

Diffusion Basis Spectrum Imaging Accurately Reflects Underlying Pathologies in Multiple Sclerosis Lesions Missed by Conventional MRI and DTI

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Introduction

Conventional MRI is sensitive to detect MS lesions, but does not have the specificity to distinguish or quantify the extent of axonal injury/loss, demyelination or inflammation [1]. Although DTI can detect axonal injury and demyelination, it does not quantify the effect of inflammation [2]. The ability to detect and quantify the severity and evolution of inflammation, axonal injury and demyelination is highly desired and will improve the evaluation of candidate treatments for stopping disability progression. To achieve this goal, we have recently developed diffusion basis spectrum imaging (DBSI) [3]. Although phantom and animal studies have demonstrated the capability of DBSI to resolve crossing fibers and quantitate the extent of coexisting axonal injury, demyelination, and inflammation, clinical DBSI studies have not yet been reported. In this study, DBSI translation to MS patients was conducted to demonstrate that DBSI-biomarkers were able to quantify pathological profiles within lesions that missed by conventional MRI and DTI.

Method Subject: Eight normal healthy controls and eight age gender matched MS patients signed informed consent, approved by the Washington University Institutional Review Board. MRI: A 3.0 Tesla Trio TIM (Siemens, Erlangen, Germany) scanner was used to acquire DBSI data with 2x2x2 mm³ resolution in the transverse plane, covering the whole brain. Diffusion weighting was applied in 99 directions with max b-value = 2000 s/mm² and TR/TE was 10000/120 ms. The total DBSI acquisition time with single-shot diffusion-weighted EPI sequence was 15 minutes. Diffusion Data Preprocessing: Phase maps were collected after diffusion data acquisition to correct Eddy current artifacts and motion artifacts images. The diffusion-weighted images were then co-registered to the anatomical MPRAGE, and FLAIR images using FLIRT [4]. DBSI Analysis: Eq. [1] was solved by fitting the 99 diffusion weighted signals using a linear combination of diffusion basis sets to estimate the number of anisotropic diffusion tensor components (N_{aniso}) and the associated principal directions. After N_{aniso} was computed, the number of isotropic component (N_{iso}) was further determined using nonnegative least-squares (NNLS) analysis. The global nonlinear optimization was conducted to solve Eq. [1]. S_k is the kth measured diffusion weighted signals. S_i and S_j are fractions of anisotropic diffusion components and isotropic diffusion component respectively [3]. Segmentation of MS Brain Lesions: A single individual will identify gadolinium contrast enhancing lesions on the axial FLAIR. T2 hyperintense lesions were selected based upon the FLAIR sequence using semi-automated and manual threshold methods by a trained MS specialist. For each contrast enhancing lesion, an analogous ROI from the contralateral hemisphere will serve as an internal, lesion-specific control. In this study, 18 clear lesions were labeled in a RRMS patient. GQI Fiber Tractography: Whole brain streamline fiber tracking was conducted using based on generalized q-sampling imaging (GQI) method [5].

$$S_k = \sum_{i=1}^{N_{aniso}} S_i e^{-b_k \lambda_i} + \sum_{j=1}^{N_{iso}} S_j e^{-b_k (\lambda_{11} - \lambda_{\perp}) \cos^2 \theta_i} \quad [1]$$

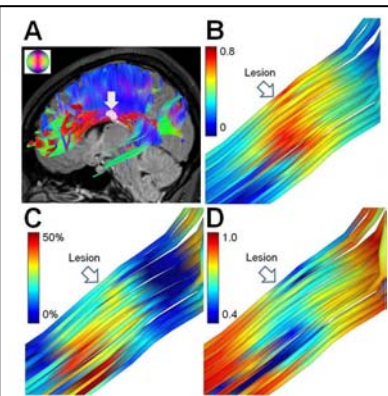


Figure 2 GQI-derived tracts (A) with DBSI-derived radial diffusivity (B), edema (C), and FA (D) rendering reveal demyelination, vasogenic edema with preserved axons passing through the corpus callosum lesion shown in Fig. 1. FA decrease was caused by the increased radial diffusivity and unchanged axial diffusivity.

region in panel A) can be rendered with DBSI-derived biomarkers (Fig. 2B – D). The presence of demyelination and edema in the corpus callosum was quantitatively rendered as red segments (increased radial diffusivity and edema) in Fig. 2B and C. Similarly reduced DBSI FA was directly presented as blue segment (decreased FA) in Fig. 2D. DBSI-based tract rendering could lead to better detection and characterization of heterogeneous MS lesions. Quantitative tract-based statistics may also better predict clinical outcome.

