

Evaluating The Impact Of Early-life Seizures On Alzheimer's Disease Progression In A 5xFAD Mouse Model

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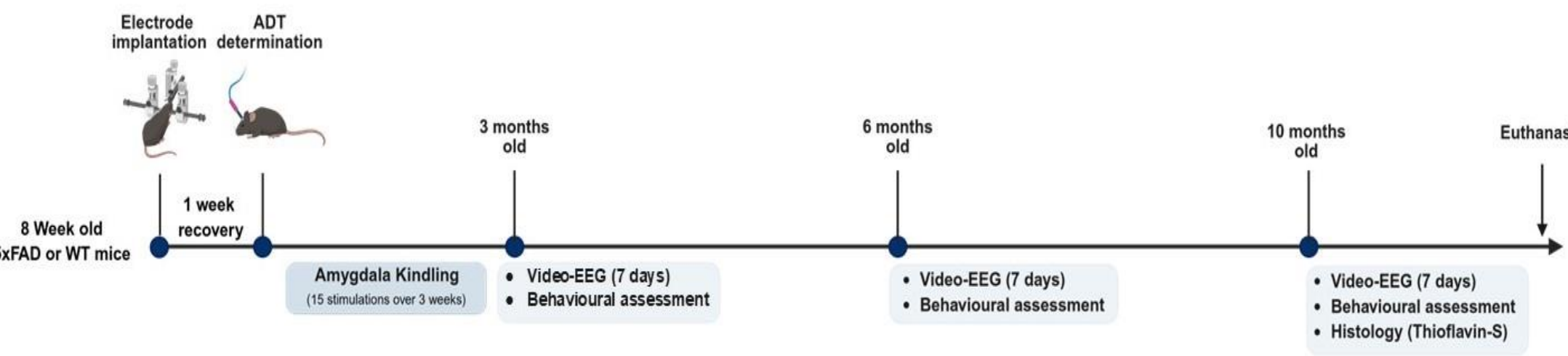


Background

Neuronal hyperexcitability and seizures are increasingly recognised as early features of Alzheimer's disease (AD) and have been associated with faster cognitive decline. However, whether early seizure activity actively accelerates AD progression or simply reflects underlying disease remains unclear. We used a longitudinal 5xFAD mouse model combined with amygdala kindling to determine the long-term effects of early seizures on network excitability, behaviour, and amyloid pathology.

