDI, white matter

Introduction

Magnetic resonance imaging (MRI) is an established imaging technique that is routinely applied in the diagnosis and management of multiple sclerosis (MS) (Barkhof et al., 1997; Brex et al., 2002). However, conventional T1-weighted and T2-weighted MRI protocols are very limited in their ability to quantify the exact nature and extent of tissue damage in the disease (Filippi and Agosta, 2010; Filippi et al., 2012). Diffusion-weighted MRI (dMRI) uses a diffusion-sensitizing gradient to probe the diffusion of water molecules in the direction of the gradient (Stejskal and Tanner, 1965). By varying the diffusion sensitization strength (b-value) and the direction of the dMRI gradients, the dMRI signal can be used to reveal microstructural features of the underlying tissues, such as axonal density and orientational organization (see e.g. (Le Bihan, 2003) for a review).
The simplest way to model the diffusion process is to assume that displacements of water molecules in tissue follow a 3-dimensional Gaussian distribution, which can be represented by a diffusion tensor (DT) (Basser et al., 1994). The DT is characterized by three main diffusion coefficients which are associated with three principal diffusion directions (the DT's eigenvectors). From the DT parameters, rotationally-invariant DT metrics can be calculated, namely, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity and radial diffusivity (RD). DT metrics have been shown to be sensitive to alterations of white matter (WM) microstructure, such as axonal density and myelination, as shown in animal models of MS (Abe et al., 2002; Song et al., 2003).
Diffusion tensor imaging (DTI) has been widely used to investigate microstructural changes both within lesions and in normal-appearing tissues in MS (Sbardella et al., 2013). A number of studies have reported decreases in FA and increases in MD in normal-appearing WM (NAWM) in people with MS compared with healthy controls (Werring et al., 1999; Filippi et al., 2001; Rovaris et al., 2002; Ciccarelli et al., 2003). Although these abnormalities occur early in the course of MS (Gallo et al., 2005), more marked DTI abnormalities in the NAWM occur in patients with more significant disability and progressive forms of MS (Preziosa et al., 2011). DTI is also sensitive for the detection of microstructural changes in cortical gray matter (GM), again both in lesions and in normal-appearing tissue, associated with physical disability and cognitive impairment in MS (Yaldizli et al., 2016; Roman and Arnett, 2016). Combined MRI-histopathological studies have demonstrated high correlations between changes in DTI indices and myelin content/axonal count in NAWM and WM lesions, suggesting that DTI abnormalities reflect pathological changes relevant to disability and disease progression in MS (Kim et al., 2006; Schmierer et al., 2007; Budde et al., 2009).
Despite its sensitivity to microstructure, one of the biggest caveats of DTI is that its metrics are affected similarly by changes in microstructure and changes in orientational organization, which reduces the interpretability of its metrics. Furthermore, DTI metrics become difficult to interpret when two or more distinct tissues with diffe-

rent diffusion characteristics are present in a single voxel, e.g. at the interfaces between WM/GM and the cerebrospinal fluid (CSF) (Alexander et al., 2001). Even in pure GM or WM voxels, the displacement probability is not well described by a Gaussian model, especially at longer diffusion times and high diffusion sensitization strengths (Alexander et al., 2002).

Recently, biophysically motivated multi-compartment dMRI models of WM have emerged (Panagiotaki et al., 2012), which explain dMRI findings more accurately and thus promise to characterize the microstructure more precisely (Ferizi et al., 2014; Ferizi et al., 2015). However, these more complex models are also more demanding, in terms of acquisition time and MR gradients.

Neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012) has recently been proposed as a simplified three-compartment model, with modest acquisition time and hardware requirements. The NODDI model describes brain tissue as a combination of three different compartments: the intra-neurite space (neurites are modelled sticks with zero radius with orientation distribution modelled by a Watson distribution); the extra-neurite space (simple Gaussian anisotropic diffusion as in the DTI model) and free water, as in CSF (isotropic Gaussian diffusion). The method produces maps of neurite density index (NDI), orientation dispersion index (ODI) and isotropic volume fraction (isoVF). Therefore, unlike DTI, NODDI explicitly estimates orientation dispersion and neurite density, both of which contribute to conventional DTI metrics such as FA. NODDI parameters have recently been shown to provide greater contrast than DTI for the detection of subtle cortical abnormalities in people with epilepsy (Winston et al., 2014). NODDI metrics have also been shown to be more informative than DTI in describing differences between main fiber tracts in terms of intra-axonal water fraction and axon dispersion when used to study the time-course of maturation in the developing brain (Kunz et al., 2014).

