Diffusional Kurtosis Imaging in Mild Cognitive Impairment and Alzheimer's Disease

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Introduction: The most evident finding to date in diagnostic imaging studies of Alzheimer's disease (AD) is regional brain atrophy. Unfortunately, at the stage when detectable atrophy has occurred, the disease may have progressed to where interventions will have a limited benefit. Although the biophysical foundation for these morphologic findings remain unknown, it is reasonable to suppose that changes in the brain tissue's microstructure may precede the onset of atrophy. Diffusion-weighted imaging (DWI), particularly diffusion tensor imaging (DTI), has been widely applied in studies of AD and mild cognitive impairment (MCI), focusing on fractional anisotropy (FA) and/or mean diffusivity (MD) indexes, reporting different degrees of white matter (WM) damage. It is well recognized, however, that DTI yields only a fraction of the information potentially accessible with DWI. This is mainly due to the fact that DTI is based upon a Gaussian approximation of the diffusion displacement probability distribution. In brain, non-Gaussian diffusion effects are believed to arise from diffusion barriers and, as a consequence, a measurement of the degree of diffusional non-Gaussianity can be regarded as a natural indicator of tissue microstructural complexity. In the present study, we use Diffusional Kurtosis Imaging (DKI), a technique that can simultaneously measure both Gaussian and non-Gaussianity behavior of water (1,2), in a cross-sectional investigation of patients with mild cognitive impairment (MCI), AD and in cognitively intact age-matched elderly controls (AM). Our hypothesis is that the diffusional kurtosis can contribute additional microstructural information beyond that provided by conventional DTI (FA and MD) and that this additional information can help better characterize changes in the microstructural complexity of the brain tissue occurring prior to atrophy.

Methods: All subjects gave informed consent and were recruited from the NYU AD Center. The AM group (n=16) had no evidence for dementia or MCI and a Global Deterioration Scale (GDS) = 1-2. The MCI group (n=13) had mild memory impairment reported by the subject and/or a reliable informant, objective evidence of memory impairment, based on performance one standard deviation (SD) below the mean for age on Logical Memory II of the Wechsler Memory Scale, a GDS = 3 (mild impairment) and insufficient cognitive and functional impairment for a diagnosis of dementia. The diagnosis of probable AD (n=14) was based on a GDS = 4-5, the criteria of DSM IV and NINCDS/ADRDA and the absence of any other condition that could account for the symptoms of dementia. There were no statistically significant differences among the groups in terms of demographic data including gender, education or age. MR experiments were conducted on a 3T Trio MR system (Siemens). The DKI pulse sequence and processing algorithm have been described previously (2-5). Imaging parameters included: 30 diffusion encoding directions, six *b*-values (b = 0, 500, 1000, 1500, 2000, 2500 s/mm^2) for each direction, TR = 2300 ms, TE = 108 ms, FOV = 256 × 256 mm^2, matrix = 128 ×128, parallel imaging factor of 2 with 24 k-lines used as references, number of averages = 2, 15 oblique axial slices to cover the frontal regions and temporal regions, slice thickness = 2 mm, voxel size 2 × 2 × 2 mm^3. A 3D T_1-weighted image was also acquired using an MPRAGE sequence. Three-dimensional motion correction was performed on the diffusion images using SPM followed by spatial smoothing using a Gaussian filter with FWHM of 2.5 mm. Estimates were obtained for the apparent diffusion coefficient (ADC) and the apparent kurtosis coefficient (AKC) for each particular *b* direction. The ADC values from all directions were used to calculate the diffusion tensor, from which the mean diffusivity (MD), fractional anisotropy (FA), $D_\parallel$ and $D_\perp$ were obtained. The MD corresponds to the diffusion coefficient averaged over all possible diffusion directions, whereas $D_\parallel$ is the diffusion coefficient in the direction of the principal diffusion tensor eigenvector and $D_\perp$ is the diffusion coefficient averaged over all diffusion directions perpendicular to the principal diffusion tensor eigenvector. With DKI, several additional diffusion metrics can be determined that quantify diffusional non-Gaussianity. All of these may be calculated from the diffusion and diffusional kurtosis tensors. For the present work, we utilize the MK, $K_\parallel$, and $K_\perp$, which are kurtosis analogs of the MD, $D_\parallel$ and $D_\perp$ (2,5). It is worth noting that the estimates of diffusion indices derived here from DKI data are, in general, more accurate than conventional measures (6). This is because conventional estimates of these indices based on DTI data are obtained from a lower order diffusion model. An automated gray-white matter segmentation approach, in combination with manually drawn regions-of-interest (ROI), was used to compare the diffusion parameters between subject groups. This approach resulted in the evaluation of eight areas: 1) segmented prefrontal gray matter (sPF-GM), 2) segmented prefrontal white matter (sPF-WM), 3) segmented temporal white matter (sTMP-WM), 4) prefrontal oval (PFo) ROI, 5) temporal oval (TMPo) ROI, 6) hippocampus (H), 7) anterior corona radiata (ACR) and 8) genu of the corpus callosum (gCC). Analysis of covariance (ANCOVA) was used to compare subject groups in terms of each regional diffusion measure. A separate analysis was conducted for each measure within each region. In each case, the regional measure was the dependent variable and the model included age as a numeric factor and group membership as a classification factor. P-values for group comparisons are reported with a Tukey multiple comparison correction. Receiver operating characteristic (ROC) and binary logistic regression analyses were used to assess the diagnostic utility of regional diffusion measures, alone and in combination, to discriminate each pair of subject groups. All reported p-values are two-sided with significance defined as $p<0.05$.

