Noninvasively Detection of the Pathological Changes of MS Lesions Responding to Treatment using Diffusion Basis Spectrum Imaging

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Introduction Studying the pathophysiology of diseases of the human central nervous system (CNS) presents a special challenge because the acquisition of tissue samples has the potential of causing harm to patients. This difficulty is compounded when studying a chronic disease such as multiple sclerosis (MS), in which lesions change with treatment and with time. This would require multiple biopsies over multiple time-points to gain a full understanding of pathogenesis. A noninvasive magnetic resonance imaging modality capable of detecting and quantifying the severity and evolution of heterogeneous MS lesion is highly desired. Recently, we have developed such an imaging method, diffusion basis spectrum imaging (DBSI), to simultaneously quantify axonal injury, demyelination, and inflammation in the CNS [1]. Intensive phantom and animal studies have shown that DBSI can accurately quantify CNS myelinated and unmyelinated axons, and cells, edema/extracellular space. Although DBSI holds promise of conducting longitudinal studies on chronic CNS diseases, the feasibility and accuracy of achieving this goal have not yet been well studied. In this study, we first conducted two sequential whole brain DBSI scans to three healthy controls on separate days. ROIs encompassing 70 voxels were drawn in the same region of the centrum semiovale to test the reproducibility and accuracy of repeated clinical DBSI scan on the level of individual image voxels. Following the reproducibility test, one MS patient with 5 gadolinium enhancing lesions was enrolled and scanned for multiple times after the initial diagnosis and treatment. The data from this longitudinal study was used to demonstrate DBSI's capability to trace the pathological substrate changes due to time and pharmaceutical treatment.

$$S_k = \sum_{i=1}^{N_{Aniso}} S_i e^{-\left|\vec{b}_k\right| \lambda_\perp} e^{-\left|\vec{b}_k\right| (\lambda_\parallel - \lambda_\perp) \cos^2\theta_i} + \sum_{j=1}^{N_{iso}} S_j e^{-\left|\vec{b}_k\right| d_j} \quad [1]$$

Method *Subject:* Three normal healthy controls and one MS patient provided informed consent, after approval of the study by the Washington University Human Research Protection Office/Institutional Review Board. *MRI:* A 3.0 Tesla Trio TIM (Siemens, Erlangen, Germany) scanner was used to acquire diffusion data. The DBSI data were collected with 2x2x2 mm^3 resolution in the transverse plane, covering the whole brain. Diffusion weighting was applied in 99 directions with max b-value = 2000 s/mm^2 and TR/TE was 10000/120 ms. The total DBSI acquisition time (one average) with single-shot diffusion-weighted EPI sequence was 15 minutes. High-resolution 1x1x1 mm^3 fluid attenuated inversion recovery (FLAIR) images were used for MS lesion identification. T1-weighted 3D magnetization prepared rapid acquisition of gradient echo (MPRAGE) sequences were acquired at 1 x1x1 mm^3 resolution. *Diffusion Data Preprocessing:* Phase maps were collected after diffusion data acquisition to correct Eddy current artifacts and motion artifacts in EPI images. The diffusion-weighted images were then co-registered to the anatomical MPRAGE, and FLAIR images using FLIRT (FMRIB's Linear Registration Tool) [2]. *DBSI Analysis:* Eq. [1] was solved by fitting the 99 diffusion weighted signals using a linear combination of diffusion basis sets consisting of cylindrically symmetric diffusion tensors with the freedom to vary $\lambda_{||}$ and $\lambda_\perp$ 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 [3]. The global nonlinear optimization was conducted employing direct pattern search to solve Eq. [1]. S_k is the kth measured diffusion weighted signals (k = 1, 2, 3, …, 99). S_i and S_j are fractions of anisotropic diffusion components and isotropic diffusion component respectively. *DBSI Reproducibility Test:* Three healthy controls underwent two DBSI brain scans each on separate days. ROIs encompassing 70 voxels were drawn in the same region of the centrum semiovale for the 3 healthy controls. Axial diffusivity, radial diffusivity, cell ratio, and edema ratio were calculated by DBSI, and then were compared voxel-wise within the same healthy control for the 2 time-points using Bland-Altman plots. *Longitudinal Scan of MS Brain Lesions:* One MS patient with five gadolinium enhancing lesions was scanned by DBSI over 4 time-points The first two scans were performed on day 0 and 12, prior to any therapy during the diagnostic evaluation. Scan 3 at day 23 was immediately after 3 doses of 1,000mg IV methylprednisolone, a corticosteroid. Scan 4 was done at day 147, after the patient had received 2 infusions of natalizumab (note longer interval from scan 3 to 4). Images from the four scans were co-registered to the anatomical T1W, and T2W images using FLIRT.

