Thalamofrontal Synaptic Dysfunction as a Mechanism for Short-Term Memory Impairment Following Adolescent NMDAR Hypofunction

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N-methyl-D-aspartate receptor (NMDAR) hypofunction is linked to schizophrenia, but prevailing models centered on reduced number and activity of inhibitory interneurons, and the resulting excitation–inhibition (E-I) imbalance, do not explain selective cognitive impairments. Here, we show that repeated adolescent NMDAR antagonism produces short-term memory (STM) deficits by weakening thalamofrontal (TF) synaptic transmission. In mice repeatedly exposed to ketamine, STM impairment coincided with reduced release probability and vesicle refilling at mediodorsal thalamus (MD) → dorsomedial prefrontal cortex (dmPFC) synapses, without detectable changes in L2/3→L2/3 synaptic release probability, intrinsic excitability, or synaptic ultrastructure. These presynaptic deficits were accompanied by diminished direction-selective activity in the dmPFC and impaired delayed alternation performance in the Y-maze. Chemogenetic activation of MD→ dmPFC projections restored both neural selectivity and behavior. Our findings identify a circuit-specific presynaptic mechanism linking adolescent NMDAR hypofunction to cognitive dysfunction, challenging interneuron-centric models and establishing TF synapses as a potential therapeutic target in NMDAR-related disorders.