Diffusion Basis Spectrum Imaging detects evolving axonal injury, demyelination and inflammation in the course of EAE

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Introduction

A novel diffusion basis spectrum imaging (DBSI) was recently introduced to resolve inflammation in the presence of axon and myelin damage in a mouse model of multiple sclerosis[1] (Fig. 1). In the current study, in vivo DBSI of the lumbar segments of spinal cord from experimental autoimmune encephalomyelitis (EAE) mice was performed, followed by histological validation.

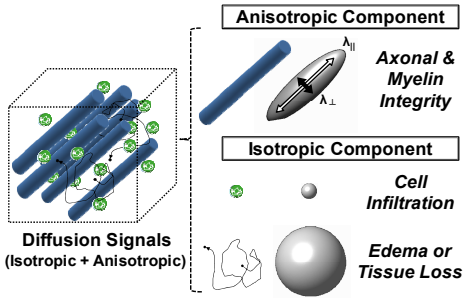


Fig. 1. DBSI considers diffusion weighted MRI data as a linear combination of multiple anisotropic components and a spectrum of isotropic components. DBSI derives parameters of axial ($\lambda_{||}$) and radial ($\lambda_{\perp}$) diffusivities, cell fraction (restricted isotropic diffusion), and water fraction (non-restricted isotropic diffusion). Together, these isotropic components represent inflammation response.

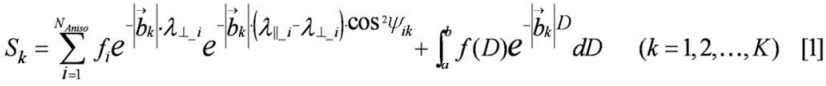
Material and Method

EAE: Rodent Model of Multiple Sclerosis

EAE was induced in 20 6 – 8 weeks old C57BL/6 female mice by active immunization of MOG35-55 peptide. Cross-sectional in vivo DBSI was performed at baseline, onset, peak and chronic phases of EAE (Fig. 2, n=5 for each group).

Diffusion Basis Spectrum Imaging

In vivo spinal cord MRI was acquired using a multiple spin-echo diffusion weighted sequence with 99 diffusion directions. The acquisition parameters were: TR 1.2 s, TE 31 ms, Δ 16 ms, δ 5 ms, b_{max} 1600 s/mm^2, 1 average, 2 mm slice thickness, FOV 1.0 × 1.0 cm^2, and data matrix 64 × 64. The total acquisition time was 2 hours. The diffusion parameters were estimated according to Equation [1][2]:



$$S_k = \sum_{i=1}^{N_{Aniso}} f_i e^{-|\vec{b}_k|\cdot\lambda_{\perp\_i}} e^{-|\vec{b}_k|(\lambda_{||\_i}-\lambda_{\perp\_i})\cos^2\psi_{ik}} + \int_a^b f(D) e^{-|\vec{b}_k|D}\, dD \qquad (k=1,2,\ldots,K) \quad [1]$$

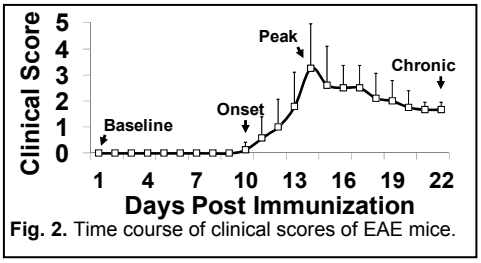


Fig. 2. Time course of clinical scores of EAE mice.

, where S_k and $|b_k|$ are the signal and *b*-value of the k^{th} diffusion gradient, N_{Aniso} is the number of anisotropic tensors, ψ_{ik} is the angle between the k^{th} diffusion gradient and the principal direction of the i^{th} anisotropic tensor, $\lambda_{||\_i}$ and $\lambda_{\perp\_i}$ are the axial and radial diffusivities of the i^{th} anisotropic tensor, f_i is the signal intensity fraction for the i^{th} anisotropic tensor, and *a* and *b* are the low and high diffusivity limits for the isotropic diffusion spectrum *f(D)*.

Histological Validation

Following in vivo DBSI, mice were perfusion fixed for histological validations.

