

InSyn1 regulates GABAergic inhibition via the dystroglycan complex and is required for cognitive behaviors in mice

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Human mutations in the dystroglycan complex (DGC) result in not only muscular dystrophy, but also cognitive impairments. However, the molecular architecture critical for the synaptic organization of the DGC in neurons remains elusive. Here we report Inhibitory Synaptic protein 1 (InSyn1) is a critical component of the DGC whose loss alters the composition of the GABAergic synapses, excitatory/inhibitory balance *in vitro* and *in vivo*, and cognitive behavior. Association of InSyn1 with DGC subunits is required for InSyn1 synaptic localization. InSyn1 null neurons also show a significant reduction in DGC and GABA receptor distribution as well as abnormal neuronal network activity. Moreover, InSyn1 null mice exhibit elevated neuronal firing patterns in the hippocampus and deficits in fear conditioning memory. Our results support the dysregulation of the DGC at inhibitory synapses as a driver of altered neuronal network activity and specific cognitive tasks via a novel component, InSyn1.