Alterations in cerebral microstructual integrity in normal aging and in Alzheimer's Disease: a multi-contrast diffusion MRI study

H. Lu[1], J. H. Jensen[1], C. Hu[1], M. F. Falangola[1], A. Ramani[1], S. Ferris[1], J. A. Helpern[1]

[1]Center for Biomedical Imaging, Department of Radiology, New York University, New York, New York, United States

INTRODUCTION: Water molecule diffusion in brain contains useful information related to the physiological state of the tissue. Many aspects of the diffusion behavior (e.g. mean diffusivity, angular anisotropy, non-Gaussianity, displacement distribution function) can be measured using various MRI techniques, such as diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), high angular diffusion imaging (HARDI), Q-ball imaging, Q-space imaging etc. Among these techniques, DWI and DTI can be performed within a clinically manageable time and have been applied to the study of aging and Alzheimer's Disease (AD) in humans (1). However, previous studies have mostly either focused on the aging process only (2) or on the AD-related alterations only (3). Here we investigate both processes simultaneously in four groups of subjects: AD patients, Mild Cognitive Impairment (MCI) patients, age-matched controls and young adult controls. Furthermore, by using a recently developed technique Diffusion Kurtosis Imaging (DKI) (4), we can not only obtain parameters provided by conventional DWI and DTI techniques, but also gain information related to non-Gaussian behavior of the water diffusion, which can be used as an index of tissue complexity in both white matter and gray matter. A unique advantage of the DKI method in comparison with other advanced diffusion techniques is that the scan duration is clinically feasible, taking approximately 12 minutes for the acquisition of the dataset.

METHODS: The experiments were conducted on a 3T MR system (Trio, Siemens Medical Solutions). DKI scans were performed on a total of 21 patients consisting of the following four groups: AD patients (n=4, age 70.5±9.3 mean±SD), MCI subjects (n=6, age 71.5±12.9), age-matched control (n=6, age 70.0±9.5), young adult controls (n=5, age 35.0±6.0). Except for the young control group, all subjects were recruited through the Alzheimer's Disease Center at our institution. The patients with AD are diagnosed based on NINCDS-ADRDA and DSM IV criteria. The MCI group are patients satisfying a series of criteria as described previously (5). The DKI experiments used 30 gradient encoding directions and 6 b values (0-2500s/mm^2) (4). Other imaging parameters were: TR=2300ms, TE=108ms, FOV=256x256mm^2, 15 oblique axial slices, voxel size 2x2x2mm^3, total scan duration 11'57". The diffusion tensor and diffusion kurtosis tensor were computed using a previously described model (4), and three parametric maps were calculated: Mean Diffusivity (MD), Fractional Anisotropy (FA) and Mean Kurtosis (MK). The following regions-of-interest (ROI) were drawn based on the b0 images: frontal white matter (FWM), frontal gray matter (FGM), hippocampus, occipital white matter (OWM), thalamus, corpus callosum, and cerebellar cortex. Linear regression was performed for the ROI results. In a second analysis, histograms were computed for the parametric maps and the results for different subject groups were compared. This analysis has the advantage that the subjectiveness intrinsic to the ROI analysis can be avoided, yielding results that are relatively insensitive to the investigator conducting the analysis.

RESULTS and DISCUSSION: Fig. 1 shows the MD, FA and MK maps for representative subjects from each group. Increasing atrophy can be seen in the images (AD>MCI>Age-Matched>Young control). In addition, the MK maps appear to show an evident change in parametric values, characterized by a loss of gray-white matter contrast during aging and a further loss with AD progression. Regression analysis using ROI values shows that FWM regions have the strongest correlation with the group classifications (p=0.0002, 0.0265 and 0.0007 for MD, FA and MK, respectively). Post-hoc Tukey's tests reveal significant difference in MD and MK (but not FA) values between AD and age-matched controls. Table 1 lists the ROI values from the FWM regions. Fig. 2 shows histograms for the three parameters. MD and FA histograms show one single peak. The MK histogram, on the other hand, appears to have three peaks, corresponding to CSF, GM and WM, respectively. This is useful in differentiating the brain atrophy effect from the microstructual change effect. Specifically, MK histogram shows that the gray-white contrast (2nd and 3rd peaks) gradually decreases from young controls to elderly controls, and in AD patients the two tissue types only show a combined peak in the histogram. Note that these alterations are in addition to the well-known brain atrophy as shown by the first peak (CSF), which is present for all subject groups. In summary, our data suggest that there is a continuous spectrum of tissue microstructual changes during normal aging and during the progression to AD, in addition to the loss of bulk tissue volume. However, it is likely that the progression toward AD will cause the time-course to significantly deviate from the normal aging process. The loss of tissue appears to mainly occur in gray matter and the microstructual change mainly in white matter. It remains to be determined which process occurs first in the early stage of the disease. The DKI technique is a useful method that can provide additional information to that provided by conventional DTI.

