Glutamate Changes in a Mouse Model of Tauopathy

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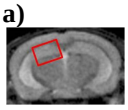
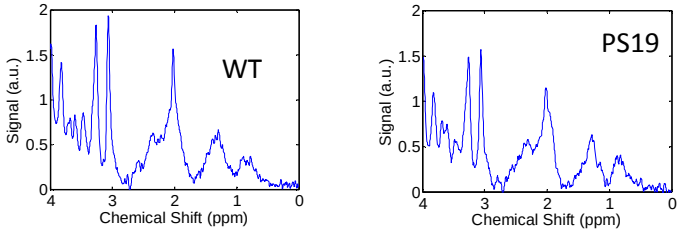
MOTIVATION: Tauopathy is a classification of dementias, including Frontotemporal dementia (FTD) and Alzheimer's disease (AD). Common to all Tauopathies is the intracellular accumulation of hyper-phosphorylated tau protein (h-p-tau), a microtubule binding protein. Fibrillar aggregates of h-p-tau accumulate in dendritic spines and disrupt the function of neurotransmitters [1]. Glutamate is a wide-spread excitatory neurotransmitter, and has been shown by magnetic resonance spectroscopy (MRS) to decrease in the hippocampus of Alzheimer's disease patients [2]. It has also been recently shown that brain glutamate levels can be mapped at high spatial resolution using chemical exchange saturation transfer imaging (GluCEST) [3]. In this study, for the first time we used GluCEST and ^{1}H MRS to characterize the glutamate changes between normal mice and a mouse model of Tauopathy.

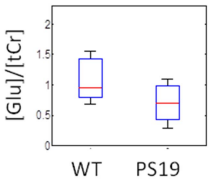
METHODS: All animal studies were approved by the university's IACUC. The mouse model we are studying is the PS19 line of the P301S transgenic mouse, overexpressing mutated human tau common in FTDP-17 patients, developed by Yoshiyama *et. al.* [4]. MRS and GluCEST maps were acquired during the same session from wild-type (WT, n=7) and transgenic PS19 (n=9) mice, aged 18-23 months. Imaging was performed on a 9.4T spectrometer (Varian Inc., Palo Alto, CA). MRS was performed using the PRESS pulse sequence (TR/TE 3000/14ms, 384 averages), with VAPOR water suppression. GluCEST imaging was performed using a custom-programmed segmented RF spoiled gradient echo centric phase encode readout pulse sequence with a frequency selective continuous wave saturation preparation pulse. CEST images were collected using a 1 second saturation pulse at peak B_1 of 250 Hz for the frequencies ± 2.4 – 3.6 with steps of 0.2ppm from water resonance. B_1 and B_0 maps were acquired to correct inhomogeneities in the final GluCEST map. All images and spectroscopic data were processed as described previously (see Cai *et. al.* for further methods).

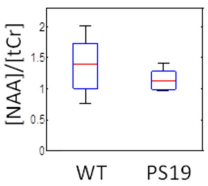
RESULTS:

Figure 1. a) Spectra were acquired from a voxel in the hippocampus with a volume of 19mm^3. **b)** Example spectra from a WT and PS19 mouse, showing visually the decrease in Glu and NAA levels from the hippocampus.





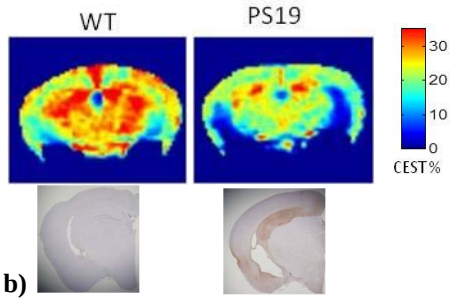


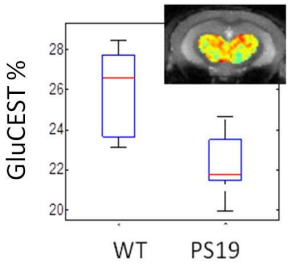


c)

c) Quantification of [Glu]/[tCr] by ^{1}H MRS reveals a decrease in the hippocampus of PS19 mice (0.70 ± 0.15, mean ± std) compared to WT (1.1 ± 0.18) . The metabolite NAA is also decreased in the PS19 mice (1.14 ± 0.086 vs. 1.38 ± 0.23). A decrease in NAA, as a marker of neuron function, indicates neuronal loss in the hippocampus of PS19 mice, which is observed grossly in histology (Fig 2b).

Figure 2. a) GluCEST maps clearly show lower GluCEST levels in the PS19 mouse brain compared to WT. **b)** PS19 mice with low GluCEST have severe tau pathology, as shown in the level of h-p-tau staining (brown) by the AT8 antibody. **c)** Average GluCEST contrast of the hypo-thalamus and thalamus region is significantly decreased in the PS19 mice (22.3 ± 0.76 % vs. 26.3 ± 1.03 %, p≤0.001, mean ± std).





CONCLUSION: Both ^{1}H MRS and GluCEST detected decreased levels of glutamate in PS19 mice with severe tau pathology. A similar trend in glutamate has been reported in mouse models of amyloid plaques [5], and AD patients [2]. Interestingly, GluCEST levels are depressed across the entire brain, not only localized to areas of severe tau pathology. The observed decrease in GluCEST can be due to differences in glutamate levels as well as exchange rates. Further studies on young mice will determine whether changes in glutamate can be detected by GluCEST before tau pathology is apparent by immunohistochemistry.

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