PLAQUES APPEAR FIRST IN LAYER 5 OF THE 5XFAD MOUSE AND ARE SPATIALLY CORRELATED WITH AXONAL DYSTROPHY

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Introduction: Neuronal loss and consequent brain shrinkage are major pathologies in Alzheimer’s disease (AD). Amyloid plaques, one of the two other major AD pathologies, are targets in AD therapeutic development. However, there have been differing opinions over the significance of amyloid plaques in the progression of the disease. We have studied a mouse model with five mutations associated with familial Alzheimer’s disease (FAD), called the 5xFAD, which recapitulates neuronal loss and brain shrinkage along with amyloid plaques.

Aims: The aim of this study was to examine the relationship between neuronal decay and plaque pathology in the neocortex of the 5xFAD mouse using two-photon imaging.

Methods: We crossed the 5xFAD mouse with the eYFP-Thy1 mouse to produce a transgenic fluorescent FAD model. A fluorescent marker of amyloid plaques was also injected to stain for plaque pathology. We used in vivo two-photon microscopy and a chronic cranial window to accomplish longitudinal imaging of neuronal decay and plaque deposition.

Results: We monitored the appearance of plaques and dystrophies in the neocortex. The majority of the initial axonal dystrophies in the 5xFAD mouse were in layer 5. Each dystrophy was intimately associated with an amyloid plaque. Long-term imaging also revealed shrinkage of the neocortex by 20-50%, similar to human AD sufferers.

Conclusion: The 5xFAD mouse was the first reported example of a mouse model with profound neocortical neuronal loss. Longitudinal in vivo imaging revealed amyloid deposition and neuronal atrophy began in layer 5, and eventually progressed to severe shrinkage of the neocortex.