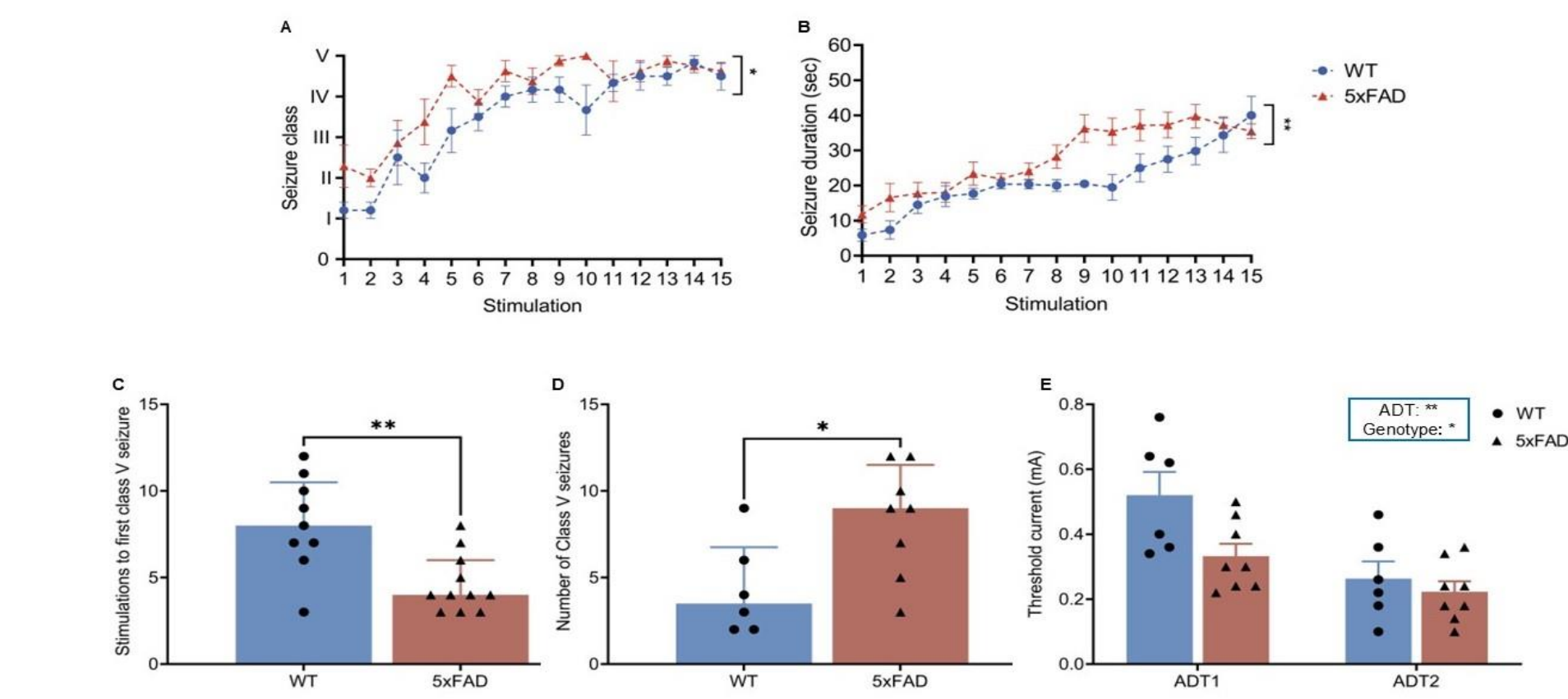
Methodology

Eight-week-old 5xFAD and wild-type (WT) littermate mice underwent stereotaxic electrode implantation followed by amygdala kindling or sham treatment. Animals were assessed longitudinally at 3, 6, and 10 months of age using one-week continuous video-EEG monitoring and a comprehensive behavioural test battery. At study completion, amyloid plaque burden in the hippocampus and cerebral cortex was quantified using Thioflavin S staining to determine the long-term impact of early seizure induction on network excitability, behaviour, and Alzheimer's disease pathology.



