The role of immediate early genes in synergistic pathology of Alzheimer's Disease and epilepsy

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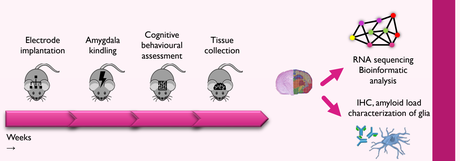
Background & Aims

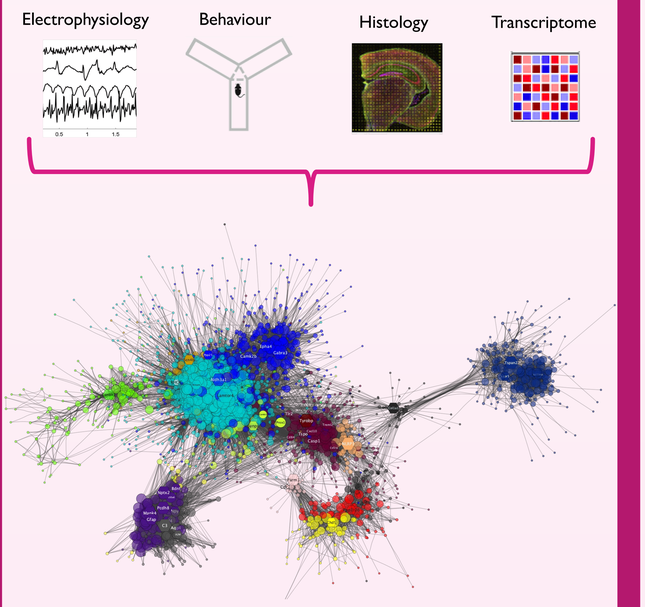
- Seizures and epilepsy frequently occur in Alzheimer's disease (AD) patients, and this co-occurrence is associated with **accelerated cognitive decline**
- We developed an animal model of **dual pathology** (epilepsy and AD) by establishing a recurrent seizure phenotype in **5xFAD** mice
- This study aimed to investigate the molecular mechanisms driving the **synergy** between recurrent seizures and AD pathology by integrating data from multiple modalities;
- Define the molecular signature of the dual pathology;
- Understand how amyloid pathology and recurrent seizures synergize & accelerate cognitive deterioration
- Identify key mediators of this synergy for pharmacological/gene therapy intervention

Experimental design

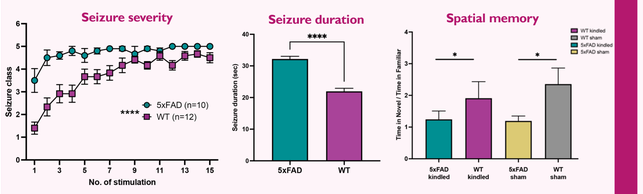
	TG 5xFAD	Control
Seizures	Kindled 5xFAD **AD + Epilepsy**	Kindled WT **Epilepsy**
Control	Sham 5xFAD **AD**	Sham WT **Double control**



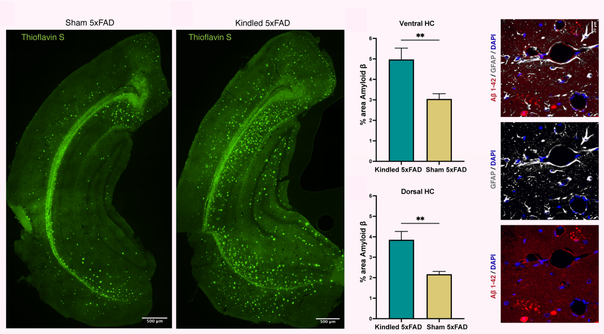
Cross-modality correlation of features & WGCNA



Hyperexcitability, accelerated kindling and impaired spatial memory in 5xFAD

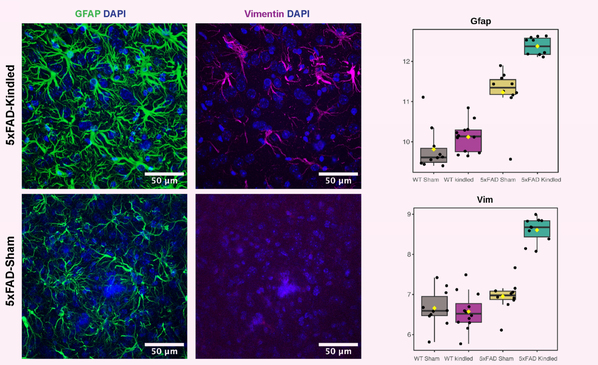


Seizure-induced increase in amyloid deposition

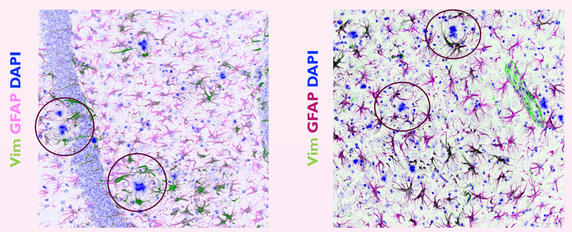


Compared to shams, the kindled 5xFAD showed enhanced amyloid deposition, evidenced by **increased amyloid plaque area** ($p<0.01$) and vascular Aβ deposition in the leptomeningeal vessels.

