Expression of ptau in hippocampal tissue and navigational abilities in mice

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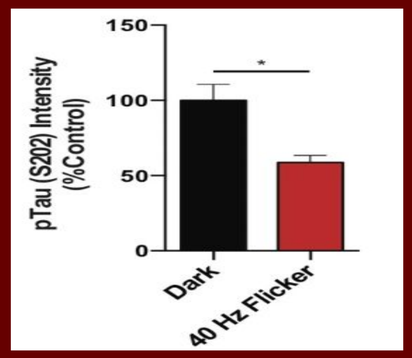
Introduction

Alzheimer's Disease is a devastating ailment that progressively reduces neurological function and is a primary cause of dementia. This disease primarily affects behavior, memory and cognitive processes, eventually becoming serious enough to severely impediment the execution of daily tasks . In Alzheimer's patients, spatial navigation, and spatial reorientation specifically, is impaired, and is often one of the first abilities to be impaired by the condition. Alzheimer's disease is characterized by the accumulation of both amyloid-beta and tau protein in the brain. One issue with Alzheimer's treatment is that these proteins have often accumulated in large amounts before the onset of symptoms, resulting in a diagnosis only after serious damage has occurred in the brain (Allison, et al. 2019).

In mice, this same spatial impairment is observed. We used 6 month 3xTg-AD female mice which accumulate both Tau and Amyloid-Beta. However, in these mice, Tau accumulations specifically have been observed to correlate positively with behavior. Research aimed at protein level reduction has found that inducing a 40 Hz rhythm can clear accumulations of Amyloid-Beta and Tau proteins (Singer, et al. 2018). Additionally, these stimuli were shown to result in an increase of glial cell activation. This finding is significant since astrocytes, a type of glial cell, clear out waste and toxic materials from the brain to assist in neurological function. Using 40 Hz optogenetics to induce this rhythm in the hippocampus in 3xTg-AD, we anticipated a lowering of Tau in our subjects and a correlating improvement in behavior.

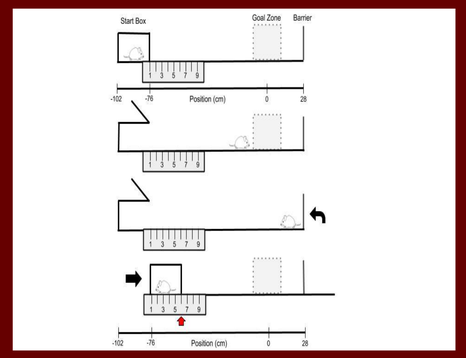


Iaccarino et al, 2016

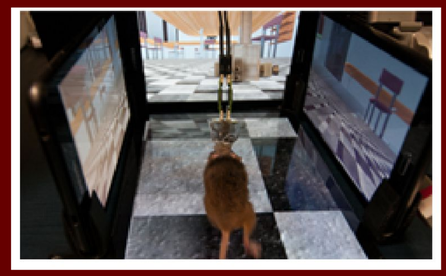
Recording array with fiberoptic implant

Methods

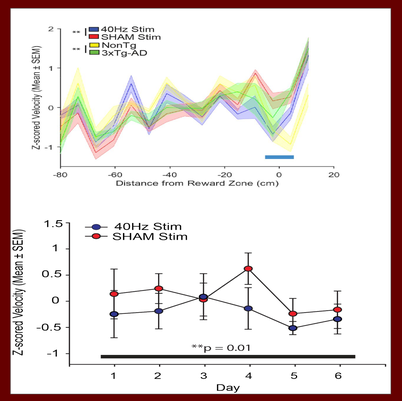
- Surgery was performed on mice subjects putting stimulating electrodes in their head targeting the medial forebrain bundle to deliver electrical stimulations during experiments to reward behavior.
- Surgery also added a fiberoptic fiber targeting the left hippocampus of mice
- Additionally subjects received a recording array implant to document sleep classification.
- Using AAV to target left hippocampus so that hippocampus expresses Channel Rhodopsin 2 that can be activated by the fiber optic implant, allowing us to drive activity in the region
- Recording and sleep procedures: Depths of tetrodes were adjusted to target specific brain regions, adjusted with reference to a reference tetrode positioned in the corpus callosum. For all mice, sessions were organized in a 60 minute sleep period, 20 minute behavioral task, then another 60 minutes of sleep per each session. After the second sleep session, mice underwent an hour of optogenetic stimulation of either 40Hz or sham. Mice were placed in a box and plugged in to initiate sleep, and mouse tracking was accomplished via a cap on their heads covered in reflective tape. Proportional still sleep time was assessed, and for recording array mice, still time was further broken down into slow wave sleep (SWS) or rapid eye movement (REM) sleep.



