

Title: Synapse biology and its relationship with psychiatric disorders

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Abstract

Drug discovery in psychiatry has been limited to chemical modifications of compounds originally discovered serendipitously. Therefore, more mechanism-oriented strategies of drug discovery for mental disorders are awaited. Schizophrenia (SZ) is a devastating mental disorder with synaptic disconnectivity involved in its pathophysiology. Reduction in the dendritic spine density is a major alteration that has been reproducibly reported in the cerebral cortex of patients with SZ. I here focus on the synaptic function of SZ-related factors, especially focusing on in vivo 2-photon synaptic imaging of the model mice.

However, no matter how beautifully we can illuminate the synapse in the mouse model, the links between synapse and brain function remain correlational, because we cannot manipulate an individual spine. In order to challenge the causal relationship between synapse and higher brain function, we established AS-PaRac1 (Activated Synapse targeting PhotoActivatable Rac1), which is unique not only because it can specifically label the recently potentiated spine in a transcription-, and translation-dependent manner, but can also selectively induce shrinkage in just those spines containing AS-PaRac1. This indicates AS-PaRac1 specifically visualizes the recently "written" spine, and "written trace" can be erased by blue light. This novel light-dependent tool of "Synaptic optogenetics" should open up new areas of memory research, and by extension, shed light on the neural networks that determine who we are.