Results

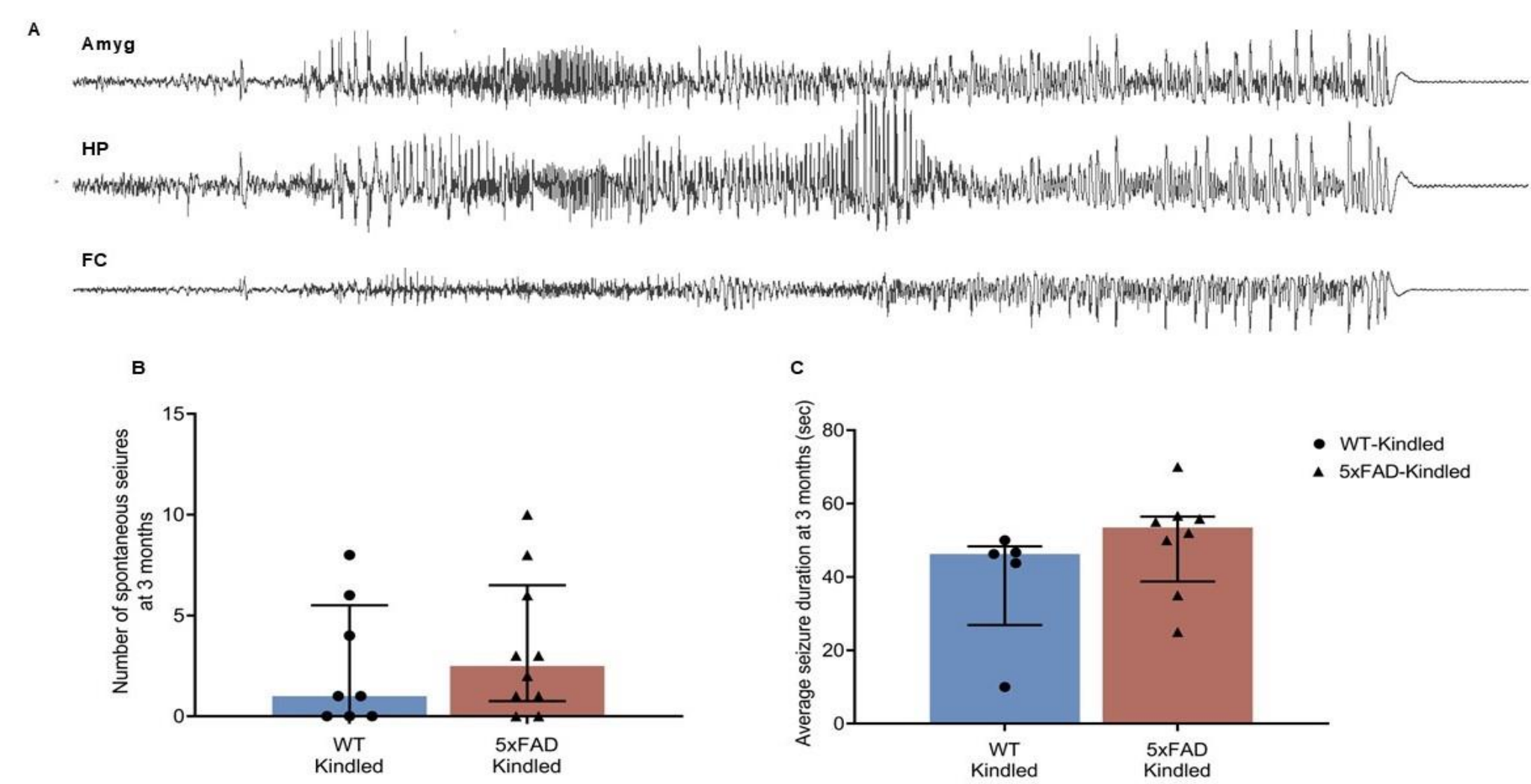
5xFAD mice exhibit increased susceptibility to kindling-induced seizures



5xFAD mice exhibited greater susceptibility to kindling-induced seizures, characterised by increased seizure severity, longer seizure duration, fewer stimulations to Class V seizures, and lower after-discharge thresholds.

