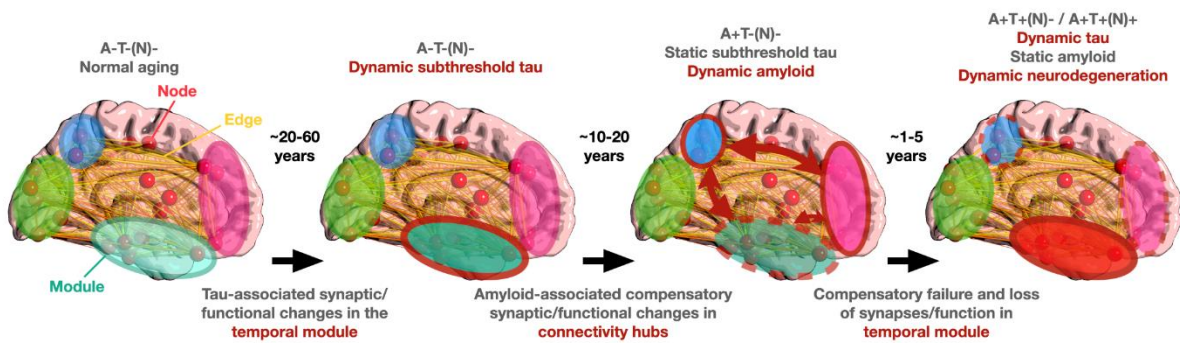# nature portfolio

Supplementary information

Alzheimer disease

In the format provided by the
authors and unedited

Supplementary Figure 1. Cascading Network Failure and Dynamic Biomarker Evolution.

The figure depicts the temporal and spatial evolution of large scale network changes occurring within the context of the A/T/(N) framework as hypothesized by the cascading network failure model of Alzheimer disease (AD). Functional network nodes, comprised of ensembles of cells and their associated synaptic activity, are represented by red balls with large-scale functional connections (edges) between these cellular ensembles depicted with yellow sticks overlaid on the medial surface of a brain hemisphere. Collections of highly interconnected nodes organized into functional modules are represented by four coloured ovals. In the second brain, age associated hyperconnectivity, or stress/burden in functional dynamics, occurring over 20-60 years within the temporal module is depicted by the solid red outline around the temporal module. This activity is hypothesized to be associated with initial phases of tau hyperphosphorylation and accumulation within the functional units in this module. In the third brain, compensatory changes in connectivity hubs attempting to relieve the accumulating functional stress in the temporal module is depicted as a dotted line around the temporal module with solid red lines and functional hyperconnections around the parietal and frontal modules. The more diffuse hyperconnectivity in this preclinical phase is hypothesized to be associated with altered synaptic homeostasis associated with upregulation of APP production in these hub brain regions and subsequent Aβ accumulation. The fourth brain depicts the stage at which the compensatory capacity of these hub brain regions is saturated and the aberrant activity in the temporal modules leads to functional failure and Aβ-independent neurodegeneration within that module with subsequent cascading effect through other modules. Selective clinical symptoms coincide with the loss of function in these selectively failing modules.