Results

The time course of EAE clinical scores is shown in Figure 2. Days 1, 10, 14, and 22 corresponded to the baseline, onset, peak and chronic phase of the disease. The DBSI parameter maps and the corresponding histological images are shown in Figure 3. The quantified values of the ventro-lateral white matter are shown in Figure 4.

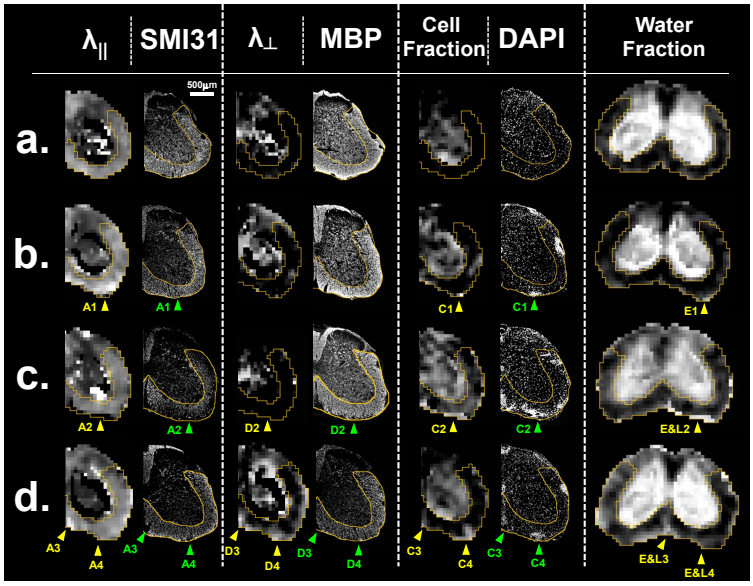


Fig. 3. The DBSI detected pathologies strongly correlate with the histological evidences in the baseline (a), onset (b), peak (c), and chronic (d) of EAE. Letters indicate the neuropathology events (A=Axonal injury, C=Cell infiltration, E=Edema, D=Demyelination, E&L=Edema and/or tissue loss) with numbers indicating the event IDs. Yellow marks the DBSI findings; green denotes the corresponding histology. At the onset of EAE, co-localized with cell infiltration (C1), axonal injury first appears at the dorsal and ventral spinothalamic tract (A1). Severe axonal loss (A2) and demyelinaion (D2) are obvious in the peak of EAE. Inflammation markers (cell and water fractions) show increased cellularity (C2), vesogenic edema and tissue loss (E&L2) in ventral funiculus. In the chronics phase, axonal loss (A3, A4) and demyelination (D3, D4) are more apparent. Most of the glia cells retreat from the ventral funiculus, except for the ventral spinothalamic tract (C3, C4), leave lots of tissue loss as permanent lesions (E&L3, E&L4).

Discussions and Conclusion

DBSI parameters revealed evolving multiple neuropathologies in the course of EAE. Histological findings substantiated in vivo DBSI results. The quantification of cell and water fractions successfully identified the spatial and temporal evolution of inflammation. The current study is the first to quantify the inflammation noninvasively in the course of EAE using MRI.

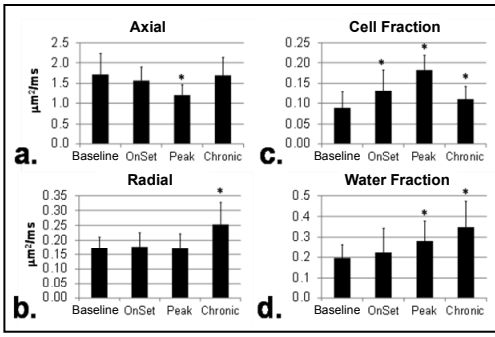


Fig. 4. Time course of DBSI parameters: $\lambda_{||}$ (a), $\lambda_{\perp}$ (b), cell fraction (c) and water fraction (d). Decreased $\lambda_{||}$ suggests severe axonal injury in the peak. Returning to normal at chronic phase may suggest reversible axonal injury acutely. The significantly increased $\lambda_{\perp}$ suggests demyelination at the chronic phase. Cell fraction reflects the increased cellularity in response to the inflammation, highest at the peak. Water fraction increases along the course of the disease likely to reflect vasogenic edema or tissue loss.

Reference

[1]Wang et. al. Brain 2011; [2]Anderson, MRM, 2005