Characterising the molecular signature of epilepsy in Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disease affecting 50 million people worldwide. There is increased prevalence of epilepsy in patients with AD, and the two diseases are thought to have a bi-directional association, however, the mechanism and primary mode of action of this association remains unknown. This study aimed to understand the relationship between AD and seizure susceptibility and to characterise the molecular signature of epileptogenesis in the setting of AD. Transgenic 5xFAD mice (N=20) and WT littermates (N=22) underwent electrical amygdala kindling to induce epilepsy phenotype, or were treated as sham (no epilepsy). Kindling rate, seizure severity and cognitive behavioural performance were compared across the kindled and sham 5xFAD and WT mice. The transcriptome of the hippocampal tissue was examined through RNA-sequencing analysis. The 5xFAD mice showed increased susceptibility to kindling-induced seizures and had significantly longer and more severe seizures compared to WT littermates ($p=0.0002$). They also showed impaired spatial memory compared to WT group, as measured by the Y-maze test. Transcriptomic profiling and weighted correlation network analysis identified modules of coexpressed genes correlated with seizure severity and impaired spatial memory. In future, the biological pathways associated with these pathology-specific modules can be pharmacologically targeted as a disease-modifying therapy.