Diffusion Kurtosis Imaging Analysis of Microstructural Differences between Patients with Alzheimer's Disease and Mild Cognitive Impairment

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Introduction: Mild cognitive impairment (MCI) has been recognized as a transitional phase between normal and Alzheimer's disease (AD). Every year 10-15% of MCI patients progress to AD. However, sensitive and specific biological indicators for picking up early disease are still lacking. It has been suggested that microstructural changes in brain grey matter are accounting for the pathologic mechanisms of AD. Diffusion tensor imaging (DTI) has long been studied to demonstrate microstructural changes in bran white matter in AD patients and MCI patients compared to normal controls. DTI assumes the diffusion to be Gaussian, which is generally not the case. A recent developed method named diffusion kurtosis imaging (DKI) is an extension of DTI that is able to delineate non-Gaussian diffusion. By offering more measurements derived from non-Gaussian model, it has been demonstrated to outperform DTI in studies of cerebral gliomas, cerebral infarction, healthy aging, hyperactivity disorder, and Parkinson. We used ROI analysis to investigate the sensitivity of the measurements from DKI for differentiating between patients with MCI and patients with AD and detecting microstructural changes in both white and grey matters.

Materials and Method: Totally 24 patients (14 AD, 10 MCI) were recruited from a local tertiary referring center. All scans were performed on a Philips 3T MRI Achieva scanner. Diffusion weighted (DW) images were acquired using a single shot EPI sequence with 32 gradient directions and two nonzero b values (1000 and 2000 s/mm^2). The imaging parameters were: TR/TE = 2000/69 ms, reconstruction resolution = 2x2x3 mm^3, 33 axial slices with no interslice gap to cover the whole brain. MPRAGE images were also acquired to serve as anatomical reference with the following parameters: TR/TE = 7.0/3.2ms, TI = 800 ms, reconstruction resolution = 1x1x1 mm^3, 167 slices. The DW images were first corrected of eddy-current distortion and heads' motion using FSL (FMRIB Software Library, Oxford, UK), and then Gaussian smoothed. MK was calculated as the mean value of the apparent kurtosis coefficients along all 32 gradient direction and three diffusion tensor's eigenvalue direction, other DTI and DKI parameters were calculated as described by Jensen et al. All parameters were derived using an in-house own written MATLAB (Mathworks, Natick, MA, USA) program. For each subject, the MPRAGE and b0 images were first oriented along the same direction. The MPRAGE was then co-registered to the b0 image. The co-registered MPRAGE image was then segmented into grey matter (GM), white matter (WM), and CSF, which were further re-sliced into the b0 image space. The processed WM and GM images were converted into binary masks for further quantification analysis of WM and GM of ROIs. In ImageJ (National Institutes of Health, Bethesda, MD) software, several ROIs were bilaterally drawn on b0 images at (a) whole temporal lobe and (b) whole brain. These ROIs were overlaid onto the DTI and DKI parameters of each subject, and the corresponding mean values of the parameters in each ROI were calculated. Mann–Whitney U test was conducted to compare mean value of parameters between AD group and MCI group in all regions. The correlations between parameters in all regions and the MMSE scores were investigated using linear regression. Pearson's correlation coefficient was also calculated. Receiver operating characteristic (ROC) curves were drawn to test regions' parameters capability in discriminating ADs from MCIs. All Statistical analyses were performed using PASW.

Table 1. DTI and DKI measurements in regions where AD patients show significant difference from MCI patients.

Brain region	Measur-ements	MCI Mean±SD	AD Mean±SD	MCI vs AD P value	AUC in ROC curve
Whole brain WM	$K_{\parallel}$	0.80±0.03	0.76±0.04	0.076	0.719
	FA	0.26±0.02	0.25±0.02	0.065	0.708
Whole brain GM	**FA**	**0.15±0.02**	**0.13±0.01**	**0.033***	**0.750**
	$D_{\perp}$	1.18±0.12	1.28±0.10	0.076	0.708
	$K_{\parallel}$	**0.75±0.04**	**0.72±0.04**	**0.047***	**0.729**
Temporal lobe WM	**FA**	**0.21±0.02**	**0.20±0.02**	**0.028***	**0.760**
Temporal lobe GM	**FA**	**0.14±0.02**	**0.12±0.01**	**0.009****	**0.823**

* Difference significant at the 0.05 level. ** Difference significant at the 0.01 level.

