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Investigating the cellular and circuit mechanisms underlying schizophrenia-related EEG biomarkers using a multiscale model of auditory thalamocortical circuits

Individuals with schizophrenia show sensory processing deficits, notably in the primary auditory cortex (A1), studied with EEG. These deficits manifest as abnormalities in event-related potentials and cortical oscillations, reflecting a broader disturbance in cortical network excitation and inhibition balance (E/I balance). We've expanded our auditory thalamocortical circuit model to investigate the biophysical source of these EEG biomarkers. The A1 model simulates a 2000 μm deep, 200 μm diameter cortical column with over 12k neurons and 30M synapses, informed by experimental data. Stimulus-related thalamic inputs were modeled using cochlear/auditory nerve and inferior colliculus models. The model replicates in vivo firing rates, LFPs, and EEG signals in healthy controls. We're now using this model to understand EEG changes in schizophrenia, informed by positron emission tomography (PET), genetics, and transcriptomics data. Specifically, we are employing the model to explore three changes associated with schizophrenia: reduced inhibition through parvalbumin (PV) interneurons, somatostatin (SST) interneurons, and N-methyl-D-aspartate receptor (NMDAR) hypofunction on PV cells. We found that all three molecular disturbances affected firing rates in a layer- and cell- specific way, mostly leaving granular layer responses unperturbed but significantly altering superficial and deep layers. In EEG recordings, they altered the 1/f slope with differential effects in lower frequencies compared to higher frequencies. PV and NMDAR reductions show opposite effects to SST reductions at both micro and macro scales. Future work includes studying cannabinoid and cholinergic pathway modifications on EEG biomarkers and extending the model to capture stimulus-specific adaptation (SSA) and mismatch negativity (MMN). This work aims to elucidate how genetic changes in schizophrenia lead to altered circuit behavior and EEG biomarkers, filling a critical gap in our understanding.