**INTRODUCTION**

Alzheimer’s disease (AD) is the only leading cause of death that is still on the rise. In order to understand the pathology and progression of AD, our lab has developed a mouse model (APPSwDI/NOS2-/-; CVN-AD) that mimics AD pathology. This model demonstrates the four major pathologies of AD – amyloid deposition, neuron loss, neurofibrillary tangle formation, and behavioral deficits. While AD is most strongly associated with plaques and tangles, myelin has been shown to be disrupted in patients with AD.

First, we studied changes in white matter tracts in the CVN-AD mouse model. If myelin is broken down, then the volume of these regions should be altered as well as the diffusion properties. Thus, through Diffusion Tensor Imaging (DTI), we examined changes in volume and changes in a diffusion parameter, known as fractional anisotropy (FA). FA represents the degree of directionality of water diffusion; a lower FA value likely reflects poor white matter myelination because diffusion is not well restricted by the myelin sheet.

Our second objective was to investigate a mechanism underlying the white matter alterations. We hypothesize that alterations in the methionine cycle contribute to the pathology and progression of AD, and that many gene expression changes may code for enzymes to increase homocysteine levels and decrease methionine levels, suggesting impaired homocysteine metabolism.

**RESULTS:**

**Voxelwise DTI**

Implicated brain regions are the same ones affected in AD patients!

**Results: Summary of Dysregulations**

Viewing the dysregulations in the context of the methionine cycle suggests...

**CONCLUSION**

- Changes in volume and fractional anisotropy were observed in the brain of CVN-AD. These changes indicate white matter atrophy in the CVN-AD model.
- The areas of WM atrophy include known AD circuitry, such as the hippocampus and fornix, validating the CVN-AD model.
- Dysregulations of genes involved in the methionine cycle were observed in the CVN-AD model.
- We speculate that the dysregulated genes may be coding for enzymes that increase homocysteine and divert methionine, altering myelination and contributing to pathology.

**METHODS**

- DTI: Magnetic resonance imaging of the mouse brain was done using a 9.4T magnet, utilizing a diffusion tensor imaging protocol with 12 directions, TE=12ms, TR=100ms, b=1.5x10^4 s/mm^2. Diffusion pulse width = 1.3 ms, separation = 6.4 ms, gradient amplitude = 1200 mT/m. A reference mouse brain atlas provided priors for automated segmentation of 38 regions. We used advanced normalization tools for image registration using the DWI and FA contrasts. SurfStat® was used for voxellevel statistics.

**REFERENCES**