T1ρ MRI as a Marker of Neurofibrillary Tangles in a Mouse Model of Alzheimer's Disease

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OBJECTIVE: To demonstrate $T_{1\rho}$ as a biomarker for AD in the PS19 mouse model of tau pathology.

BACKGROUND: Alzheimer's disease (AD) mouse models mimicking either the amyloid-beta or hyperphosphorylated tau pathologies, the post-mortem diagnostic markers of AD, have been characterized using biochemical and histological techniques [1]. However, the only MRI characterizations reported on transgenic (Tg) mouse models of AD have studied the amyloid-beta pathology [2,3]. A relaxometry study of the $T_{1\rho}$ relaxation time in human AD patients showed a difference of 8% in the $T_{1\rho}$ relaxation times of white matter and 5% in gray matter of the medial temporal lobe [4]. It is hypothesized that the $T_{1\rho}$ relaxation time constant is also sensitive to the pathologic biochemical changes due to mutated tau protein that leads to intracellular neurofibrillary tangles (NFTs). To test this hypothesis, we are currently studying a cohort of 10 mice, half transgenic tau mice expressing the P301S mutation [5] in a human tau isoform, and age-matched wild-type (WT) mice with $T_{1\rho}$ MRI.

METHODS: All animal studies were approved by the IACUC. Tg animals were bred from the PS19 line of the P301S model [1]. MRI was performed on a 9.4T Varian small-bore scanner (Varian Inc., Palo Alto, CA) on 4 mice aged 13-15 months. A volume transmit/receive mouse-head coil (M2M Imaging Corp., Cleveland, OH) was used, with a maximum FOV of 20mm^2. Four $T_{1\rho}$-weighted images were obtained, at spin-locking times of TSL=1, 20, 30, 40ms for quantifying the $T_{1\rho}$ relaxation time parameter [6]. This 3D balanced GRE acquisition obtained an 8mm coronal section of the brain with a matrix size of 256x128 (zero-filled to 256x256) for a nominal resolution of 78μmx78μm with 16 slices each 500μm thick, TE/TR 3.6/6.9ms, a T_1-delay of 8s, and two averages per spin-locking time for a total acquisition time of ~40min/animal. The animal's breathing rate and temperature were monitored while anesthetized with 1.5% isoflurane. The four MRI contrasts were exponentially fit on a pixel-by-pixel basis to create a color-coded parametric map of the $T_{1\rho}$ at each pixel. ROIs of the hippocampus and cortex were manually drawn on $T_{1\rho}$-weighted images, and masks were applied to the corresponding slices in the $T_{1\rho}$ maps to record mean values. Immunohistochemistry was performed on the PS19 mice after harvesting the brain. An antibody for phosphorylated tau staining brown and a counter-stain with hematoxylin were used to visualize neuronal nuclei [7].

RESULTS:

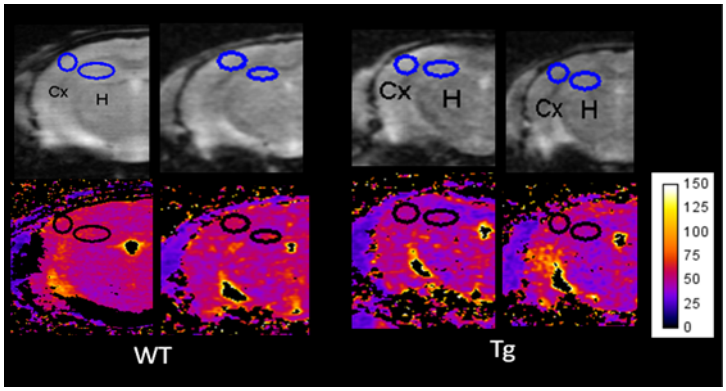

Figure 1: $T_{1\rho}$-weighted images with ROI locations (top panel), and color-coded maps of $T_{1\rho}$ (ms) of age-matched WT mice (n=2) and Tg PS19 mice (n=2), a model of tauopathy in AD. Decreased $T_{1\rho}$ values are measured in the Tg mice, in both the hippocampal and cortical regions, compared to WT. There is a significant decrease in $T_{1\rho}$ values of Tg mice in the hippocampus and cortex, compared to WT. In the hippocampus, mean $T_{1\rho}$ were 57.2 ± 6.5ms (mean ± std between pixels) in WT and 45.9 ± 5.9ms in Tg, a 21% decrease ($p<0.01$). Mean $T_{1\rho}$ in the cortex were 57.2 ± 6.4ms in WT and 49.7 ±6.4ms in Tg, a 13% decrease ($p<0.01$).

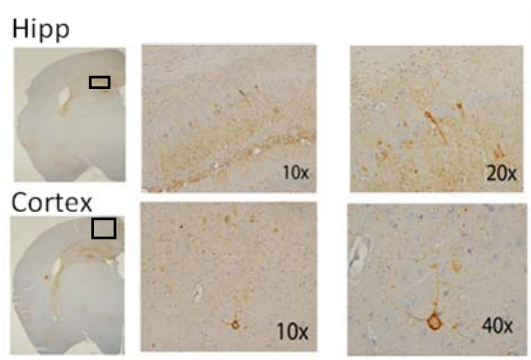

Figure 2: Hyperphosphorylated tau inclusions are seen in the brown stain in magnified views. The hippocampus and cortex are two primary regions presenting pathology in the PS19 tau mouse model.

CONCLUSIONS: The $T_{1\rho}$ relaxation time constant is sensitive to changes in the hippocampus and cortex of mice expressing the pathologic tau protein that leads to intracellular neurofibrillary tangles (NFTs). A decrease in the average $T_{1\rho}$ relaxation time was measured in the PS19 mouse model relative to age-matched control mice. Our ongoing study will be completed with 10 mice and will include relaxometry ($T_{1\rho}$ and T_2) and histological analyses. The current study will generate crucial baseline values that can be assessed in this animal model in longitudinal studies that test novel therapeutic agents, for example.

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