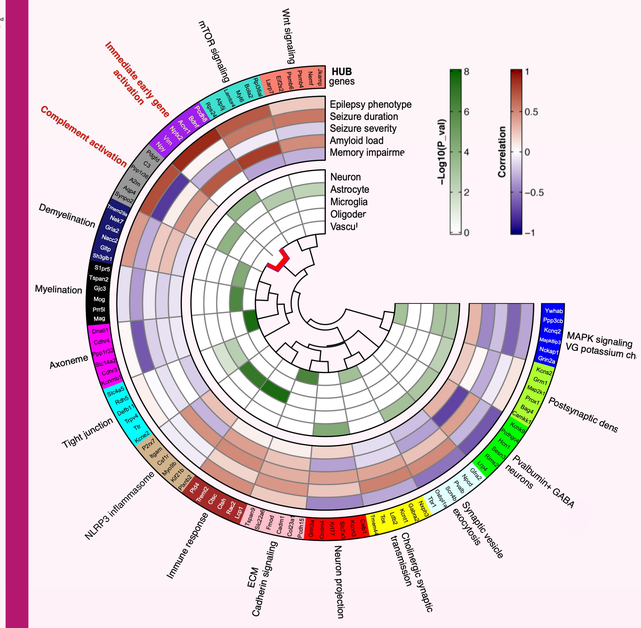
Pronounced astrogliosis in dual pathology



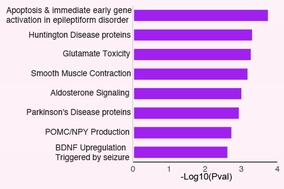
Vim+ astrocytes cluster around amyloid plaques



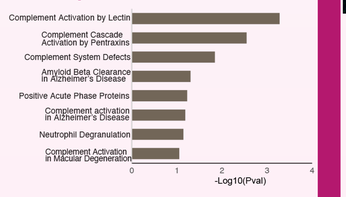
Distinct transcriptomic modules highly correlated with dual pathology



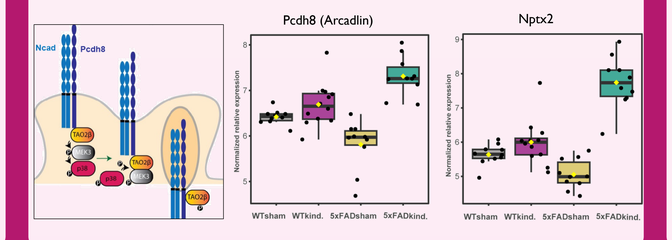
Immediate early gene activation



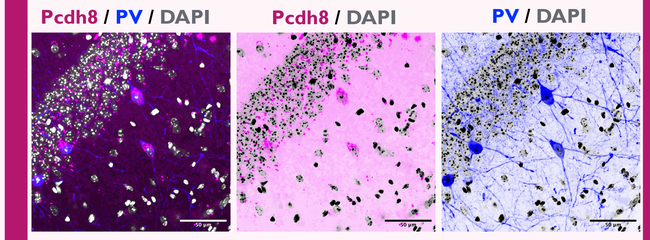
Complement activation



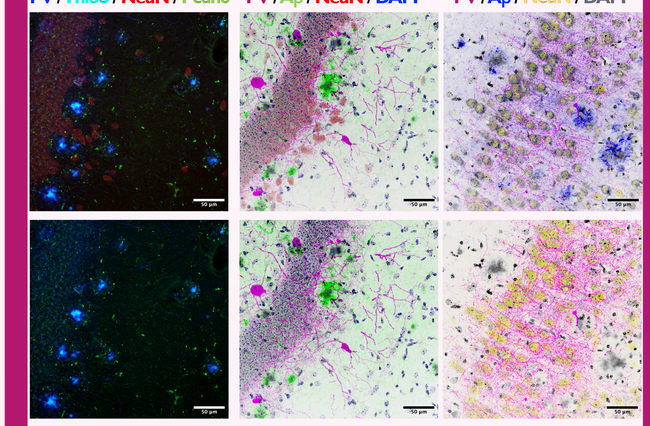
Immediate early genes Protocadherin 8 (**Pcdh8**) and Neuronal pentraxin 2 (**Nptx2**) are **regulatory hubs** of dual pathology-associated (purple) module and are highly overexpressed in kindled 5xFAD. **Pcdh8** is involved in elimination of dendritic spines, while **Nptx2** reinforces the excitatory input onto PV-interneurons.



Selective colocalization of Pcdh8+ puncta with PV-interneuron somas and dendrites



Selective localization of Pcdh8 around plaques



Discussion & Conclusions

- 5xFAD are more susceptible to epileptogenesis and seizure-induced damage than WT; recurrent seizures severely exacerbate the already present neuroinflammation and gliosis
- The synergistic relationship between seizures and Alzheimer-like pathology may be mediated through differential regulation of trans-synaptic adhesion molecules
- We propose a mechanistic paradigm where seizure-induced increase in Aβ leads to **complement-mediated synaptic damage**, while sustained overexpression of **Pcdh8** leads to reduction in dendritic spines. This in turn results in perturbations of neuronal representations and loss of encoded information. This mechanism could potentially drive the accelerated cognitive decline observed in the **seizure-prone subpopulation of AD patients.**

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