In this pilot study, we applied NODDI to a small cohort of MS patients and age- and gender-matched healthy controls (HCs). We compared its metrics with standard DTI parameters to explore whether NODDI better detects and distinguishes microstructural disruption in MS patients (in both lesional tissue and NAWM) compared with HCs.

Methods

Subjects

Five MS patients (mean age 39 ± 9 years, 3 female) with relapsing-remitting MS and five age- and sex-matched healthy controls not known to have neurological or psychiatric disorders (Tab. I) were scanned. The MS patients had a mean disease duration of 11 years (range 6–16 years) and had moderate neurological disability, corresponding to a median Expanded Disability Status Scale (EDSS) score of 4 (range 3.5–6). None of the patients had experienced a relapse in the previous 4 weeks and all were stable on disease-modifying therapy (either beta interferon or glatiramer acetate). Written informed consent was obtained for participation in the study, which was approved by the local institutional ethics committee.

Table I - Age, sex and disease characteristics in controls and MS subjects.

	Controls	Subjects
Age in years, mean (SD)	37.6 (12.3)	39.2 (8.6)
Sex (female:male)	3:2	3:2
Disease duration, mean (SD)	n/a	11 (3.4)
EDSS, median (range)	n/a	4 (3-6)

Imaging protocol

All scanning was performed on a Philips Achieva 3T TX scanner, using a 32-channel head coil. We acquired the following sequences: (i) multi-echo PD/T2 sequence for tissue segmentation and lesion marking: voxel size 1x1x3 mm^3, FOV=240x240 mm^2, 50 slices, TE=19/88 ms, TR=3500, SENSE=1.7 (scan time ≈ 4 minutes) (ii) NODDI DWI protocol adapted from Zhang et al. (2012): voxel size 2.5 mm^3, axial FOV=220x220 mm^2, 60 slices, SENSE=2, TE=73 ms, TR=12 s, b-values 300/711/2000 s/mm^2 with 6/15/30 isotropically distributed directions and 10 interleaved non-diffusion weighted (b=0) images (scan time ≈ 15 minutes).

DWI analysis

The DWI data were corrected for motion and eddy current distortions using the eddy tool of FSL5 (Jenkinson et al., 2012; Andersson and Sotiropoulos, 2016). We then de-noised the NODDI source images using the joint anisotropic non-local means algorithm (Tristán-Vega and Aja-Fernández, 2010) to increase SNR. NODDI fitting was performed with the NODDI Matlab Toolbox using the default settings (http://www.nitrc.org/projects/noddi_toolbox). Maps of NDI, ODI and isoVF were generated. For comparison, standard DTI parameter maps of FA, MD, AD and RD were derived from the same dataset with the open-source Camino toolkit (Cook et al., 2006), using only the b=0 and b=711 s/mm^2 data for each subject.

Post-processing and ROI analysis

In each dataset, WM was segmented on the high-resolution PD/T2w scan, using both PD and T2w images as inputs for the SPM12 brain segmentation algorithm (Ashburner and Friston, 2005). The resulting WM probability maps were then thresholded to 90%, to exclude mixed-tissue WM and minimize segmentation errors. In MS patients, lesions were manually marked by an experienced neurologist on the PD/T2w scans. The T2w scan was then non-linearly registered with NiftyReg (Modat et al., 2010) to the mean b=0 of each subject and the resulting transformation was applied to the WM mask and lesion mask to align them with the NODDI and DTI maps. In the healthy controls the whole WM mask was used for ROI analysis. In MS patients, a mask of NAWM was generated by subtracting the lesion mask from the whole WM mask and eroding with a small structuring element (3x3x3), to exclude misregistration and partial-volume effects at the tissue interfaces. Significant differences between the per-subject means

over the whole WM/NAWM/lesion ROI were tested with a non-parametric Mann-Whitney-U test ($p<0.05$).

Results

Figure 1 shows a qualitative comparison of DTI and NODDI maps in a sample MS subject. In comparing the images, NDI and FA can be seen to show similar contrast in coherent WM tracts like the corticospinal tract or the corpus callosum. In fiber crossing or fanning regions such as the crossing region between posterior corona radiata and forceps major, NDI contrast is more homogeneous than FA, which is affected more by the greater dispersion of WM tracts. The MS white matter lesions are generally well delineated using both DTI and NODDI. FA shows a marked reduction in WM lesions, while AD, RD and MD are all increased. The NODDI metrics show low NDI, low ODI and high isoVF in WM lesions.
Figure 2 reports a quantitative comparison of WM-tissue-specific DTI and NODDI indices. MS lesions show a statistically significant increase in AD and RD, and consequently MD, compared with HC WM. FA in MS lesion tissue is statistically significantly lower than in NAWM and HC WM. NODDI indices confirm the presence of microstructural changes in lesions; in fact, NDI and ODI are reduced and isoVF is increased in lesions compared with HC WM. Furthermore, NODDI indices show significant differences between MS NAWM and HC WM tissue, with a decrease in NDI and increase in ODI in NAWM (opposite to what is observed in lesion tissue).

