Title

Sensitivity of multi-shell NODDI to Multiple Sclerosis white matter changes: a pilot study

Short title

Multi-shell NODDI in Multiple Sclerosis

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Abstract

Diffusion tensor imaging (DTI) is sensitive to white matter (WM) damage in Multiple Sclerosis, 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, such as crossing and

dispersing fibres. NODDI (neurite orientation dispersion and density imaging) is an advanced diffusion weighted imaging technique that provides distinct indices of fibre density and dispersion.

We obtained NODDI in lesions and NAWM of 5 MS patients and 5 controls and compared it with traditional DTI. Both DTI and NODDI identify tissue damage in NAWM and lesions. NODDI was able to detect additional changes and improved contrast in MS-NAWM microstructure over DTI, because it distinguishes orientation dispersion and fibre density better.

We show that NODDI application is viable in MS patients with improved sensitivity and possibly greater specificity to microstructure features such as neurite orientation over DTI parameters.

Keywords

Diffusion, Multiple Sclerosis, White Matter, NODDI

Introduction

Magnetic resonance imaging (MRI) is an established imaging technique in that is routinely applied in the diagnosis and management of multiple sclerosis patients (MS) (Barkhof et al. 1997; Brex et al. 2002). Nevertheless, conventional T1-weighted and T2-weighted MRI are very limited in quantifying 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-sensitising gradient to probe the random walk of water molecules in a specific direction (Stejskal and Tanner 1965). The dMRI signal reveals microstructural features of the underlying tissues, such as axonal density and orientational organisation by varying the diffusion sensitisation strength (the b-value) and the direction of the dMRI gradients (see e.g. (Le Bihan 2003) for a review).

The simplest way to model the diffusion process is assuming that displacements of water molecules in tissue follow a 3-dimensional Gaussian distribution, which can be represented by a diffusion tensor (DT)(Basser, Mattiello, and LeBihan 1994). The DT is characterised by three main diffusion coefficients which are associated to three principal diffusion directions (the DT's eigenvectors). From the DT parameters, rotationally-invariant DT metrics can be calculated such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity and radial diffusivity (RD). DT metrics have 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).

DTI has been widely used to investigate microstructural changes both within lesions and normal-appearing tissues in MS (Sbardella *et al.*, 2013). A number of studies have reported decreases in FA and increases in MD within normal-appearing WM (NAWM) in people with MS compared with healthy controls (Werring et al., 2000; 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 to the detection of microstructural changes within cortical grey matter (GM), including lesions and normal-appearing GM, associated with physical disability and cognitive impairment in people with MS (Yaldizli *et al.*, 2015; Roman and Arnett, 2016) In MS, DT imaging (DTI) is able to detect subtle changes in both lesions in the white matter (WM) and normal appearing WM, (NAWM) as well as grey matter (GM), also explaining disability and cognitive dysfunction 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 organisation, which impairs the interpretability of its metrics. Furthermore, DTI metrics become difficult to interpret when when two or more distinct tissue with different diffusion characteristics are present in a single voxel, e.g. at the interfaces between WM/GM and the cerebro-spinal fluid (CSF) (A. L. Alexander et al. 2001). Even in pure GM or WM voxels, the displacement probability is not well described by a Gaussian, especially at longer diffusion times and high diffusion sensitisation strengths (D. Alexander, Barker, and Arridge 2002).

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

Neurite orientation dispersion and density imaging (NODDI) (Zhang et al. 2012) has been recently 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 (modelled as diffusion within sticks with zero radius with an 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 such as CSF. The method produces maps of neurite density index (NDI), orientation dispersion index (ODI) and isotropic volume fraction (isoVF). Unlike DTI, NODDI explicitly estimates orientation dispersion and neurite density, which both contribute to conventional DTI metrics such as FA. NODDI parameters have been shown recently to increase contrast over DTI for the detection of subtle cortical abnormalities in people with epilepsy(Winston et al. 2014). NODDI metrics have also shown to be more informative than DTI in describing differences between main fibres in terms of intra-axonal water fraction and axon dispersion in agreement with expected classification and maturation (Kunz et al. 2014).

In this pilot study we apply NODDI to a small pilot cohort of MS patients and age and gender matched healthy controls (HC). We compare its metrics with standard DTI

parameters in order to reveal whether NODDI detects and provides more distinction of the microstructural disruption in MS in both lesional tissue and NAWM compared to healthy controls.

Methods

Subjects

Five MS patients (mean age 39 +/- 9 years, 3 female) with relapsing-remitting MS and 5 age and sex-matched healthy controls not known to have neurological or psychiatric disorders (see Table I) were scanned. The MS patients had a mean disease duration 11 years (range 6 – 16 years) and had moderate neurological disability with 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 patients 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.