The linear track task includes an unmarked reward zone in each trial, but the starting location changes between trials. The changing start location forces the mouse to rely on distal cues from surroundings to orient, rather than combining with self-motion cues to provide position estimates.



Mouse performing virtual reality navigation task. Like the linear track, this task includes unmarked reward zones with changing visuals, forcing the mouse to rely on distal cues.

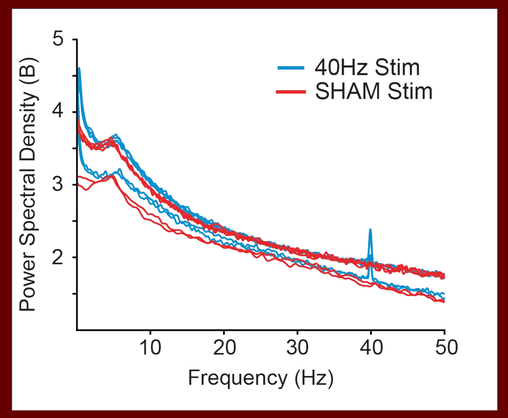


Average z-scored velocity as a function of distance from reward zone

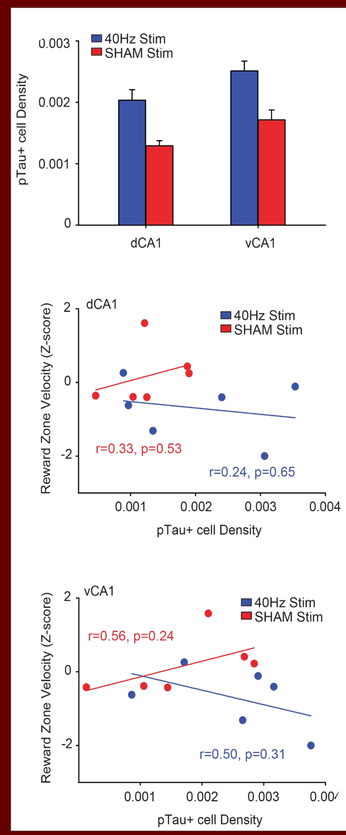
Results

- ptau + cell density did not significantly correlate with navigation performance the next day in either region of CA1 for either 40Hz stimulated mice (rs>0.50, ps>0.31) or SHAM stimulated mice (rs>0.56, px>0.24)
- raw densities are: dCA1 t(10)=1.455, p=0.177. vCA1 t(10) = 1.319, p=0.217

Power Spectral Density Graph



Dorsal and Ventral Ptau Density



Conclusion

- Alzheimer's disease is characterized by buildup of ptau and amyloid beta in neural tissue, often accumulating and causing severe damage before detection
- In an attempt to reduce protein levels and restore tissue health, 40 Hz stimuli have been shown to be effective
- Mice were given surgical implants to send optogenetic stimuli to specific brain regions during completion of navigational tasks
- 40 Hz stimulation did not reduce pTau levels in dorsal or ventral hippocampus
- No correlation was discovered between behavior and ptau levels in either subject group

Acknowledgements and References

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