The impact of Alzheimer's Disease on the human synaptome

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Introduction: Synapse pathology is one of the leading determinants of the onset and progression of Alzheimer's Disease (AD). With current therapies aimed at reducing and clearing pathogenic Aβ and tau failing, it is becoming increasingly apparent that we need to look at AD pathology differently, considering the impact of these toxic proteins on molecular diversity at the level of the synapse.

Aim: As part of the UK Dementia Research Institute (DRI) multi- 'omics atlas project for AD (MAP-AD), we aimed to use synaptome mapping approaches to systematically characterise synapse types and to identify vulnerable and resilient synapses throughout AD progression.

Methodology: By combining immunofluorescent labelling of synaptic proteins, high throughput single-synapse resolution spinning disk microscopy, and in-house machine learning algorithms, we implemented a comprehensive synaptome mapping pipeline for human post-mortem tissue, assessing multiple cortical brain regions in early- (Braak II-IV) and late-stage (Braak V-VI) AD.

Results: Our study identifies the spatiotemporal differences in both excitatory and inhibitory synaptic protein density, size, and intensity and the analysis of changes to the synapse types and diversity in AD will be presented.

Conclusion: Uncovering the impact of synapse diversity on AD will provide invaluable information for identifying synapse-specific biomarkers and therapeutic strategies and to help resolve the fundamental mechanisms of cognitive decline in AD.