Results

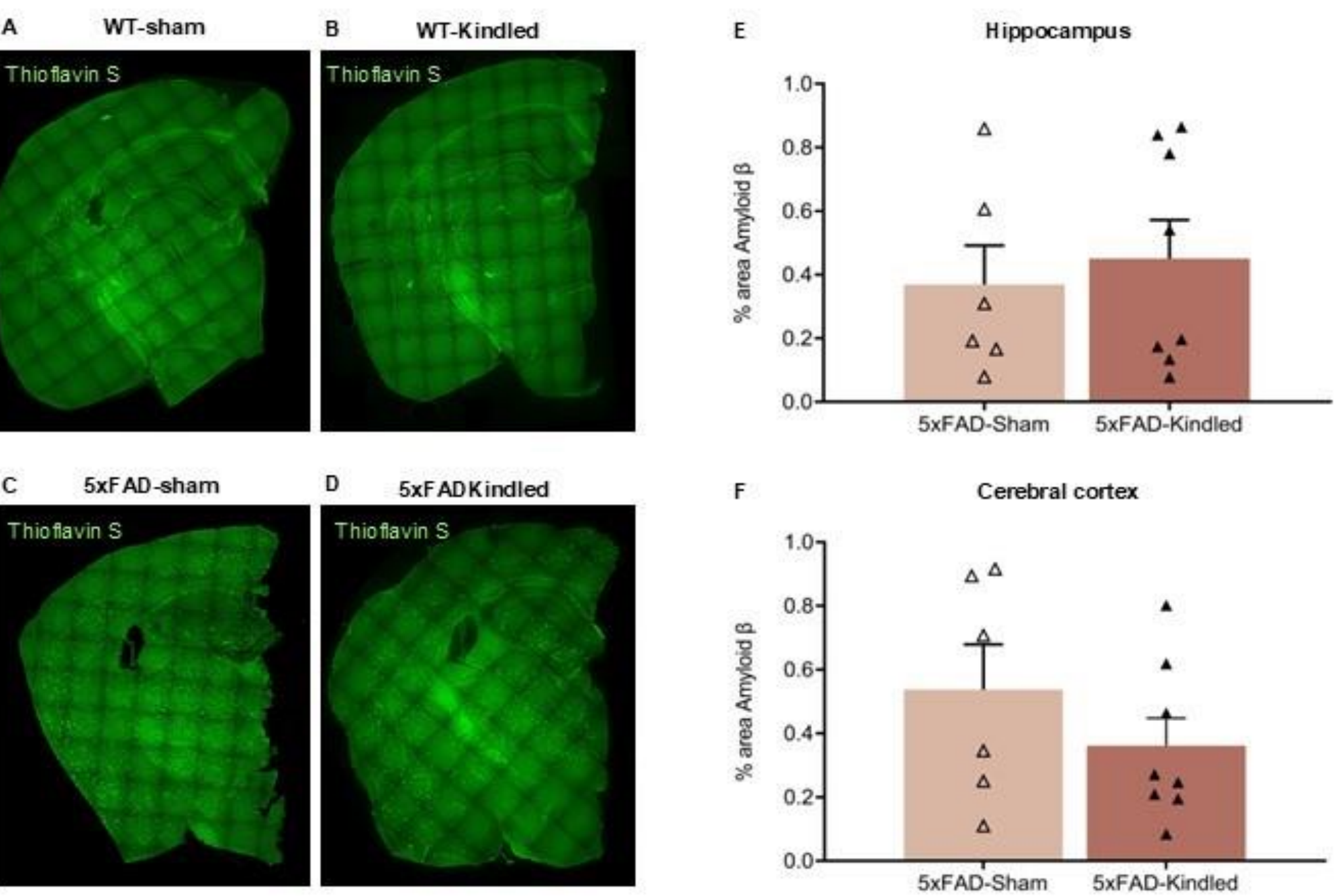
Spontaneous seizures are transient following kindling



Spontaneous seizures were detected only during the early post-kindling period (3 months) and were absent at later timepoints. Seizure frequency and duration did not differ significantly between WT and 5xFAD mice, suggesting that early seizure induction resulted in transient rather than persistent network instability.

