Comparison of directional diffusion kurtoses and diffusivities in EAE- induced spinal cord

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Introduction

Axonal loss in MS patients could be clinically silent for a long period before there is irreversible neurological disability [1]. A non-invasive diagnosis that can detect the disease in an early stage and clarify the pathophysiological situation is essential to monitor disease progression and develop effective therapeutic treatment. The inflammatory neurodegenerative disease experimental autoimmune encephalitis (EAE) resembles MS in many aspects and is characterized by both axonal loss and demyelination. Several diffusion MRI techniques have been applied to differentiate the EAE or MS pathology and they were demonstrated to be more sensitive than conventional MRI imaging [2, 3]. Diffusion kurtosis imaging (DKI), which makes use of a 4th order cumulant expansion of diffusion-weighted (DW) signal vs b-value to extract non-Gaussian diffusion properties[4, 5], was applied in fixed EAE rat spinal cords (SC) in the current study. Its feasibility of diagnosing the disease was assessed.

Methods

Four rats with EAE induction, together with four normal rats as controls, were sacrificed at the same time and perfusion-fixed 35 days after the induction. The lumbar regions of the spinal cords were excised and placed in 4% paraformaldehyde solution before DKI experiments. All MRI experiments were performed using a Bruker PharmaScan 7T scanner. SE 8-shot EPI sequence with navigator echo was used with the following parameters: TR/TE=3000/45ms, δ/Δ=9/17ms, slice thickness=2mm, FOV=40mm, data matrix=256x256, NEX=2. A total of 5 b values (1.2, 2.4, 3.6, 4.8, 6ms/μm^2) were applied with an encoding scheme of 30 gradient directions [6]. The apparent diffusion coefficients (D_{app}) and apparent kurtoses (K_{app}) were obtained from $\ln[S(b)]=\ln[S(0)]-bD_{app}+(1/6)b^2D_{app}^2K_{app}$ [4,5]. Kurtoses along the eigenvectors of diffusion tensor (DT) were computed by transformation of diffusion kurtosis tensor to the coordinate system of the eigenvectors [7]. $K_{//}$ is the kurtosis along the direction of principle eigenvector and $K_{\perp}$ was the average of the other two orthonormal directions. A newly proposed anisotropy of kurtosis, FA_K, is defined as $\sqrt{(3/2)\sum_{i=1}^{3}(K_i - MK)^2 / \sum_{i=1}^{3} K_i^2}$. Regions of interest (ROIs) were drawn manually on the white matter (WM) in 2 slices of EAE and normal groups. As the EAE lesion was spatially inhomogeneous, ROIs in the former group were defined only in lesion areas classified by the T2 weighted image. The DKI-derived parameters (MK, $K_{//}$, $K_{\perp}$ and FA_K) and that of DTI (MD, $\lambda_{//}$, $\lambda_{\perp}$ and FA) were measured and compared by Mann-Whitney test.

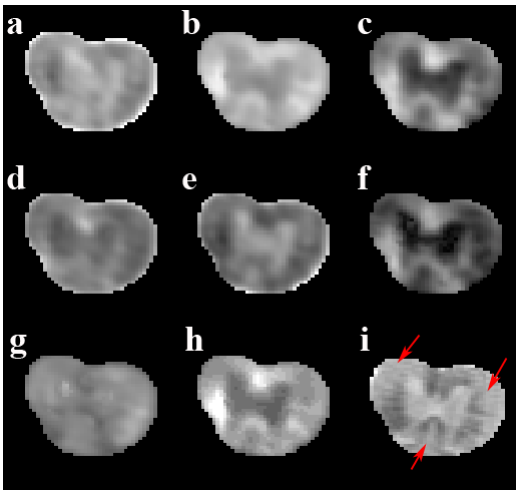

Figure 1. Different maps of an EAE-induced rat SC. **(a)** MD, **(b)** MK, **(c)** FA, **(d)** $\lambda_{//}$, **(e)** $\lambda_{\perp}$, **(f)** FA_K, **(g)** $K_{//}$, **(h)** $K_{\perp}$, **(i)**T2WI. The arrows indicate the active lesion area.

