Assessment of Brain Microstructure in a Transgenic Mouse Model of β-Amyloid Deposition

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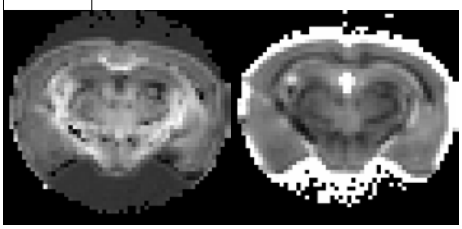
INTRODUCTION: Transgenic mouse models have been essential in understanding the pathogenic role of the β-amyloidogenic pathway of Alzheimer disease (AD). The PS/APP transgenic mouse model overexpresses both mutant human APP and PS1, and shows an early and extensive amyloid deposition (1). Diffusion tensor imaging (DTI) has been applied to study different lines of transgenic mouse models of AD, mainly indicating decrease in anisotropy for some white matter tracts and decreases of mean diffusivity (MD) in the cortex and hippocampus (2-4). Recently, our laboratory has developed a generalization of diffusional tensor imaging (DTI) called diffusional kurtosis imaging (DKI), which quantifies the non-Gaussian nature of the diffusion process resulting from tissue microstructure diffusion barriers, such as cell membranes (5-7). We have used DKI to investigate the cortex and hippocampus of PS/APP mice at an age (> 18 months) when they have significant amyloid burden . Histograms of DKI-derived metrics (MD and mean kurtosis, MK) were obtained. MK histograms displayed distinct patterns for the two groups (non-transgenic controls and PS/APP mice) with higher mean kurtosis in the cortex of PS/APP mice.

METHODS: A total of six 20 month-old mice (non transgenic controls (Ntg) =3; PS/APP transgenic =3) were perfused with phosphate-buffered saline (PBS) (pH 7.4) through the left cardiac ventricle, followed by 10% buffered formalin. After perfusion fixation, the brains were removed, embedded in agar (0.4%), positioned at the center of a plastic tube and tightly sealed for MR measurements. All experiments were performed on a 7 T MR system (SMIS, Guilford, UK) using an 8 rod, 1.5 cm ID bird cage coil, tuned to 298.1 MHz. DKI images were acquired using a spin echo Stejskal-Tanner design sequence. To achieve the diffusion weighting, a TE of 40 ms, Δ of 20 ms and gradient duration δ of 3.8 ms were employed. Other parameters included NX=1 (all directions), 15 slices (600 μm thick), FOV of 128 mm^2, matrix size of 64^2, TR of 2000 ms. For each of 7 b-values (200, 500, 1000, 1500, 2000, 2500, 3500 s/mm^2) 30 gradient directions were applied uniformly sampling the unit sphere. The diffusion tensor and diffusional kurtosis tensor were computed using a previously described model (3), and parametric maps were calculated for MD and MK. Brain regions of interest (ROIs) at the level of cortex and hippocampus were manually drawn in four consecutive slices. Histograms were calculated for each mouse using all of the voxels within an ROI. The MD used value intervals (bins) ranging from 0 to 3 $\mu m^2/ms$ at 0.047 $\mu m^2/ms$ increments (bin size). The MK used bins ranging from 0 to 2 (dimensionless) with a bin size of 0.031. The histograms were then normalized against the total number of voxels for each ROI, so that the sum of all values within one histogram equals unity. ROI drawing and histograms were obtained using ImageJ (http://rsb.info.nih.gov/ij/).

Figure 1



RESULTS and DISCUSSION: Shown in Figure 1 are the representative parametric maps of MD (right) and MK (left) from one slice at the level of the dorsal hippocampus for a PS/APP mouse. Figure 2 shows the MD and MK histograms from each group. Cortex and Hippocampus MD histograms profiles are similar for the two groups with the PS/APP mice demonstrating a wider distribution of values. The MK histograms however, show distinct peaks for Ntg and PS/APP. Table 1 shows the MD and MK values for individual animals along with group means. The group MK values are substantially higher in the cortex (p=0.02) and hippocampus (p=0.11) of PSAPP mice compared with Ntg. Although the number of mice is not enough for a complete statistical analysis (data are part of an ongoing project), the data clearly show a trend of high kurtosis in brain regions associated with significant amyliod burden in these mice. We hypothesize that the presence of Aß plaques in this model may create more water diffusion barriers resulting in a higher kurtosis. Although previous reports have shown decreases of MD in the cortex and hippocampus in a similar transgenic mouse model of AD (3), our results did not show difference of MD values between the two groups either for cortex (p=0.17) or hippocampus (p=0.19). A possible explanation for this difference is the fact that in this study we are using formalin fixed ex vivo brains and formalin fixation alters the magnitude of the water diffusion. These data demonstrate the application of diffusional kurtosis measurements and emphasizes its significant advantage of allowing quantification of microstructural complexity in gray matter associated with Aβ deposition. Further studies are being performed to correlate MK quantification indices with the degree of Aß-load, neuron density and myelin density.

Figure 2

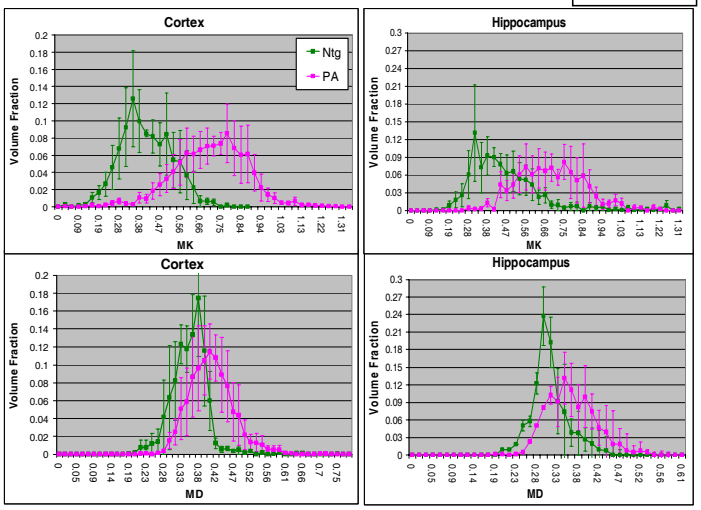


Table 1

MD	Cortex	Hippocampus	MK	Cortex	Hippocampus
	Mean ± sdv	Mean ± sdv		Mean ± sdv	Mean ± sdv
Ntg 1	0.38± 0.03	0.40± 0.03	Ntg 1	0.52± 0.08	0.63± 0.19
Ntg 2	0.33± 0.06	0.34± 0.03	Ntg 2	0.38± 0.12	0.46± 0.12
Ntg 3	0.38 ± 0.03	0.36 ± 0.02	Ntg 3	0.35 ± 0.07	0.35 ± 0.05
Mean ± sdv	**0.36 ± 0.04**	**0.37 ± 0.03**	**Mean ± sdv**	**0.42 ± 0.09**	**0.48 ± 0.12**
PS/APP 1	0.47± 0.04	0.46± 0.03	PS/APP 1	0.85± 0.09	0.83± 0.08
PS/APP 2	0.40± 0.04	0.40± 0.03	PS/APP 2	0.67± 0.13	0.62± 0.12
PS/APP 3	0.38 ± 0.03	0.38 ± 0.03	PS/APP 3	0.63 ± 0.12	0.65 ± 0.13
Mean ± sdv	**0.42 ± 0.04**	**0.41 ± 0.03**	**Mean ± sdv**	**0.71 ± 0.12**	**0.70 ± 0.11**

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