DTI-based Hemispheric Differences in the 3xTgAD Model of Alzheimer's Disease

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Introduction:

Alzheimer's Disease (AD) is the most common form of dementia, characterized by memory loss, changes in behavior and cognitive difficulties[1]. Diffusion Tensor Imaging (DTI) is a Magnetic Resonance Imaging (MRI) tool used to study restricted water movement in an anisotropic environment. Pairing DTI with network theory provides a method to study structural changes in brain connectivity.

Methods:

Sample prep:

- *Ex vivo* brains preserved in 4% paraformaldehyde from the 3xTgAD triple human-transgene mouse model (Dr. Aaron Wilber's Psychology lab)
- Washed in physiological saline for 24 h prior
- Immersed in Fluorinert (3M, Corp) within a 10-mm glass NMR tube prior to scanning

DTI data acquisition:

- ^{1}H MRI performed at 11.75 T (500 MHz)
- Multi-slice, diffusion-weighted 2D spin-echo sequence
- Resolution = 100 x 100 x 500 µm
- 18 diffusion encoding directions & 4 unweighted acquisitions
- TE / TR = 30 ms / 2 s
- Δ=11 ms and δ=3ms with 15 averages
- Approximate acquisition time = 17 h

Post-processing and data analysis:

- Data was zero-filled & sine-squared filtered prior to FT
- DSI Studio[2] for full anisotropic characterization
- 14 regions of interest (ROI) in the cortical area and two segmented nodes for the left and right hippocampi
- Segmented nodes were categorized into 5 separate regions: Piriform, Temporal, Parietal, and Left & Right Hippocampus (Fig. 1)
- Tracts were reconstructed with the following limits:
  FA $\geq$ 0.1, Angular threshold $\leq 60^{\circ}$, Seeds $\leq 10^6$
  Min tract length = 1 mm, Max tract length = 25 mm
- Individual ROI were assessed to study pathological and anatomical structure changes compared to WT models[3]

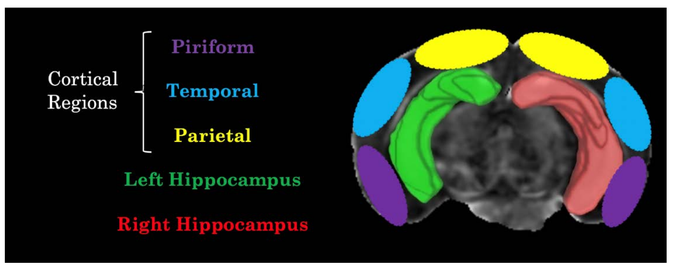

Figure 1: Regions of the brain used for node categorization

References:

1. U.S. Department of Health & Human Services.
2. Yeh F, et al. 2013. 8(11): e80713.
3. Lo CY, et al. 2010. J Neuroscience 30(50):16876-16885.

Certain **network metrics** demonstrate **phenotypic** and **hemispheric** differences for transgenic AD mouse brains

Figure 2: Hemispheric differences of betweenness centrality across age and within phenotype

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Results:

- Tract counts were imported into Gephi for extracting graph properties including: Degree & Weighted degree, Clustering Coefficient, Closeness (betweenness, closeness, eigenvector & harmonic) and Eccentricity

- Betweenness centrality increases in the right hemispheric piriform region (dark blue) of the AD model while a decreasing trend is seen in the left hemispheric piriform region (light blue) of the WT over age (**Fig. 2**)
  - ✓ Notably, scale differences across phenotype are drastically different, potentially due to the degeneration of neurons requiring a secondary bridging point and resulting in longer characteristic path lengths

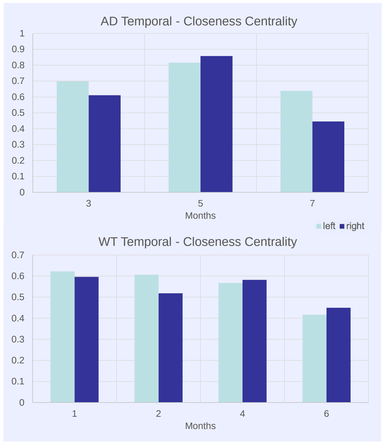

Figure 3: Hemispheric differences of closeness centrality across age and within phenotype

- Temporal hemispheric and phenotypic differences are not observed for closeness centrality; however, a general decrease for the highest age is observed in both 3xTgAD and WT samples (**Fig. 3**)
  - ✓ This decrease with age may reflect paring of neural connections during maturation; however, closeness centrality also may highlight differential time courses or connection remodeling for AD vs WT specimens

Conclusions:

- By coupling DTI and network theory, this research can be utilized as a method to detect and study progression of AD and other neurodegenerative diseases
- Future work will extend this study by incorporating male data to investigate sex differences as a function of age across phenotypes

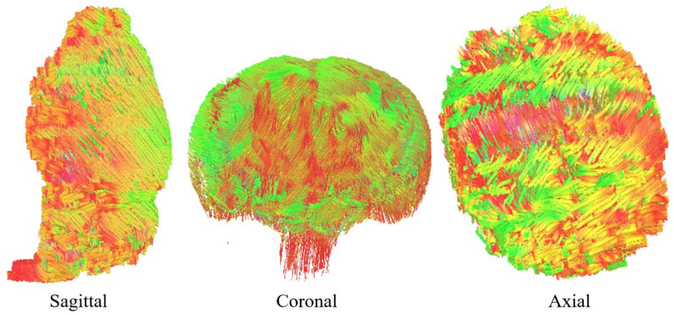

Figure 4: Tractography-based representation of neuronal paths in a mouse brain

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