Background Genetics Impacts Changes in White Matter and Hippocampal Microstructure in a Mouse Model of Familial Alzheimer's Disease (5xFAD)

Grudny, M. (UF, Psychiatry); Neuner, S. (The Jackson Labs); Dunn, A. (The Jackson Labs); Pompilus, M. (UF, Psychiatry); Febo, M. (UF, Psychiatry) and Kaczorowski, C.C. (The Jackson Labs)

Introduction

The heterogeneous phenotypical expression of Alzheimer's disease (AD) among the population, even in individuals with aggressive mutations thought to cause neuronal dysfunction and significant impairments in thought, mood and memory, strongly suggests an interaction between such mutations and background genetics. Kaczorowski's ongoing research is paving the way to understanding how intrinsic genetic factors impact the functional trajectory of cognitive aging and AD [1]. Recent work indicates the level of phenotypic expression of AD cognitive impairment in mice harboring mutations to the amyloid precursor protein (APP), presenilin-1 and -2 (PSEN1/2) is determined to a significant degree by background genetics. Thus, genetic diversity may contribute to the heterogeneity in the expression of AD mutations and may be key to revealing factors controlling vulnerability and resilience in AD and other neurodegenerative diseases. Here, we further explore the impact of background genetics on detailed diffusion imaging markers of brain tissue microstructure in the 5xFAD mouse.

Methods

Aged (>14 m.o.) male and female 5xFAD mice on either C57BL/6 or D2 background, and their sex- and age-matched wildtype counterparts, were imaged on an 11.1 Tesla MRI scanner with a Resonance Research Inc. gradient set (RRI BFG-113/60, maximum gradient strength of 1500 mT/m at 150 Amps and a 130 μs risetime) and controlled by a Bruker Paravision 6.01 console. An in-house 2.0 x 3.5 cm quadrature surface transmit/receive coil tuned to 470.7MHz (^{1}H resonance) was used for B1 excitation and signal detection (AMRIS Facility, Gainesville, FL). Diffusion weighted scans were acquired using a 4-shot, 2-shell spin echo planar diffusion imaging (DTI EPI) sequence in Bruker Paravision, with TR = 4 seconds, TE = 19 ms, number of averages = 4, gradient duration δ = 3 ms, diffusion time Δ = 8 ms, 54 images with 3 different diffusion weightings, two b=0, 6 directions with b=600 s/mm^2, and 46 directions with b=2000 s/mm^2. Image resolution was 128 x 96 and 17 slices (resolution: 0.117 mm x 0.117 mm x 0.7 mm). Images were processed for DTI and Neurite Orientation Dispersion and Density Imaging (NODDI) [2] (Fig. 1).

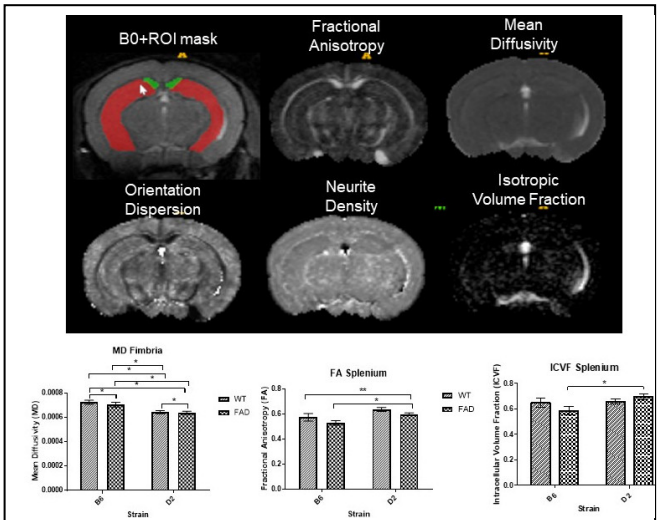

Fig.1. Genetic background impacts the effects of Alzheimer's disease mutations on diffusion MRI metrics. (top) Representative DTI and NODDI maps. (Bottom) Strain x FAD mutations interaction on FA, MD and neurite density (intracellular volume fraction). Two ANOVA (alpha =0.05)

Results and Discussion

Two-way ANOVA indicates a significant strain x mutation interaction in white matter regions, such as the fimbria and splenium, for DTI metrics - mean diffusivity (MD) and fractional anisotropy (FA) ($p < 0.05$). While FAD mutations reduced FA and MD in both B6 and D2 mice, overall FA and MD values differentiated these strains. This suggests significant microstructural white matter differences between the strains that are further impacted by the presence of the AD mutations. NODDI metrics did not show major strain nor mutation differences, except for differences in neurite density (Fig. 1) that were dependent on the presence of the FAD mutations. Trends were present, however, and differences due to sex might be important in future research.

Conclusions

Our results show a significant impact of background genetics on the effect of FAD mutations on *in vivo* diffusion MRI metrics. We are currently finalizing analysis for regions of interest based on registration to a segmented atlas of the mouse brain.

Acknowledgements

The National High Magnetic Field Laboratory is supported by the National Science Foundation through NSF/DMR-1157490/1644779 and the State of Florida. Supported also by NIH/NIA grant R01AG054180 to Catherine Kaczorowski.

References

[1] Neuner, S.M., *et al*., Neurobiol Aging, **46**, 58-67 (2016). [2] Zhang, H., *et al*., Neuroimage, **61**, 1000-16 (2012).