Table 2. Correlations of DTI and DKI measurements with MMSE score.

Brain region		$D_{\parallel}$	$D_{\perp}$	FA	MD	$K_{\parallel}$	$K_{\perp}$	MK
Whole brain WM	Correlation	**-0.476***	**-0.526***	0.426	**-0.514***	**0.468***	0.189	0.274
	P value	**0.034**	**0.017**	0.061	**0.020**	**0.038**	0.425	0.243
Whole brain GM	Correlation	**-0.574****	**-0.614****	0.265	**-0.602****	**0.498***	0.290	0.398
	P value	**0.008**	**0.004**	0.258	**0.005**	**0.026**	0.216	0.082
Temporal lobe WM	Correlation	**-0.541***	**-0.641****	**0.549***	**-0.614****	0.306	**0.514***	**0.472***
	P value	**0.014**	**0.002**	**0.012**	**0.004**	0.190	**0.020**	**0.035**
Temporal lobe GM	Correlation	**-0.537***	**-0.580****	0.235	**-0.570****	**0.444***	0.396	**0.471***
	P value	**0.015**	**0.007**	0.319	**0.009**	**0.050**	0.084	**0.036**

* Correlation significant at the 0.05 level. ** Correlation significant at the 0.01 level.

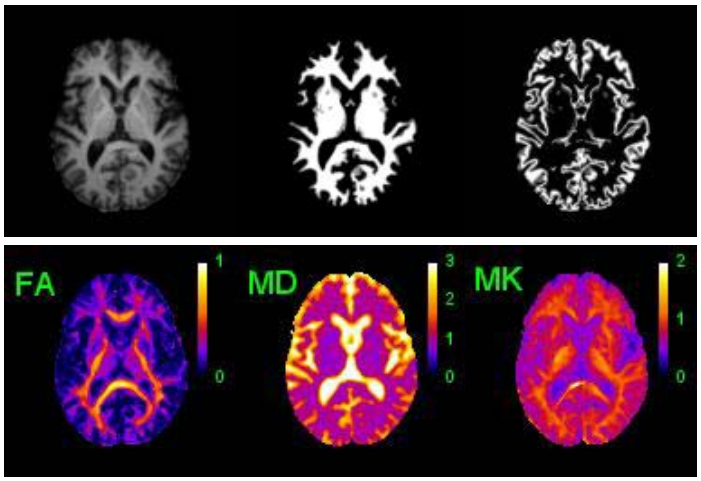

Figure 1. Up left to down right: MPRAGE, WM, GM, FA, MD, MK.

Results: Table 1 shows the result of Mann–Whitney U test and the area under curve (AUC) of the ROC curves. FA shows the best discriminating ability followed by $K_{\parallel}$. Table 2 shows correlations of DTI and DKI measurements with MMSE scores. $D_{\parallel}$, $D_{\perp}$, and MD showed significant MMSE score related decrease for all four brain regions. In temporal lobe WM, FA value was positively correlated with MMSE score. $K_{\parallel}$ showed significant positive correlation with MMSE score in other three brain regions except temporal lobe WM, while $K_{\perp}$ was significantly increasing with MMSE only in temporal lobe WM. MK was significantly positively correlated with MMSE score in temporal lobe WM and GM.

Conclusion: While previous studies of Alzheimer's disease and MCI, in which DTI model were used, found no significant difference between these two groups in regions like whole brain GM, temporal lobe WM or GM, our study, with a more precise diffusion model of DKI, found promising difference in these regions which may characterize brain tissue microstructural changes during the disease deteriorating. In addition, the extra measurement of $K_{\parallel}$ bears possibility of providing information of GM in new aspects which will help improve the understanding and delineation of this disease. Further, only a few studies had demonstrated the correlation between MD or FA and MMSE score, and the results were controversial. It is worth noting that in our study, in addition to MD and FA, $D_{\parallel}$ and $D_{\perp}$ along with the new measurements of $K_{\parallel}$, $K_{\perp}$, and MK also significantly correlated with MMSE score in not only WM but also GM. It suggests that DKI model's measurements may be more sensitive indicators for reflecting Alzheimer's disease progression.

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Reference: **1.** Jensen, J.H., et al., MRM, 2005. **2.** Lu, H.Z., et al., Nmr in Biomedicine, 2006. **3.** Jensen, J.H. and J.A. Helpern, Nmr in Biomedicine, 2010.