Discussion

Our findings suggest that NODDI may be very helpful in MS, providing *in vivo* measurements of tissue microstructural changes, complementary to DT indices.
A key finding of this work is that NODDI indices, compared with HC values, appear to be sensitive to microstructural changes in NAWM (decreased NDI, increased ODI). Particularly intriguing is the finding of increased ODI in NAWM of MS patients compared with a decreased ODI in lesions. This suggests the presence of a loss of fiber coherence (i.e. an increase in fiber dispersion) in NAWM and a reduction of axonal density, which cannot be directly detected with DTI metrics.
From the reduced NDI we can further infer a loss of axonal density both in NAWM and in WM lesions in MS compared with HCs, which is consistent with findings from previous studies using DTI (e.g. Bammer et al., 2000; Werring et al., 1999) and complementary MRI techniques such as magnetization transfer ratio imaging (Cercignani et al., 2001). The reduction in NDI in WM lesions and NAWM is also in keeping with previous pathological studies showing marked axonal loss within lesions and to a lesser degree in NAWM (Schmierer et al., 2004; Schmierer et al., 2007; Klawiter et al., 2011).
An unexpected result is the lower ODI values found in lesional tissue compared with HC WM and NAWM in MS subjects. However, a recent *ex vivo* combined MRI and pathological study found a similar trend of decreased ODI in MS spinal cord lesions (Grussu et al., 2015). Nevertheless, the ODI results in the lesions should be interpreted with caution given that, in the presence of severe axonal loss (as shown by low NDI), the degree of dispersion was estimated from only a small fraction of the signal in the tissue, which might have resulted in numerical instabilities in the NODDI model fit.
The major limitation of this study is the small sample size. However, even in this pilot investigation in just five MS patients, NODDI appears to be sensitive to microstructural tissue damage, providing information complementary to that provided by conventional DTI. NODDI may clarify changes in neurite density and dispersion due to MS pathology, particularly in regions where intravoxel fiber coherence is naturally low. The preliminary data presented here need further confirmation in larger cohorts and in patients with different types of MS. We studied a group of patients with long-standing relapse-

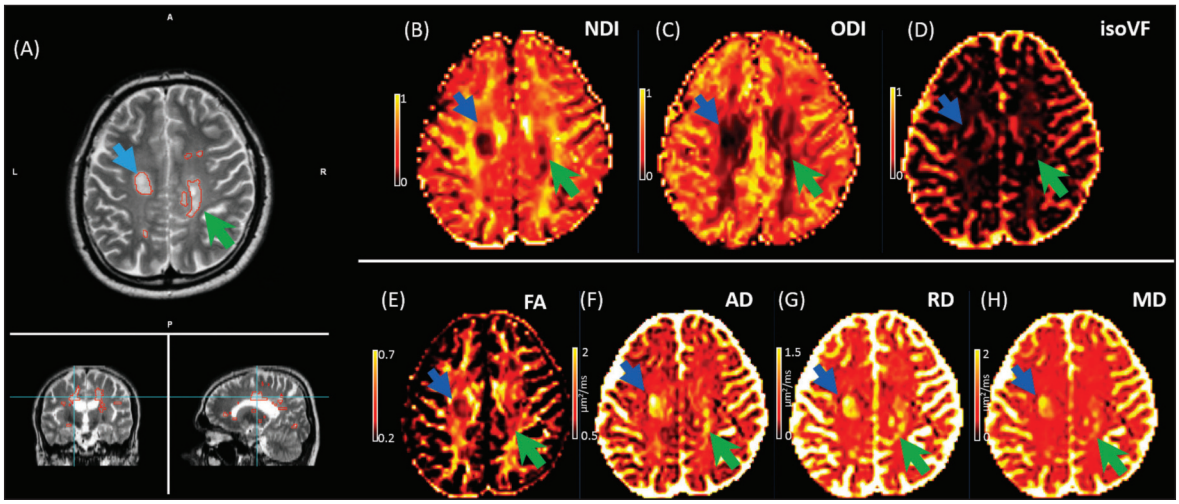

Figure 1 - Illustration of NODDI and DTI parameters in one slice of a single MS subject.
The MS lesion tissue in the major white matter tracts is clearly marked in the AD, MD and RD and NDI maps (blue arrow). NDI provides superior contrast to DTI metrics in periventricular lesion (green arrow) especially in regions with CSF partial volume and fiber crossings contributing to the estimated parameter values.