Results

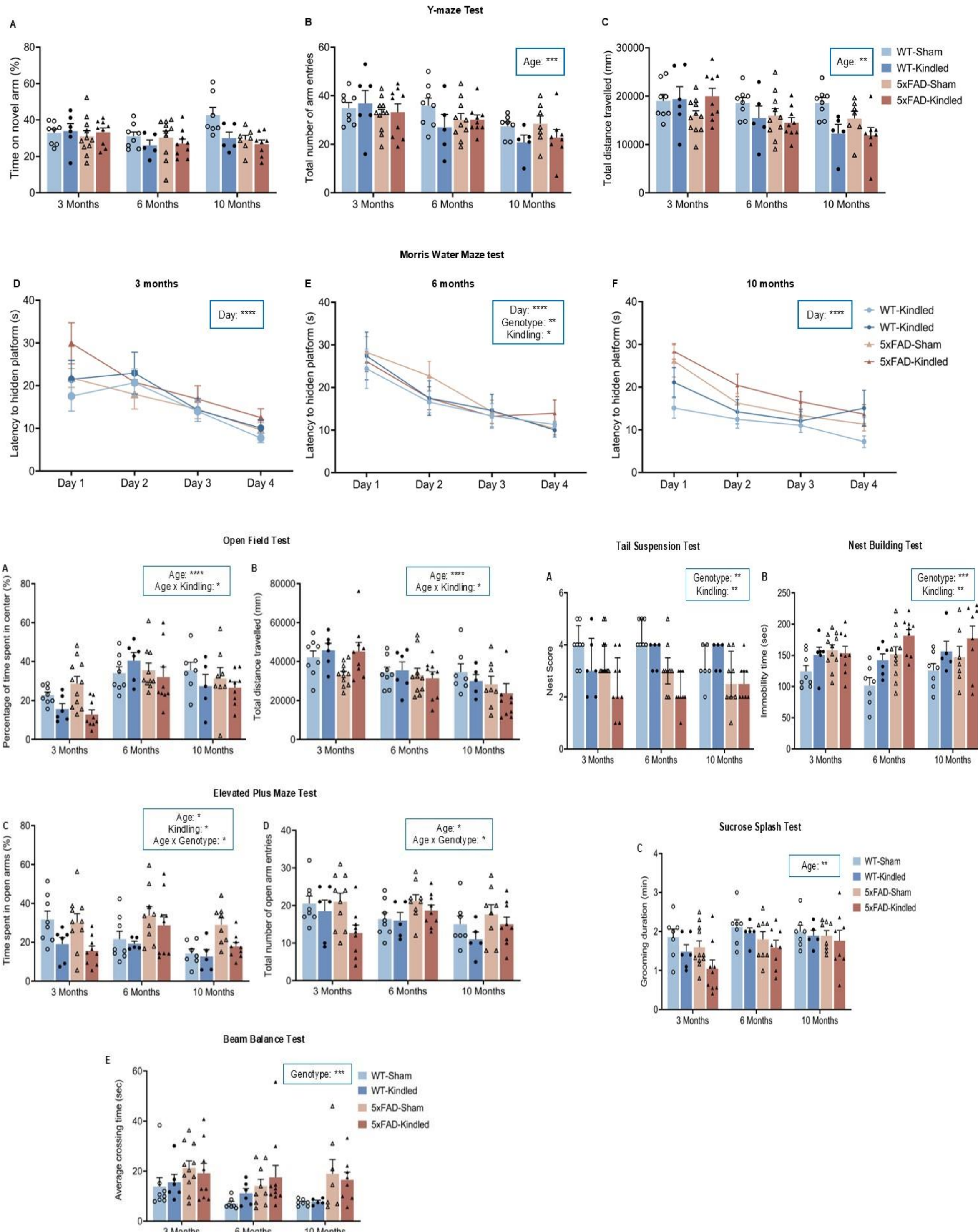
Early seizures produce selective behavioural impairments



Despite increased seizure susceptibility and selective behavioural impairments, early seizure induction did not increase amyloid plaque burden in either the hippocampus or cerebral cortex of 5xFAD mice, indicating that early seizures did not accelerate overt Alzheimer's-like pathology.

Results

Early seizures produce selective behavioural impairments



Behavioural effects were task-dependent rather than global. Kindling and 5xFAD genotype independently impaired spatial learning, stress-coping behaviour, and nest-building performance, whereas short-term spatial memory remained preserved. Age influenced locomotor activity and anxiety-like behaviour, but no evidence of synergistic behavioural deterioration between genotype and kindling was observed.

Clinical Relevance: These findings suggest that early neuronal hyperexcitability may contribute to functional impairment without necessarily accelerating amyloid pathology, supporting hyperexcitability as a potential therapeutic target in early Alzheimer's disease.