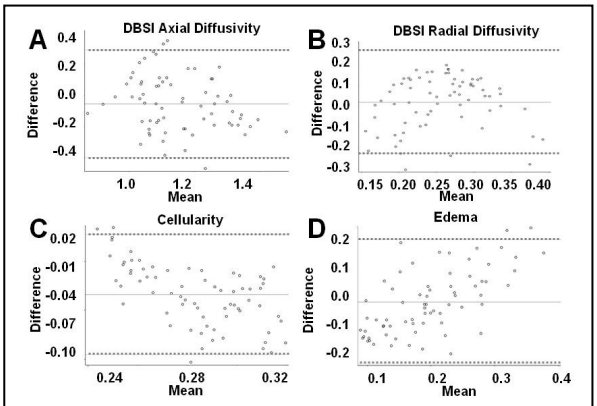

Figure 1 Bland-Altman plots suggest good reproducibility of DBSI axial (A), radial diffusivity (B), cellularity ratio (C), and edema ratio (D) on 70 centrum semiovale voxels from 3 healthy volunteers over two separated MRI scans.

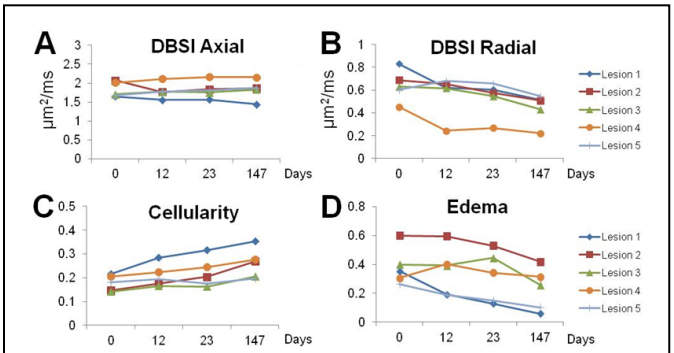

Figure 2 Unchanged DBSI axial diffusivity (A) and reduced DBSI radial diffusivity (B) indicated stabilized axonal injury and recovering demyelination, respectively, after treatments; Cellularity increase (C) and edema decrease suggested a potential recovery of oligodendrocytes and alleviation of edema in response to treatment.

Results and Discussion Bland-Altman plots for DBSI-derived axial diffusivity, radial diffusivity, cell ratio, and edema ratio (Fig. 1) show that fewer than 5% of voxels differed by more than 2 standard deviations (dotted lines) between repeated scans for the 70 voxels in the centrum semiovale. Our data suggested excellent DBSI reproducibility and indicate feasibility of a planned future longitudinal DBSI study. Over the four DBSI scans of the 5 MS brain lesions, DBSI axial diffusivity was mostly unchanged (Fig.2, A), suggesting the axon injury did not further deteriorate during the study period. DBSI radial diffusivity decreased over the four scans in 4 of 5 lesions (all but lesion 5 in Fig.2, B), suggesting myelin damage was highest at the beginning during enhancement, and subsequently underwent some recovery. In addition, DBSI found that cellularity increased in 3 of 5 lesions (Fig.2, C), which suggests increasing numbers of cells, such as oligodendrocytes. Edema ratio was highest at time 0 and decreased over the four scans in four lesions (all but lesion 4 in Fig.2, D), which may reflect dynamics of blood-brain barrier breakdown and vasogenic edema development and recovery. This study provides a basis for future longtitudinal DBSI studies on MS patients. Our goal is to develop improved imaging methods to evaluate the effectiveness of various MS treatments, and ultimately to help to customize patient-specific treatment plans.

References [1] Wang,Y. *et al. Brain*. 2011. 134:3590; [2] Jenkinson, M. Neuroimage, 2002.17, 825-41; [3] Whittall KP, Journal of Magnetic Resonance 1989;84:134-52.