

# **Neuregulin1-ErbB4 Signaling and Dopaminergic Transmission: Schizophrenia-at-risk Factors and their Contribution to Plasticity at Glutamatergic Synapses**

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Roughly 1% of the population worldwide suffers from schizophrenia. This devastating disorder is likely caused by as yet little understood interactions between genetic and environmental factors during development and postnatal maturation of the brain. Schizophrenia has also been called a “synaptic disease” by some, due to changes in both glutamatergic and dopaminergic neurotransmission, and impaired inhibitory interneurons.

Since 2002, variations in the genes encoding Neuregulin1 (NRG1) and its major tyrosine kinase receptor in neurons, ErbB4, have been identified as at-risk factors for schizophrenia in numerous association studies. Moreover, NRG1-ErbB4 signaling plays a major role in brain development and maturation, e.g. the proliferation and migration of interneuron precursor cells.

The presentation will focus on recent results showing that the NRG1-ErbB4 signal transduction pathway regulates long-term potentiation (LTP) at glutamatergic hippocampal synapses. We have shown that exogenously applied NRG1 acutely reverses LTP, suggesting that it may activate a filter system for synaptic plasticity *in vivo*. Moreover, NRG1 temporarily increases extracellular dopamine concentration, and NRG1-ErbB4 induced reversal of LTP requires dopamine D4 receptor activation. The exclusive expression of ErbB4 in GABAergic cells suggests that the effects of NRG1 are mediated by interneurons.

The finding of the simultaneous modulation of glutamatergic and dopaminergic transmission by NRG1-ErbB4, presumably via interneurons, places this signaling pathway in a position to consolidate several genetic, developmental, and functional aspects of the etiology of schizophrenia.