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Organizing central memory synapses –Nrx-1 and glial cells

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The molecular machinery of synapses, including neurotransmitters and postsynaptic receptor ensemble, are essential for quality and salience of transmitted information; But so is their exact placement along a neuron's arbor. Therefore, locations and numbers are tightly regulated and stereotypic. We showed that such delicately placed synapses are key to general memory computations and integration of aversive and positive extinction memories in Drosophila.
Neurexins (Nrxn), transsynaptic molecules, span the synaptic cleft to interact with postsynaptic partners. They organize synaptic interfaces as they guide apposition of presynaptic components with the correct postsynaptic receptors and regulate key components like voltage-gated Ca2+ channels. Mutations, even single nucleotide exchanges, have been associated with lack of synapses, severe phenotypes, and mental disorders. Nrxns'transsynaptic partners and it's role vary depending on the synapse's purpose –e.g. in inhibitory vs. excitatory synapses. Recent research has also shown the involvement of glial Nrxn in clustering postsynaptic glutamate receptors in microdomains. Drosophila null-mutants display defects in glutamatergic neuromuscular junction anatomy and function and pan neuronal lack of Nrx-1 leads to learning and memory defects. However, the detailed mechanisms through which neuronal and glial Nrxns organize synapses are not well understood across species, particularly on the level of single CNS or GABAergic synapses.
To investigate synapse organization, we use Drosophila, because it has one synaptic Nrxn (Nrx-1) with nine similar isoforms whereas mammals have three partly redundant Nrxn genes with thousands of diverse isoforms. Additionally, is not only the connectivity of memory neurons and the stereotypic placement of synapses known, but the gene expression and physiology of single neurons can be modified experimentally, too.
We study the anatomical and functional effects of loss of Nrx-1 as well as single nucleotide mutations induced via CRISPR-Cas9, that have been associated with mental disorders in patients. Thereby, focusing on a defined number of GABAergic CNS synapses between two neurons essential for the extinction of aversive- and expression of other memories. Anatomical parameters will be assessed with t-GRASP and electron microscopy, behaviour with learning and memory paradigms. The roles of different parts of the presynaptic machinery, transsynaptic partners and glial Nrx-1 function are studied with a knock down screen.

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