Assessment of normal-appearing brain tissue changes in multiple sclerosis using diffusion kurtosis imaging

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Target audient: researchers interested in the application of diffusion kurtosis imaging or investigation of multiple sclerosis.

Introduction: Multiple sclerosis (MS) is an inflammatory and demyelinating disease of central nervous system, considered to be the most frequent cause of nontraumatic neurologic disability in young and middle-age adults [1]. Early diagnosis of MS is crucial to prompt treatment and monitoring of curative effect. Conventional MRI has been widely used for the investigation and diagnosis of MS [2]. However, recent studies of histopathology and ultra-high field MRI on MS has revealed that disease progression includes not only the white matter (WM) lesions detected by conventional MR images but also the regions that appear to be normal [1], especially cortical lesions which are undersized, have poor contrast with the surrounding normal gray matter (GM) or contaminated by the partial volume effects from the CSF. Diffusion kurtosis imaging (DKI), as an extension of conventional diffusion tensor imaging (DTI), is considered to be a potent tool to investigate tissue microstructural complexities in both GM and WM, and has been applied in several neuropathological studies [3-5]. A recent study also illustrated that the kurtosis metrics were less sensitive to CSF partial volume effect than conventional diffusion metrics [6]. In this study, we aimed to assess the tissue changes of normal-appearing WM (NAWM) and GM (NAGM) of MS patients using DKI at 3 Tesla clinical MRI system.

Methods: Subject: Seven MS patients with motor impairment (4 males, 3 females; mean age = 44.7 ± standard deviation (SD) = 12.9 years) and twenty two healthy volunteers (11 male, 11 females; mean age = 44.2 ± 12.7 years) were studied after signed, informed consent.
Image acquisition: All scans were performed on a Philips 3T MRI Achieva scanner (Philips Healthcare, Best, The Netherlands) with body coil excitation and 8-channel SENSE head coil for reception. Four averaged minimally weighted (b_0) and 2 averaged 32 gradient directions with two b values (1000 and 2000 s/mm^2) were acquired using single-shot EPI sequence with following parameters: TR/TE = 2000/69 ms, nominal resolution = 2.55x2.55x3 mm^3, reconstruction resolution = 2x2x3 mm^3, 44 axial slices with no interslice gap to cover the whole brain, SENSE factor = 2, 3/4 partial Fourier encoding, total scan time = 19 min 39 s. For anatomical reference, T1-weighted images were acquired using 3D-MPRAGE sequence with the following parameters: TR/TE = 7.0/3.2ms, TI = 800 ms, nominal/reconstruction resolution = 1x1x1 mm^3, 167 slices, scan duration 10 min 41 s. Axial T2w images with the same geometry as the DKI acquisition of the brain were also obtained using multishot-TSE sequence (TR/TE= 3000/80 ms, reconstruction resolution = 0.33x0.33x3 mm^3, 44 slices, total scan time = 2 min 48 s.).
Data processing and analysis: Diffusion-weighted images were first co-registered to b_0 followed by spatial Gaussian smoothing with full-width-half-maximum of 2.5 mm using Automated Image Registration (AIR5). DKI-derived maps, including fractional anisotropy (FA), mean diffusivity (MD), longitudinal/axial diffusivity ($\lambda_{\parallel}$), transverse/radial diffusivity ($\lambda_{\perp}$), mean kurtosis (MK), longitudinal/axial kurtosis ($K_{\parallel}$), and transverse/radial kurtosis ($K_{\perp}$), were calculated using Diffusional Kurtosis Estimator (DKE) [7] running in MATLAB (Mathworks, Natick, MA, USA). The T1 MPRAGE images were first coregistered to b = 0 images and segmented into WM and GM using SPM8. The WM and cortical GM masks were checked by an experienced observer with T1w and T2w images to exclude any visible lesions and transferred to all DKI-derived maps for quantification. Independent samples T tests were performed to test group difference of each metric respectively, using SPSS (Chicago, IL, USA).

Results and Discussion: Fig. 1 shows the mean ± SD of each DKI-derived metric in NAWM and NAGM for both normal control subjects and MS patients. In the upper part of Fig. 1, NAWM of MS patients has reduced FA, increased MD, increased $\lambda_{\perp}$ with no significant change in $\lambda_{\parallel}$, agrees well with former studies of DTI [8], suggesting the demyelination and moderate axonal loss in NAWM before severe damage in structural integrity and plaque emerges. At the same time, pathological evidence of decreased axonal density in NAWM [8] accords with the significantly reduced kurtosis metrics indicating a decrease in the tissue complexity or diffusional heterogeneity. In the lower part of Fig. 1, though the $K_{\perp}$ difference between two groups is not significant, the rest DKI-derived metrics of NAGM show a diminishing trend, suggesting the maintenance of normal blood-brain barrier function in despite of the subtle axonal loss, neuronal demyelination and shrinkage [9].

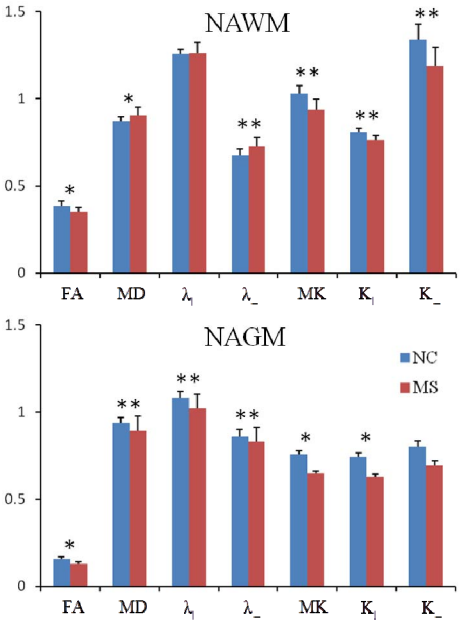

Fig. 1. Mean DKI-derived metrics of NAWM and NAGM in normal controls and MS patients. The error bar represents the SD. The calibration bars for the diffusivities are in units of μm^2/ms, while others are dimensionless. Significant differences between groups are indicated by * $p < 0.05$ and ** $p < 0.01$.

Conclusion: In this preliminary study, we have demonstrated that microstructural changes in NAWM and NAGM of patients with MS could be assessed using DKI. Providing supplementary information from kurtosis metrics, DKI-derived metrics may potentially be effective imaging markers for investigation and diagnosis of MS.

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