EARLY DIFFUSION CHANGES IN A MOUSE MODEL OF NEUROFIBRILLARY TANGLES

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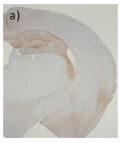
OBJECTIVE: To determine if neurodegeneration in the PS19 mouse model of tau pathology can be detected using diffusion measures of mean diffusivity and fractional anisotropy.

BACKGROUND: DTI MRI has shown that in patients with Alzheimer's Disease (AD) cognitive decline correlates with mean diffusivity (MD), and with synapse loss [1]. AD has two characteristic pathologies however, both plaques full of amyloid-beta peptides and tangles comprised of hyper-phosphorylated tau (h-p-tau) protein. In the amyloid-beta mouse model of AD, MD is elevated and increases with age in pathologic mice [2]. Here we are studying the PS19 mouse model of tau pathology, which expresses h-p-tau and shows signs of synapse loss, microgliosis, and neuron loss [3]. We seek to study whether this mouse model follows the same trend in diffusion measures of MD and fractional anisotropy (FA) as AD patients and the amyloid-beta mouse model.

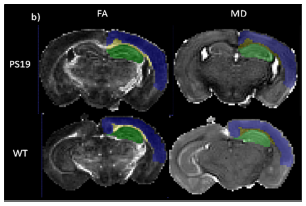
METHODS: To test this hypothesis, we are accumulating DTI data from excised brains of PS19 (TG) and wild-type (WT) mice aged 8-10 months (n=4 TG, n=2 WT), and 15-18 months (n=2 TG, n=2 WT). All animal studies were approved by the IACUC. TG animals were bred from the PS19 line of the P301S model [3]. The brains of ten mice were dissected after transcardial perfusion and fixation (0.01mM PBS followed by 4% PFA/PBS) and stored at 4°C until imaging. The excised tissue was imaged with a 9.4T vertical bore spectrometer (Varian, Palo Alto, CA). A custom solenoid coil was used which tightly encircled a canister holding the brain immersed in fomblin. Diffusion weighted images were acquired (b_0 and b=902 s/mm^2 in six radial directions, each with +/- gradients, totaling 14 images) using a multi-echo diffusion weighted sequence. Imaging parameters were as follows: TR/TE 800/30 ms, FOV 17 x 8.5 x 10 mm^3, matrix 135 x 68 x 80, for 125um^3 isotropic resolution, and a total scan time of 13.25 hours. MD and FA maps were calculated using Camino [4]. A 2D ROI analysis was performed, segmenting the hippocampus, corpus callosum, and cortex from the bregma slice -2.055, which is typically used to quantify histology [5]. Hypothesis testing was performed for each ROI, for both young and old mouse cohorts, using an independent t-test to determine the effect of genotype. Note that there were not enough samples to determine significance within the older cohort of mice. Accurate regional comparisons of tau pathology with DTI measures, determined by immunohistochemistry, will be necessary in order to interpret trends in FA and MD.

RESULTS:

Figure 1: a) Immunohistochemistry staining of h-p-tau in a PS19 mouse from our aged cohort (AT8 antibody, 1.25x magnification), showing strong pathology in the hippocampus and cortex. This is a representative bregma slice -2.055 used to quantify histology.



b) Corresponding 2D slices of fractional anisotropy (FA) and mean diffusivity (MD) maps from young PS19 and WT mice, with segmented ROIs: hippocampus (green), corpus callosum (yellow), and cortex (blue). Notice the enlarged ventricles in the TG mouse compared to WT.



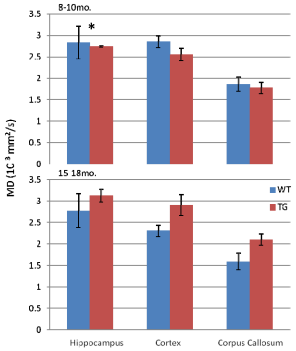


Figure 2: Average MD values from each region in young and old mouse cohorts. While MD is reduced in younger TG mice in all regions compared to WT, in older mice MD increases in the TG cohort but naturally decreases in the WT cohort. *Indicates a significant difference of p≤0.01. Error bars indicate standard deviation.

Table 1: In young TG mice compared to age-matched WT mice, FA is significantly different in the hippocampus (4.41% increase, p≤0.01) and cortex (-15.6% decrease, p≤0.01); MD is significantly decreased in the hippocampus of young TG mice (3.01% decrease, p≤0.01). Looking at the effect of age, in older mice MD was greater in all regions measured in the TG cohort compared to WT. FA is slightly higher in the hippocampus of TG mice and was reduced in the cortex of TG mice. Acquiring data from more mice will improve on these results. *Indicates a significant difference of p≤0.01.

		8-10mo.			15-18mo.		
		WT	TG	sign.	WT	TG	sign.
	N samples	N=2	N=4		N=2	N=2	
Hipocampus	FA	0.26 ± 0.057	0.27 ± 0.01	p≤0.01	0.22 ± 0.0067	0.25 ± 0.010	.
	MD	2.8 ± 0.38	2.7 ± 0.016	p≤0.01	2.8 ± 0.39	3.1 ± 0.15	.
Cortex	FA	0.21 ± 0.052	0.18 ± 0.0038	p≤0.01	0.20 ± 0.021	0.19 ± 0.010	.
	MD	2.8 ± 0.14	2.6 ± 0.15	0.84	2.3 ± 0.13	2.9 ± .25	.
Corpus Callosum	FA	0.59 ± 0.039	0.58 ± 0.019	0.16	0.60 ± 0.041	0.66 ± 0.00044	.
	MD	1.9 ± 0.17	1.8 ± 0.13	0.65	1.6 ± 0.20	2.1 ± 0.14	.

CONCLUSIONS: PS19 mice at a young age have lower MD measures in the hippocampus, perhaps corresponding to an early disease state. The non-significant trend we observe of increasing MD in PS19 mice over WT mimics the observation in AD patients of higher MD in the corpus callosum, frontal and temporal lobes [1].

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