Results and Discussion Two representative lesions from the RRMS subject were compared using standard methods, and using DTI and DBSI. One lesion was located in corpus callosum (Fig.1, A), and the other was located at frontal lobe (Fig.1, B). Both lesions exhibited comparable features: hyper-intensity on FLAIR, DTI axial diffusivity map, DTI radial diffusivity map, and hypo-intensity on MPRAGE (Fig.1, C). In contrast, DBSI revealed the two lesions to be very different (Fig.1, D). DBSI measures within the frontal lobe lesion showed reduced axial diffusivity, but unchanged in corpus callosum lesion. DBSI-derived radial diffusivity was increased in both the corpus callosum and frontal lobe lesion, but was greater in the frontal lobe lesion. In addition, the DBSI-derived isotropic component with low diffusivity presumed to derive from cells was reduced in the corpus callosum lesion, while it was increased in the frontal lobe lesion. Both lesions displayed a significantly increased proportion of isotropic component with high diffusivity, considered reflective of increased extracellular space or edema. Those findings suggested that DBSI could accurately quantify heterogeneous compositions within different voxels, which may appear homogenous when analyzed using T1W or FLAIR imaging. DTI-derived axial and radial diffusivities are inaccurate and misleading in this case because DTI cannot separately analyze isotropic diffusion components within voxels. Figure 2 shown the axonal tracts passing through corpus callosum lesion (white

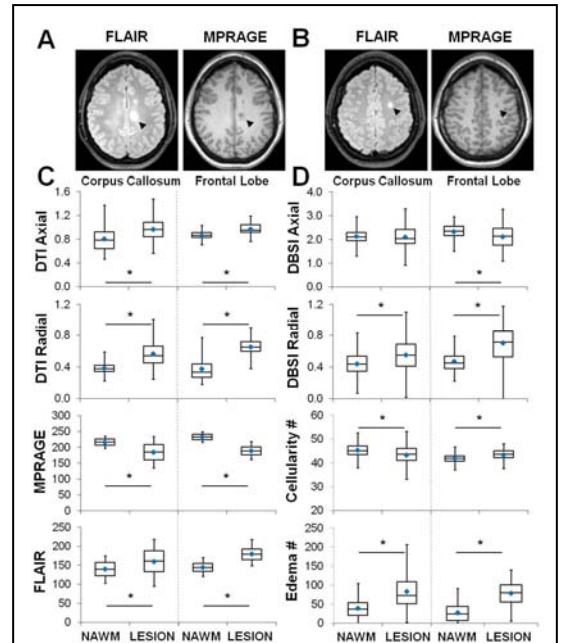


Figure 1 Corpus callosum (A) and frontal lobe (B) lesions were hyper-intense on FLAIR, and hypo-intense on MPRAGE, both with increased axial and radial diffusivities (C). In contrast, DBSI revealed that the two lesions are distinctly different where corpus callosum lesion was demyelinated without axonal injury (increased DBSI radial and unchanged axial diffusivity) while the frontal lobe lesion was demyelinated with axonal damage (increased DBSI radial and decreased axial diffusivity). (D). In addition, DBSI revealed that cellularity was reduced in corpus callosum lesion with significant edema. The frontal lobe lesion exhibited significant increase in both cellularity and edema. Findings may suggest that these two lesions are at different stages of inflammation. (*: p<0.05)

References [1] Filippi, M. *et al. Lancet Neurol.* 2012; 11:349-60. [2] Song, SK. *et al. Neuroimage.* 2002; 17:1429. [3] Wang, Y. *et al. Brain.* 2011; 134:3590; [4] Jenkinson, M. *Neuroimage.* 2002;17, 825-41; [5] Yeh, FC. *et al. IEEE Trans Med Imaging.* 2010; 29;