Biophysical Computational Modeling of Neuronal Network Activity in Control and SHANK2-Linked Autism Brain Organoids

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Multiple mechanisms contribute to Autism Spectrum Disorder (ASD), including mutations in the SHANK2 gene. SHANK2 encodes a postsynaptic scaffolding protein that organizes key excitatory receptors, including AMPA and NMDA, essential for neuronal signaling. Disruptions lead to abnormal synaptic connectivity and altered activity. Experimental studies show that SHANK2-mutated networks follow a distinct bell-shaped activity pattern, with an initial phase of rapid hyperconnectivity and excitability, followed by a sharp decline in network activity. However, the mechanisms driving this transition remain unclear. This study developed a computational model of a SHANK2-linked brain organoid, which has never been done, and investigated how changes in AMPA and NMDA function, along with increased connectivity, affect network dynamics. A biophysical neural network model was built using the Brain Modeling Toolkit, with excitatory pyramidal neurons and realistic morphology and electrophysiology. Control networks received low-frequency AMPA and NMDA input, while the SHANK2 condition increased NMDA input and recurrent connectivity, with other parameters held constant. The control network showed sparse, asynchronous firing, while the SHANK2 model produced dense, rhythmic firing with sustained depolarization, indicating increased temporal summation and hyperexcitability. These findings suggest that increased NMDA signaling and synaptic hyperconnectivity drive abnormal activity in SHANK2-linked ASD and may explain the observed bell-shaped pattern: early hyperconnectivity leads to synchronized overactivity, followed by network saturation that limits further functional connectivity and contributes to reduced activity.

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