GluCEST MRI Detects of Sex-Specific Glutamate Changes in Subregions of Hippocampus in Early-Stage Mouse Model of Alzheimer's Disease

Narayan Datt Soni[1], Anshuman Swain[1,2], Halvor Juul[1], Quy Cao[3], Mohammad Haris[1], David A. Wolk[4,5], Virginia M-Y Lee[5,6], John A. Detre[7], Ravi Prakash Reddy Nanga[1], and Ravinder Reddy[1]

[1]Department of Radiology, CAMIPM, PSOM, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Bioengineering, School of Engineering and Applied Sciences, University of Pennsylvania, , Philadelphia, PA, USA; [3]Department of Biostatistics, PSOM, University of Pennsylvania, , Philadelphia, PA, USA; [4]Center for Cognitive Neuroscience, University of Pennsylvania, , Philadelphia, PA, USA; [5]Alzheimer's Disease Research Center, PSOM, University of Pennsylvania, , Philadelphia, PA, USA; [6]Center for Neurodegenerative Disease Research, PSOM, University of Pennsylvania, , Philadelphia, PA, USA; [7]Department of Neurology, PSOM, University of Pennsylvania, , Philadelphia, PA, USA

INTRODUCTION: Regional glucose hypometabolism resulting into glutamate loss has been shown as one of the characteristics of Alzheimer's disease (AD). Since impact of AD varies between sexes, we utilized GluCEST MRI for high-resolution spatial mapping of cerebral glutamate and investigated subregional changes in a sex-specific manner.

METHODS: Eight-month-old male and female $APP^{NL\text{-}F/NL\text{-}F}$ (AD: n=36) and wild-type (WT: n=39) mice underwent GluCEST MRI, followed by ^{1}H-MRS in hippocampus and thalamus/hypothalamus using 9.4T preclinical MR scanner.

RESULTS: GluCEST measurements revealed significant ($p \leq 0.02$) glutamate loss in entorhinal cortex (8.7%), hippocampus (11.3%), and hippocampal fimbriae (19.2%) of male AD mice. Similar loss of hippocampal glutamate in male AD mice (11.2%; p=0.01) was also observed in ^{1}H MRS. Apart from glutamate ^{1}H MRS results also revealed significant reductions in the levels of NAA, total creatine, and taurine in male AD mice. Surprisingly, female AD mice did not exhibit any perturbations in GluCEST and ^{1}H MRS findings. We additionally performed IHC studies which revealed a higher level of GFAP in the hippocampus and cerebral cortex of male AD mice. While it unaltered in female AD mice.

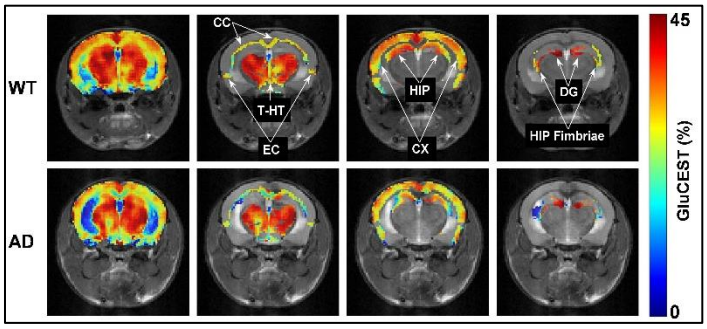

Fig 1. Representative GluCEST maps from WT and AD

DISCUSSIONS: GluCEST MRI detected glutamate reductions in the fimbria and entorhinal cortex of male AD mice, which was not previously reported. These two regions are associated with relay of signal between hippocampus and cerebral cortex and altered glutamate levels suggest impaired signaling and could be associated with impaired cognitive functions in AD. Reductions in levels of NAA, taurine and tCr in male AD mice indicate loss of neurons, neuroplasticity, and compromised brain energetics due to disrupted Creatine/phospho-Creatine exchange, respectively. Resilience in female AD mice against these changes indicates an intact status of cerebral energy metabolism, which could be attributed to extensively studied neuroprotective functions of estrogen.

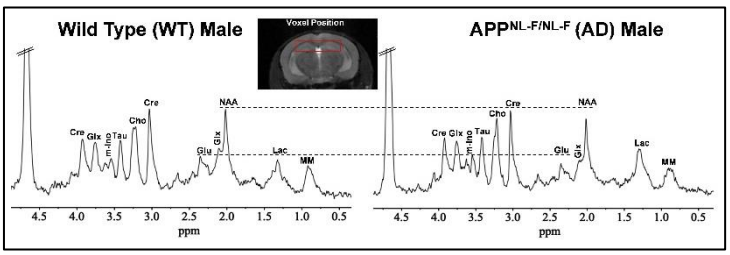

Fig 2. ^{1}H MR spectra from hippocampus of a WT and an AD mouse.

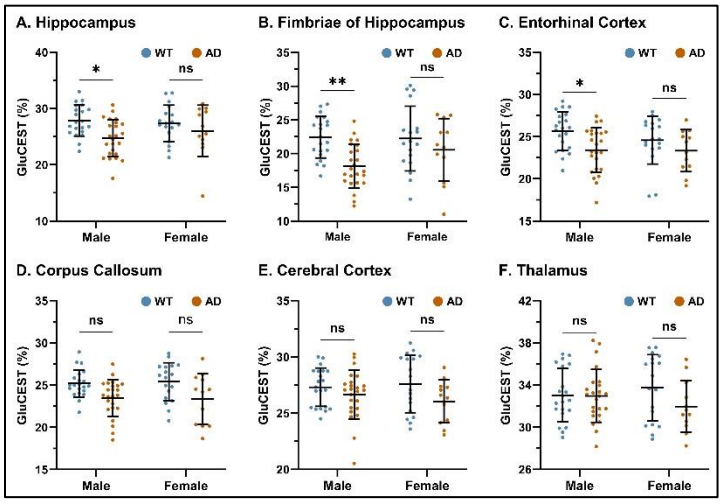

Fig 3. Regional GluCEST (%) from WT and AD mice.

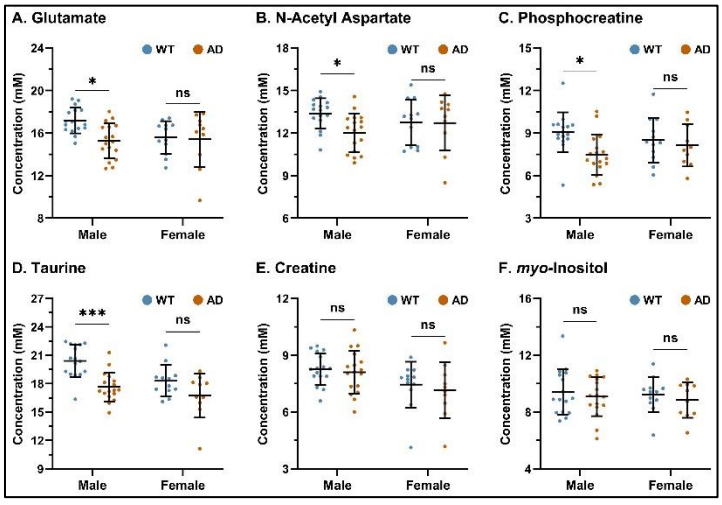

Fig 4. Hippocampal neurometabolites in WT and AD mice.

Acknowledgements: This study was supported by NIBIB of the NIH through Grant number P41EB02946 and the NIA through Award number R01AG063869.