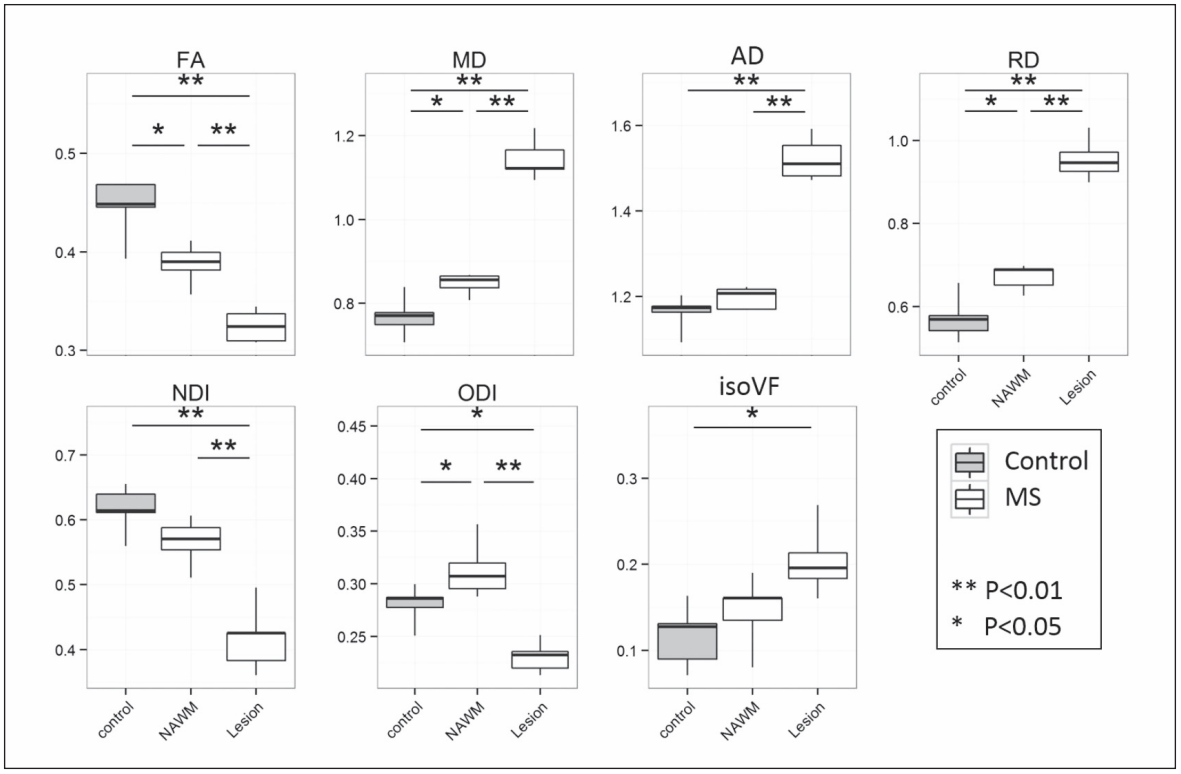

Figure 2 - Boxplot of average DTI and NODDI parameters over ROIs of healthy control white matter tissue and normal-appearing white matter (NAWM) and lesion tissue in MS patients.
Symbols highlight statistically significant differences (**p<0.01,*p<0.05).

onset MS with moderate neurological disability, but a larger clinical study involving patients with a range of disability is required to investigate the relationship between NODDI metrics and disease progression. It would also be interesting, in the future, to recruit patients with active inflammatory disease and gadolinium-enhancing lesions, so as to study NODDI metrics in acute lesions.

While NODDI is explicitly designed to represent both WM and GM tissue, this study focused only on WM regions in MS. It would therefore also be of interest, in future studies, to explore the GM. The main methodological limitation is the relatively large voxel size of our diffusion imaging protocol (2.5 mm^3). Reducing voxel size whilst maintaining a clinically feasible scan duration is possible only with the implementation of strategies that take advantage of stronger imaging gradients and more advanced MRI encoding schemes, such as multiband imaging (Setsompop et al., 2012).

In conclusion, we have shown that NODDI is a viable technique to apply in MS, in which it provides promising new biomarkers for lesion and NAWM characterization. Furthermore, compared with DTI parameters, it shows greater specificity in detecting microstructural features such as neurite orientation. The sequence can be readily implemented on all commercially available MRI scanners, and this, together with the relatively short acquisition time of the protocol, makes NODDI suitable for inclusion in clinical studies of MS.

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