Neural Networks in Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) chief neuropathological hallmark consists of extracellular amyloid plaques and intra-neuronal neurofibrillary tangles. Failure of neural plasticity and homeostatic pathways is strongly implicated in the pathophysiology of AD and associated cognitive decline. This failure often precedes plaque pathology, is associated with b-amyloid deposition, and can manifest as neuronal hyperactivity and abnormal functional connectivity. The precise mechanism by which amyloid deposits impair neuronal plasticity in early AD is not well understood. Until recently it is not clear the change in functional properties during learning in AD. We have probed the capacity of cortical circuits for plasticity using a well-validated implicit learning paradigm (stimulus-selective response potentiation or SRP) introduced by Mark Bear[1-3]. Implicit learning, developed phylogenetically earlier than conscious learning, is ubiquitous in the neocortex including area V1, and plays a fundamental role in re-shaping cortical circuits to meet changing environmental demands. In brief, exposing the mouse repeatedly to phase reversing oriented gratings induces SRP, doubling visual evoked potential responses to the presented orientation but not to other stimuli. This is a true memory phenomenon that shares core molecular features with LTP, requires sleep for consolidation and has a behavioral correlate (stimulus induced "fidgeting"). Visual cortex confers a strong advantage for dissecting how mechanisms of plasticity malfunction in AD, since it allows a precise quantification of how neuronal properties change with visual learning. In the experiments, a transparent window is surgically placed over the brain 14 days (-14 days) before the learning paradigm begins. The mice has undergone two-day habituation sessions in front of a gray screen (-2 and -1 day). At day 0, we employed fluorescence imaging and GCaMP6s reporter mice to generate retinotopic maps, identifying low and high visual areas. On experimental day 1, the mouse has passively viewed a 0.5 Hz phase-reversing, full-field, 0.05 cycle/°, 100% contrast, sinusoidal grating stimulus, presented at X° (-45° or +45°) orientation for a total of 400 phase-reversals. This procedure is then repeated over the next 4 days. On experimental day 6, this now familiar stimulus has been presented interleaved with a novel X+ 45° stimulus. The collected data are preprocessed, deconvolved, and thresholded appropriately. We use the Spike Time Tiling Coefficient (STTC)[4] metric of inter-neuronal correlation strength to measure functional connectivity between neurons firing in supragranular (L2/3) layer of mouse area V1. We apply graph similarity algorithms to compare the functional connectivity during the disease progression without intervention, normal aging, and disease progression (using the 5xFAD mice, a mouse model for AD) following the delivery of time-specific synthetic microneurotrophin vs. placebo.

REFERENCES

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