Bilateral focused ultrasound-induced blood-brain barrier opening improves spatial memory in the 3xTg Alzheimer's mouse model.

Maria Eleni Karakatsani[1], Maria Murillo[1], Robin Ji[1], Tara Kugelman[1], Karen Duff[2] and Elisa Konofagou[1,3], [1]Department of Biomedical Engineering, [2]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, [3]Department of Radiology, Columbia University, New York, NY 10032, US

Background, Motivation and Objective

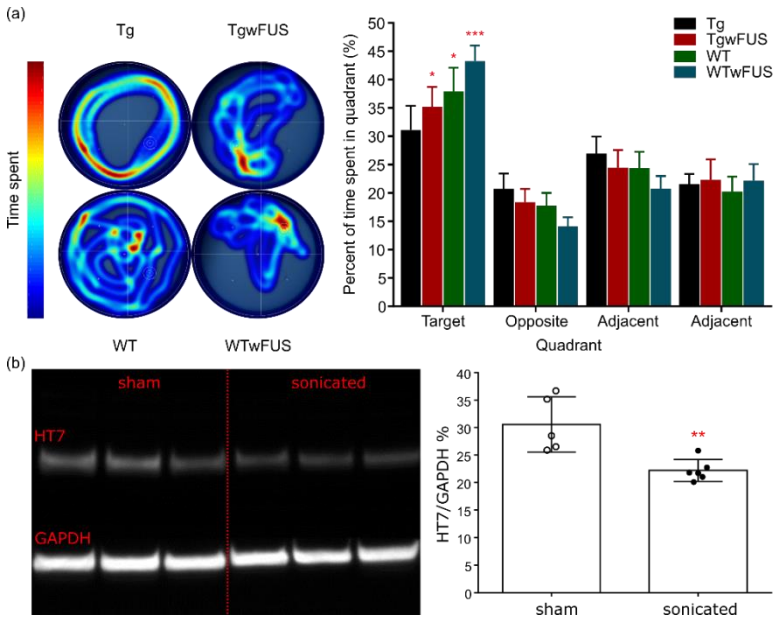
Focused ultrasound (FUS) has been proven to eliminate amyloid plaques and reduce the hyperphosphorylated tau protein in the hippocampal formation of different mouse models of Alzheimer's disease (AD) by opening the blood-brain barrier and triggering an immune response. Given the beneficial effects of FUS on isolated AD pathologies, it is essential to investigate its functional and morphological outcomes on brains bearing both pathologies simultaneously.

Statement of Contribution/Methods

Eleven transgenic mice of the 3xTg line (14 months old) and eleven age-matched wild-type animals received bilateral sonications encompassing the hippocampus once per week for four consecutive weeks. The week following the last treatment, sonicated animals and control littermates underwent behavioral testing in the Morris water maze (MWM). All mice received a 5-day training familiarizing with reaching the escape-platform within 60 seconds. Following the training, the platform was removed and the amount of time spent in each MWM quadrant was quantified. The following week all animals were sacrificed and their brains processed for biochemical analysis and immunohistochemistry.

Results/Discussion

Animals that received FUS spent significantly more time in the quadrant where the platform was located: on the order of 35.18% for the transgenic and 67% for the wild-type animals relative to the opposite sector. The functional improvement correlated well with the 27.2% decrease in total tau levels following the FUS-induced BBB opening as shown by the Western Blot quantification. Bilateral sonication significantly improved the spatial memory of the transgenic animals with complex AD pathology. FUS was shown to improve short-term memory performance both in the absence and presence of human-mimicking AD pathology associated with pathological protein reduction in the brain.



(a) Spatial distribution heatmaps of the time spent in each quadrant and the associated quantification. (b) Western blot analysis using the HT7 antibody that binds to tau protein and GAPDH as the control protein. Quantification of the mean intensity of each HT7 band over the corresponding GAPDH band shows significant decrease of the pathological protein following sonication.