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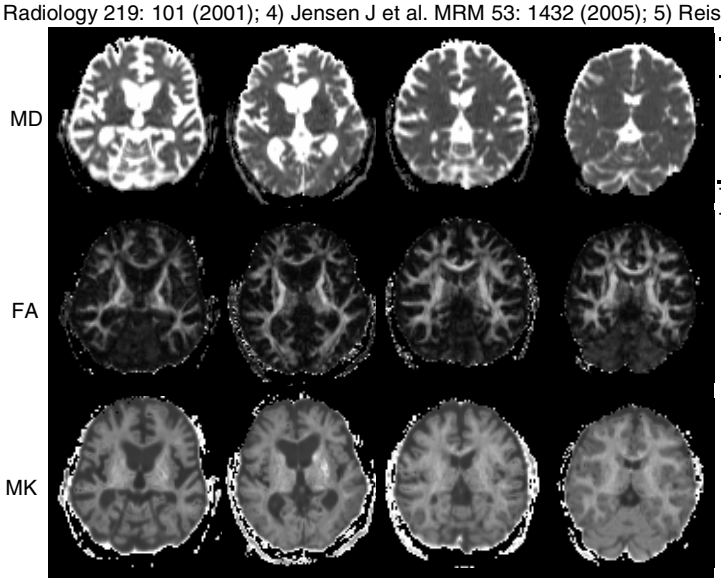

Fig. 1: Diffusion parametric maps for four subjects. The gray scales are 0-3 μm^2/ms for MD, 0-1 for FA, and 0-2 for MK.

Index	AD	MCI	Age-matched	Young control
MD	1.017±0.078	0.987±0.065	0.920±0.036	0.908±0.015
FA	0.362±0.043	0.370±0.025	0.379±0.029	0.408±0.025
MK	1.104±0.086	1.136±0.073	1.190±0.044	1.217±0.028

Table 1: Diffusion parameters (mean±SD) in FWM for the four subject groups. The unit for MD is μm^2/ms. FA and MK is dimensionless.

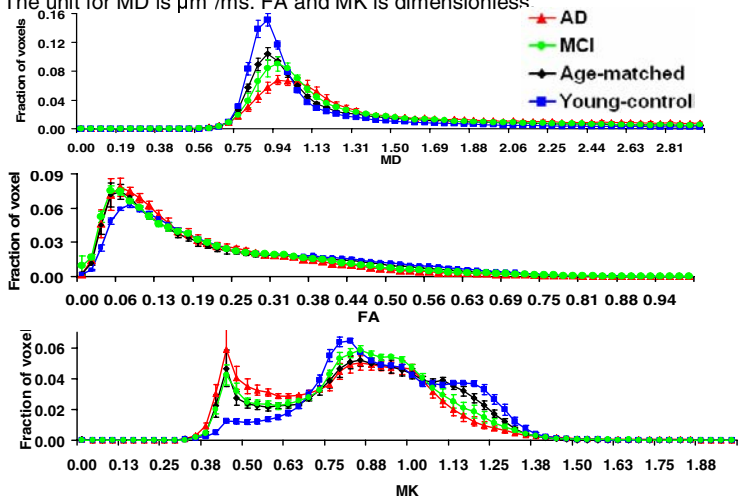

Fig. 2: Histograms of MD (top), FA (middle) and MK (bottom) averaged over all subjects in each group. Error bars indicate ±SEM.