Results and Discussions

The MD, MK, FA, $\lambda_{//}$, $\lambda_{\perp}$, FA_K, $K_{//}$, $K_{\perp}$ map and T2-weighted image (T2WI) of an EAE-induced rat SC were shown in Fig. 1. The measurements and the comparison between normal and lesion were shown in Fig.2. There is statistical significance between the two groups in all measurements except MD and MK. The directionally averaged MD and MK were less sensitive to EAE pathology. The FA_K was found to be most sensitive to EAE-induced damage with the largest percentage difference as compared to other indices. It is important to note that the $K_{//}$ was found to be significantly increased and decreased in $\lambda_{//}$ in the lesion area. Former studies [8] suggested that reduction of $\lambda_{//}$ could due to cytoskeletal perturbation or debris formation when the axonal structures breakdown. These possible barriers were verified here as the corresponding increase in $K_{//}$, implying that diffusion along WM axonal direction is more restricted when there is plaque. In addition, $\lambda_{\perp}$ was increased whereas $K_{\perp}$ decreased due to demyelination and axonal loss resulting in less hindrance of water molecules diffusion in this radial direction. The scatter plot of directional diffusivities and kurtoses was shown in Fig. 3. A single slice from one sample of each group was used to make the plot. The two groups can be clearly distinguished from both directional kurtoses compared with the diffusivities. The high sensitivity of $K_{//}$ to diffusion environment might be able to differentiate various axonal degeneration stages [1] and monitor the disease progression.

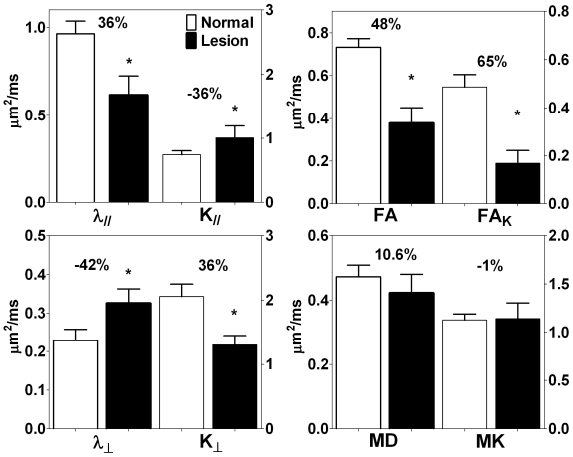

Figure 2. Comparison of DKI- and DTI-derived parameters in the normal and lesion tissue. Percentage difference between two groups was shown on top of each parametric measurement. (* p<0.05 indicate significant difference of measurement between normal and lesion tissue).

Conclusion

Apart from having high sensitivity, the unique non-Gaussian information revealed by DKI is potential to give a more accurate diagnosis and treatment to the MS patients as compared to DTI. Directional kurtoses quantifying the restriction in a specific direction is found to be useful in the current study such that they may serve as new metrics for clinicians to stage the disease.

References [1] Bjartmar C et al. J Neurol Sci 2003:206(2):165-171. [2] Kim JH et al. Neurobiol Dis 2006;21(3): 626-632 [3] Assaf Y et al. MRM 2002;47(1):115-126 [4] Jensen JH et al. MRM 2005;53(6):1432-1440. [5] Lu H et al. NMR Biomed 2006;19(2):236-247. [6] Jones DK et al. MRM 1999;42(3):515-525. [7] Qi LQ et al. J.Computational and Applied Math. (*in press*). [8] Sun SW et al. NeuroImage 2006:32(3) 1195-1204

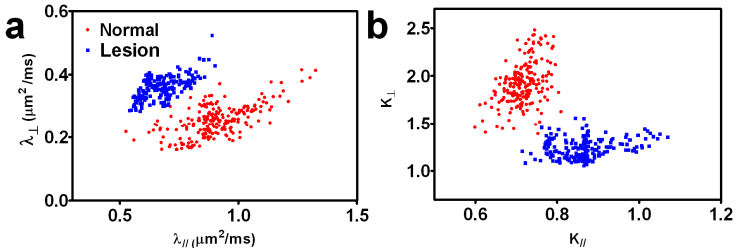

Figure 3. Scatter plot of (a) directional diffusivities (b) kurtoses from ROIs in a single slice of one sample in each group.