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 1x1x3mm3, FOV=240x240mm2, 50 slices, TE=19/88ms, TR=3500, SENSE=1.7 (scan time ≈ 4 minutes) (ii) NODDI DWI protocol adapted from (Zhang et al. 2012): voxel size 2.5mm^3, axial FOV=220x220mm^2, 60 slices, SENSE=2, TE=73ms, TR=12s, b-values 300/711/2000s/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 was corrected for motion and eddy current distortions using the eddy tool of FSL5 (Jenkinson et al. 2012; Andersson and Sotiropoulos 2015). We then performed and de-noised 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=711s/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 was 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 structure element (3x3x3), to exclude mis-registration and partial-volume effects at the tissue interfaces. Significant differences between the means in each 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 an MS subject. In a qualitative review of the images, NDI and FA show similar contrast in coherent white matter tracts like the cortico-spinal tract or the corpus callosum. In fibre 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 white matter tracts. The MS white matter lesions are generally well delineated using both DTI and NODDI. FA shows a marked reduction in white matter lesions, while AD, RD and MD are all increased. The NODDI metrics show low NDI, low ODI and high isoVF in white matter 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 to HC WM. FA in MS lesion is statistically significantly lower than NAWM and HC WM. NODDI indices confirm microstructural changes in lesions; in fact, NDI and ODI are reduced and isoVF is increased in lesions compared to HC WM. Furthermore NODDI indices show significant differences between MS NAWM and HC WM tissue, with a decrease of NDI and increase in ODI in NAWM (opposite to what is observed in lesions).

Discussion

Our findings suggest that NODDI may be very helpful in MS by providing in vivo measurements of tissue microstructural changes, complementary to DT indices.

A key finding of this work is that NODDI indices appear to be sensitive to microstructural changes in NAWM compared to HC values (decreased NDI, increased ODI). Particularly intriguing is the increased ODI in NAWM of MS patients compared to a decreased ODI in lesions This suggests the presence of a loss of fibre coherence (i.e. an increase in fibre 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 loss of axonal density in both NAWM and white matter lesions in MS compared to HC, 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 MTR (Cercignani et al. 2001). The reduction in NDI in white matter

lesions and NAWM is also in keeping with previous pathological studies with marked axonal loss within lesions and to a lesser degree in the 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 to HC WM and NAWM in MS subjects. However, a recent combined MRI and pathological study ex vivo found a similar trend of decreased ODI in MS spinal cord lesions (Grussu et al. 2015). Nevertheless, ODI results in the lesions should be interpreted with caution as with severe axonal loss (as seen by low NDI), the degree of dispersion is estimated from only a small fraction of the signal in the tissue, which might cause 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 5 MS patients, NODDI appears to be sensitive to microstructural tissue damage providing complementary information to conventional DTI. NODDI may disentangle changes in neurite density and dispersion due to MS pathology, particularly in regions where intra-voxel fibre coherence is naturally low. The preliminary data presented here needs further confirmation in larger cohorts and in patients with different types of MS. We studied a group of patients with long-standing relapse-onset MS with moderate neurological disability and a larger clinical study involving patients with a range of disability is required to investigate the relationship between NODDI metrics and disease progression. Future studies in patients with active inflammatory disease with gadolinium-enhancing lesions to study NODDI metrics within acute lesions would also be of interest.

While NODDI is explicitly designed to represent both white and grey matter tissue, this study focused only on white matter regions in MS and future studies of grey matter would be of interest. The main methodological limitation is the relatively large voxel size of our diffusion imaging protocol ($2.5mm^3$). 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).

Conclusion

In conclusion, we have shown that NODDI is viable to apply in MS and provides promising new biomarkers for lesion and NAWM characterisation and improves specificity to microstructure features such as neurite orientation over DTI parameters. The fact that the sequence can be readily implemented on MRI scanners from all manufacturers and the relatively short acquisition time of the protocol allows NODDI to be included in clinical studies of MS.

Figures and Tables

Table I: Age, sex and disease characteristics in control and MS subjects.

