IN VIVO AXONAL TRANSPORT DEFICITS IN A MOUSE MODEL OF FRONTOTEMPORAL DEMENTIA

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Background: Axonal transport is required for the movement of vital organelles and energy in neurons. *In vivo* deficits in this process have been previously reported in multiple mouse models of Alzheimer's disease. Specifically, these deficits have been detected prior to the onset of plaque and tangle pathology. However, there are limited *in vivo* measurements of axonal transport in models of other neurodegenerative diseases such as frontotemporal dementia (FTDP-17). In the r(tta)Tg4510 mouse model, the P301L mutation found in familial forms of both Alzheimer's disease and FTDP-17 is over expressed primarily in the forebrain and can be conditionally expressed throughout the lifetime of the mouse. Thus, the mouse model has a copy of the tetracycline (tta) gene and a copy of P301L gene (tau) that can be activated separately or together. When both Tta and tau are active (tau+/tta+), this mouse model displays increasing levels of tau filaments and neurodegeneration within the forebrain and hippocampus beginning at 3 months of age. A longitudinal MRI imaging analysis has also been conducted on mice at 3, 5, and 8 months of age indicating a significant decrease in volumes of both the cerebral cortex and hippocampus and an increase in the volume of the lateral ventricles as the mice aged.

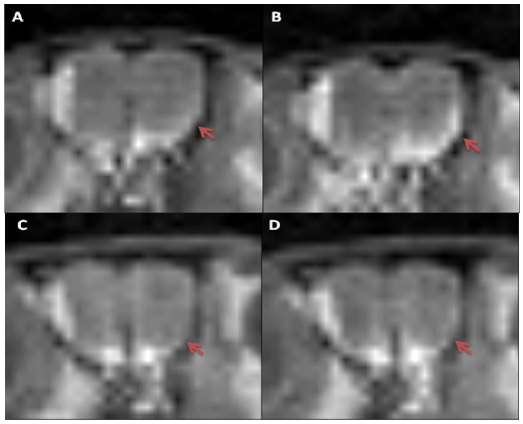

Figure 1: Representative Images from olfactory bulb slices from MEMRI scans of WT first cycle (**A**) and last cycle (**B**) and Tau+/Tta+ first cycle (**C**) and last cycle (**D**) mice. Red arrows indicate representative locations of ROI measurements from the ONL.

Methods: ***Animal Model:*** The r (tta)Tg4510 mouse model of FTDP-17 was used for these studies. Mice were given 2 uL of $MnCl_2$ in each nostril at one hour prior to imaging. Animal protocols were approved by Institutional Animal Subjects Committee at Baylor College of Medicine.

Imaging Protocol: All images were taken by a 9.4T Bruker Avance BioSpec Spectrometer with a 21cm horizontal bore (Bruker BioSpin, Billerica, MA) and a 35mm resonator. Mice were anesthetized using 5% isoflurane with oxygen and placed into the animal holder with a water phantom, where they were kept at 2% isoflurane for the rest of the imaging time. One hour post nasal lavage, mice were imaged using Manganese Enhanced Magnetic Resonance Imaging (MEMRI) Protocol with TE=8.5ms, TR=504ms, FOV=3.0cm, matrix size=128x128x128, number of cycles=15 with each cycle taking approximately 2 min9sec24ms using Paravision software (Bruker BioSpin, Billerica, MA). During imaging, body temperature was maintained at 37.0°C using an animal heating system (SA Instruments, Stony Brook, NY).

Data Analysis: Obtained images were analyzed using Paravision software. Regions of interest (ROI) within the olfactory neuronal layer (ONL) and the water phantom consisting of one pixel (ONL) and 9 pixels (water) were selected and copied across each of the 15 cycles. Signal intensities (SI) of ONL and water phantom ROIs were measured. SI values obtained for ONL were then normalized the water phantom SI values. The correlation between normalized signal intensity in the ONL and time were assessed using Prism (GraphPad Software, San Diego, CA).

Results: Using the MEMRI technique on 10 month old r(tta)Tg4510 mice and wild type littermates, we found significant axonal transport deficits present in the r(tta)T4510 mouse model. A visual representation of these deficits is displayed in Figure 1. Using linear regression analysis, the slopes for WT (n=5), Tau+/Tta-(n=2), and Tau+/Tta+ (n=9) were y= 0.007038x + 0.9633, y= 0.009200x+ 0.9406, and y= -0.0009587x+ 0.962 respectively. A quantitative representation of this data is displayed in Figure 2.

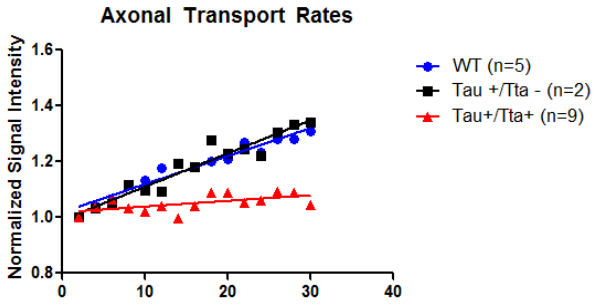

Figure 2: A quantification of normalized signal intensity of WT, Tau+/Tta-, Tau+/Tta+ mice. A linear regression analysis is displayed for each group as well.

Discussion: Results from our study indicate that axonal transport deficits are present at 10 months of age in a forebrain specific mouse model of FTDP-17. Other studies have indicated that axonal transport deficits are strongly correlated to synaptic dysfunction and cognitive decline as a result of decreased movement of energy-producing organelles such as mitochondria to the synapse. In addition, the olfactory bulb has shown to play a major role early in Alzheimer's disease patients, and has not been thoroughly investigated in other tauopathies. Further characterization of the r(tta)Tg4510 mouse model will be conducted at earlier age points in order to determine the earliest age of functional decline in axonal transport to identify possible therapeutic interventions at this time point.

References:

(i) Smith, KDB, et al. Neuroimage (2007);35(4):1401
(ii) Berger, Z, et al. The Journal of Neuroscience (2007); 27(14):3650
(iii) Ludvigson, A, et al. Brain Struct Funct (2010); 216(1):31
(iv) Yang, D., et al. Neuroimage (2011); 54(4):2652