Alterations in the Cortical Connectome in the Evolution of Alzheimer's Disease

The neuronal “connectome” represents the network of elements and connections underlying the neurostructural substrate of cognition and memory. Disruption or reduction of the connectome (e.g., changes in dendritic branching and/or spines) appears to play a key role in the onset and progression of dementia. Mild cognitive impairment (MCI), which is associated with subtle memory loss, is regarded as a prodromal stage in the development of Alzheimer’s disease (AD). Here we characterized, first, the earliest alterations in the cortical connectome associated with MCI; and secondly, additional connectome changes associated with the progression of MCI into frank AD.

Connectome changes in branching and spines were evaluated in pyramidal neurons from the parietal, temporal, and frontal cortices. Results showed that that neurons from both parietal and temporal cortices displayed a comparable loss of connectome circuitry: ~ -30% and -50% in MCI and AD, respectively. However, in the frontal cortex, in MCI there is a massive neuroplastic enhancement in branching and spines which amounts to a 75% increase in the connectome for these neurons. In the subsequent progression from MCI to AD, there is a 68% reduction of the connectome in the frontal cortex.

These results indicate that in the evolution of AD, layer II-III neurons of the temporal and parietal regions undergo a progressive stepwise loss of branching and spines, initially in MCI and additionally, in AD. However, by contrast, neurons in the frontal cortex show an initial neuroplastic response in MCI. This could be a compensatory mechanism – unique to the frontal cortex – which is helping to maintain circuitry and minimize cognitive dysfunction before being overwhelmed by the subsequent further progression of AD.