Prognostic and Diagnostic Measure for Circuit Disruption in Alzheimer's Disease

Price, Kacey

Alzheimer's disease (AD) is a neurodegenerative disease known for significant brain atrophy and pathological lesions that are thought to damage synaptic connections between cells. In particular, gamma-aminobutyric acid (GABA) based synapses that inhibit neurons are thought to be disrupted in AD, causing hyper-excited circuitry and cognitive impairment. Currently, AD diagnosis methodologies are unclear until advanced stages, or via post-mortem analysis. The purpose and modeling goal was to create a dynamic causal model (DCM) to serve as a prognostic and diagnostic measure for early state AD. Another goal was to determine a drug that would be most effective in pharmacological intervention to increase GABAergic function and memory performance. The DCM was created in STELLA by isee systems with differential equations describing the state of cell population at a given time. The parameters of firing variance and GABA receptor conductivity (GRC) underwent sensitivity runs, and results of a power spectral density analysis showed that these parameters controlled gamma power in a non-linear fashion. The firing variance should be larger than about 150 to increase gamma power, but the GRC must be specifically four S/m to reach maximum power. This suggests that a drug combination that induces these effects such as Ketamine of GABA agonists could improve memory function by enhancing gamma power. For diagnosis, this DCM can be applied to suspected patients and use the variance and conductivity parameters as biomarkers. Both goals were successful because the gamma spectra, which relate to cognitive performance, were found to be sensitive to the model parameters that can be altered by currently utilized pharmacological interventions.

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