Investigating the synergistic relationship between recurrent seizures and Alzheimer's Disease

Harutyunyan A[1], Anderson A[2], Kwan P[1,2,3], Jones NC[1,2,3]

[1]Department of Medicine, Royal Melbourne Hospital, University of Melbourne, [2]Department of Neuroscience, Monash University, [3]Department of Neurology, Alfred Health

Introduction

- There is increased prevalence of epilepsy in patients with Alzheimer's Disease (AD)[1]
- Epilepsy and AD are thought to have a **bi-directional association**[2]
- The primary mode of action and mechanism of the association remains unknown
- **5xFAD** is a transgenic mouse model harbouring five AD-related mutations. It exhibits **amyloid pathology, spatial memory impairment** and **spontaneous seizures**[3]
- This study aimed to investigate the mechanism of the **bi-directional association** between seizures and AD pathology and identify **key molecular pathways**

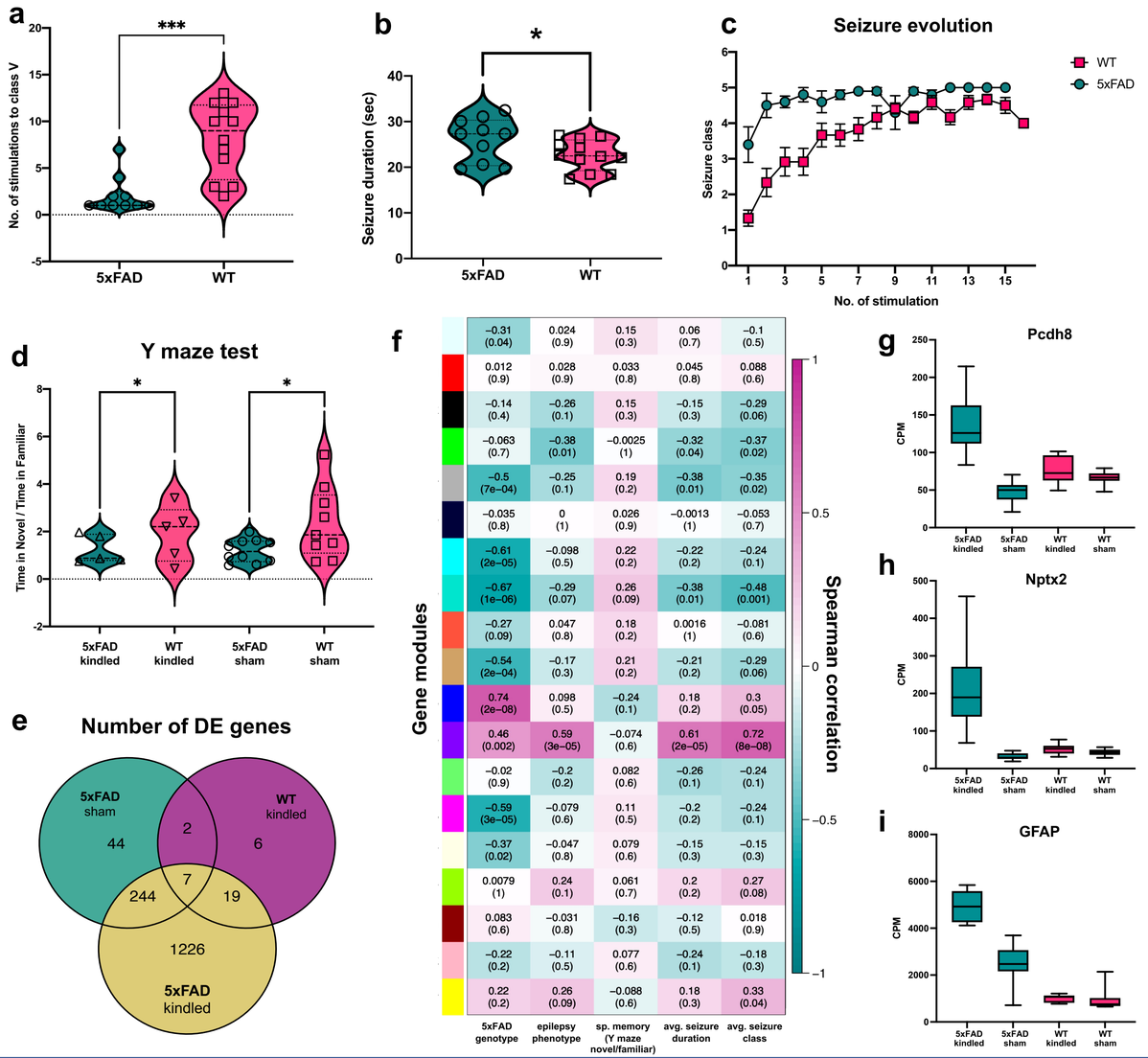
Methods

- **6 month-old 5xFAD** mice **(N=20)** and **WT** littermates **(N=22)** underwent electrical amygdala kindling to achieve recurrent seizure phenotype or were treated as sham
- Kindling rate, seizure severity and spatial memory were compared across **kindled** and **sham 5xFAD** and **WT** groups (Mann-Whitney test and balanced ANOVA)
- The gene expression profile of the **hippocampus** was examined through **RNA sequencing** analysis
- Groups of genes associated with seizures and AD were identified through **WGCNA**

Results

- The number of **kindling stimulations** required to invoke the **first class-V** seizure was **significantly (p<0.0004) smaller** for the 5xFAD group compared to WT (figure **a**)
- The 5xFAD mice had on average longer and more severe seizures (figures **b, c**)
- Both **kindled** and **sham 5xFAD** spent **less time** exploring the novel arm of the Y maze compared to the WT (figure **d**)

Results



Results

- A total of **296**, **33** and **1496 DE genes** were identified between the control (sham WT) and all other groups (non-kindled 5xFAD, kindled WT, kindled 5xFAD, respectively) (figure **e**)
- **WGCNA** identified **19 modules** of coexpressed genes
- The **Blue neuroinflammation**-associated module shows strong correlation to 5xFAD strain (figure **f**)
- The **Purple extracellular matrix**-associated module shows strong correlation to epilepsy phenotype
- Trans-synaptic adhesion molecules **Pcdh8** and **Nptx2** are **regulatory hubs** of seizure-associated module and are overexpressed in kindled 5xFAD (figures **g, h**)
- Gliosis and inflammation-related genes are highly overexpressed in kindled 5xFAD (figure **i**)

Discussion

- 5xFAD are more susceptible to epileptogenesis and seizure-induced damage
- Recurrent seizures exacerbate the already present neuroinflammation and gliosis in 5xFAD mice
- The synergistic relationship between seizures and Alzheimer-like pathology may be mediated through differential regulation of trans-synaptic adhesion molecules and immediate-early genes

References

1. Vossel, K.A., et al., *Epileptic activity in Alzheimer's disease: causes and clinical relevance.* Lancet Neurol, 2017. **16**(4): p. 311-322.
2. Stefanidou, M., et al., *Bi-directional association between epilepsy and dementia.* The Framingham Heart Study, 2020. **95**(24): p. e3241-e3247.
3. Jawhar, S., Trawicka, A., Jenneckens, C., Bayer, T. A., & Wirths, O. (2012). Motor deficits, neuron loss, and reduced anxiety coinciding with axonal degeneration and intraneuronal Aβ aggregation in the 5XFAD mouse model of Alzheimer's disease. *Neurobiology of aging*, *33*(1), 196.e29–196.e1.96E40.