Title: Unraveling PCDH19-related pathogenic mechanisms in Developmental and Epileptic Encephalopathy 9 (DEE9)

Abstract
Mutations in *PCDH19* gene, which encodes protocadherin-19 (PCDH19), cause Developmental and Epileptic Encephalopathy 9 (DEE9). Heterogeneous loss of PCDH19 expression in neurons is considered a key determinant of the disorder; however, how PCDH19 mosaic expression affects neuronal network activity and circuits is largely unclear. Here, we show that the hippocampus of *Pcdh19* mosaic mice is characterized by structural and functional synaptic defects and by the presence of PCDH19-negative hyperexcitable neurons. Furthermore, a global reduction of network firing rate and increased neuronal synchronization has been observed in different limbic system areas. Finally, network activity analysis in freely behaving mice revealed a decrease in excitatory/inhibitory ratio and functional hyperconnectivity within the limbic system of *Pcdh19* mosaic mice. Altogether, these results indicate that altered PCDH19 expression profoundly affects circuit wiring and functioning and provide new key to interpret DEE9 pathogenesis.

Title: Spatial determinants for the interactions of glutamatergic and GABAergic synapses in dendrites of hippocampal pyramidal neurons.

Abstract
Traditionally, plasticity was considered to belong mostly to excitatory synapses while inhibitory transmission was assumed to be relatively invariant. However, recent evidences demonstrate several types of inhibitory synaptic plasticity, raising the important question of how GABAergic and glutamatergic synaptic plasticity are coordinated during neuronal activity. We investigated how synaptic plasticity induced at individual glutamatergic spines affects the strength of neighboring GABAergic synapses. To this end we induced "single spine LTP" by pairing the postsynaptic depolarizations with repetitive glutamate uncaging at individual spines while simultaneously measuring the strength of adjacent dendritic GABAergic synapses by GABA uncaging. We found that, after the induction of single-spine LTP, GABAergic synapses located within 3 micrometers from a potentiated spine showed depression (iLTD), while further synapses still showed iLTP. This "spread" of heterosynaptic plasticity from spines was dependent on the protease activity of calpain induced by calcium influx through L-type voltage gated calcium channels. Presently we are extending the study of the aforementioned plasticity short range interplay at specific hippocampal CA3-CA1 sub-circuits. Our findings show that both glutamatergic and GABAergic synaptic plasticity are finely coordinated at dendritic level suggesting that the dendritic E/I ratio can be selectively tuned in spatially restricted dendritic sub-regions. In this scenario, the unique distribution of dendritic excitatory and inhibitory inputs and the consequent plasticity interplay is expected to influence the non-linear dendritic input summation thus efficiently tuning the neuronal excitability.

Title: Astrocytic EphB receptors control NMDAR functions and memory

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Abstract
The activation of classical NMDA receptors (NMDARs) requires the binding of glutamate and of a co-agonist. D-serine released from astrocytes is acting as such a co-agonist at several central synapses. In the hippocampus, while D-serine is the co-agonist of synaptic NMDARs, glycine is the one at extra-synaptic sites. The close apposition of astrocytic processes with synaptic neuronal elements could be an interesting signal for synaptic release of D-serine. Interestingly, it has been shown in astrocytic cultures that astrocytic EphB3 receptors play a role in the synthesis and release of D-serine. However, we do not know whether it could impact synaptic NMDAR activity. Here, we first established that the stimulation of EphB receptors by exogenous ephrinB3 led to an increase of D-serine availability at CA3-CA1

synapses, inducing an increase of NMDAR activity. Importantly, the inhibition of endogenous EphB receptors impaired NMDAR activity. These effects depended on astrocytes as EphB3 receptors activation by exogenous ephrinB3 had no impact on NMDAR activity under conditions where calcium activity was inhibited specifically in astrocytes. Finally, the knock down of EphB3 receptors specifically in astrocytes lead to LTP and novel object recognition memory impairment, both rescued by exogenous D-serine. Altogether our data indicate that astrocytic EphB3 receptors play a key role in synaptic NMDAR functions and memory.