	Controls	Subjects

Age, mean (SD)	37.6 (12.3)	39.2 (8.6)
Sex (F:M)	3:2	3:2
Disease duration, mean(SD)	n/a	11 (3.4)
EDSS, median (range)	n/a	4 (3-6)

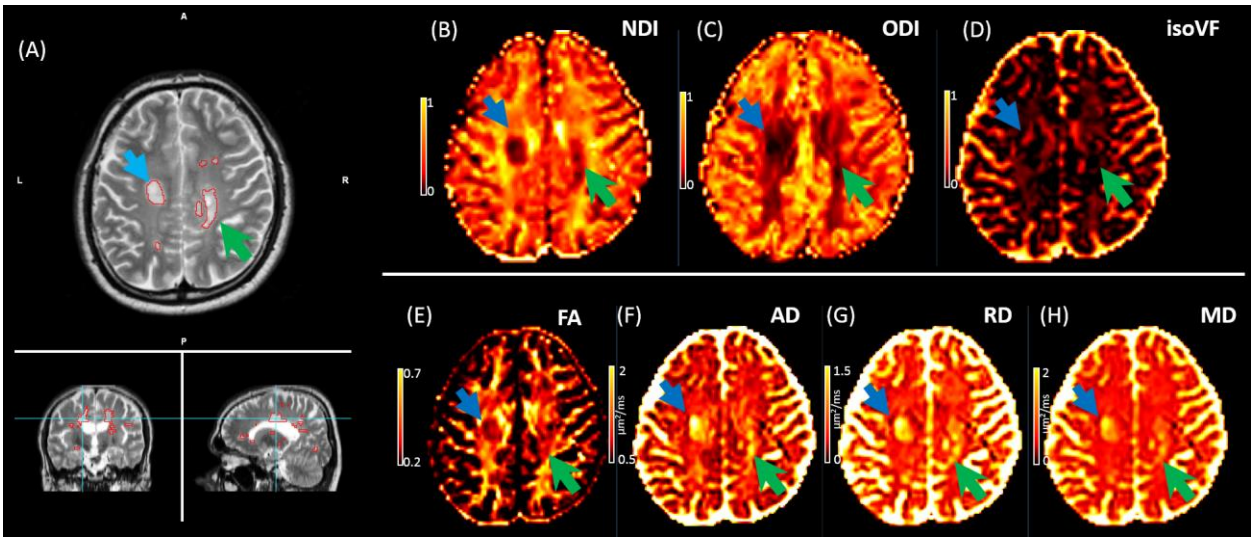

Figure 1: Illustration of NODDI and DTI parameters in one slice of a single MS subject.The MS lesion in the major white matter tracts is clearly marked in AD, MD and RD and NDI map (blue arrow). NDI gives superior contrast over DTI metrics in periventricular lesion (green arrow) with CSF contribution

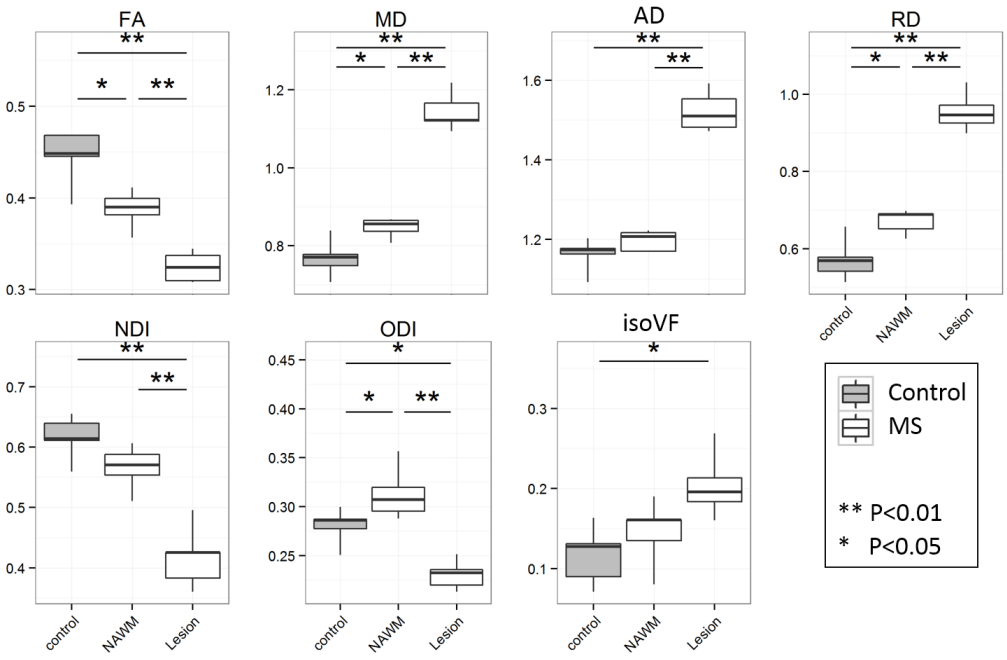

*Figure 2: Boxplot of average DTI and NODDI parameters over ROIs of HC WM and MS NAWM and lesion tissue. Symbols highlight statistically significant differences (**p<0.01,*p<0.05).*

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