Results: Table 1 shows the results of our analyses for all indices that were found to be statistically significant after Tukey's multiple comparison correction. Results from the ROC analysis are shown in Table 2. ROC analyses identified MK and $K_\perp$ in the ACR as the best individual discriminators of MCI from AM, with the measures having an Area Under the ROC Curve (AUC) of 0.80 to 0.82, respectively. The ROC analysis identified $K_\perp$, MK, $D_\perp$ and MD in the PFo region as the next best discriminators of MCI from AM, with each measure having an AUC between 0.77 to 0.79.

Table 1: Group comparisons for regions with indices of $p<0.05$ (Tukey corrected). sPF-GM = segmented prefrontal gray matter; sPF-WM = segmented prefrontal white matter; sTMP-WM = segmented temporal white matter; PFo = prefrontal oval ROI; TMPo = temporal oval ROI; H = hippocampus; ACR = anterior corona radiate; gCC = genu of the corpus callosum.

COMPARISON	INDEX	REGION
AD vs. MCI	MD	H
	$D_\perp$	H
	$D_\parallel$	H
AD vs. AM	MD	All
	$D_\perp$	All
	$D_\parallel$	All
	MK	ACR, TMPo, sTMP-WM, gCC
	$K_\perp$	ACR, TMPo, sTMP-WM, gCC, sPF-WM
	$K_\parallel$	ACR
MCI vs. AM	MD	PFo
	$D_\perp$	PFo
	MK	ACR, PFo
	$K_\perp$	ACR, PFo

Table 2: The threshold criterion identified by ROC analyses as providing the highest overall accuracy for the discrimination of MCI from AM. (see Table 1 for abbreviations)

REGION	MEASURE	CRITERION	SENSITIVITY	SPECIFICITY
ACR	MK	≤ 1.09	76.9% (10/13)	75% (12/16)
ACR	$K_\perp$	≤ 1.26	76.9% (10/13)	75% (12/16)
PFo	MD	> 1.01	61.5% (8/13)	87.5% (14/16)
PFo	$D_\perp$	> 0.84	84.6% (11/13)	68.8% (11/16)
PFo	MK	≥ 1.06	76.9% (10/13)	75.0% (12/16)
PFo	$K_\perp$	≥ 1.17	61.5% (8/13)	87.5% (14/16)

Discussion: Studies have demonstrated regional increased rates of cerebral atrophy several years before elderly people reach the stage known as MCI. While these observations are consistent with the presence of prodromal AD, the mechanism(s) responsible for this observation are still poorly understood and the delineation of normal elderly from MCI patients appears to be the most challenging task. Our working hypothesis is that alterations of tissue microstructure might be evident prior to the onset of clinically relevant cerebral atrophy. Here we have demonstrated the ability to characterize tissue microstructural changes during MCI using DKI metrics. While the current study does not address cerebral atrophy directly, these data are part of a larger longitudinal study that will eventually allow us to address our hypothesis.

References: 1) Jensen JH & Helpern JA. ISMRM (Abstract # 2154) 2003, Toronto, Canada. 2) Jensen JH & Helpern JA NMR in Biomed, 23(7):698-710, 2010. 3) Jensen JH, et al. Magn Reson Med 2005; 53:1432-1440. 4) Lu H, et al. NMR Biomed 2006; 19(2):236-247. 5) Tabesh A, et al. Magn Reson Med 2010; epub PMID: 21031494 6) Veraart J, et al. Magn Reson Med 2010; epub PMID: 20878760.

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