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Seeing the nanoscale organization of synapses to better resolve synaptic function

Visualization of the submicron organization of excitatory synapses has revealed an unexpectedly ordered architecture consisting of nanocolumns of synaptic proteins that group into nanomodules, which scale in number as spine size increases. How these features are related to synaptic function has remained unclear. Here, we demonstrate that nanoclusters of proteins critical for synaptic development and plasticity undergo dynamic association and segregation by liquid-liquid phase separation (LLPS) in living neurons. Live-cell super resolution STED imaging, FRAP, and chemical disruption of LLPS of endogenous post-synaptic proteins tagged with EGFP by CRISPR-Cas9 knock-in, demonstrate that PSD-95 and AMPARs, but not NMDARs, form dynamic LLPS conjugates in living neurons. The phase states of PSD-95 and AMPARs are dynamically regulated by neuronal development, extracellular calcium, and structural plasticity, linking phase separation to synaptic remodeling. These live-cell data of endogenous proteins suggest that LLPS forms distinct synaptic microenvironments that concentrate proteins critical for synaptic plasticity and development.

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