Presentation Abstract

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Title: Early postnatal ablation of mGluR5 in parvalbumin-positive fast-spiking interneurons results in profound alteration of their normal development

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Abstract: Subtle alterations in the normal postnatal development of GABAergic inhibitory circuits may lead to neuropsychiatric disorders, the symptoms of which appear when individuals reach early adulthood. In schizophrenia, alteration in the subtype of fast-spiking interneurons expressing the calcium-binding protein parvalbumin (PV) is one of the most replicated findings in postmortem brain studies. These results are supported by reverse-translational approaches in which expression of specific schizophrenia-linked genes, such as DISC1, lead to selective alterations in PV-interneurons.

We previously showed that decreasing glutamatergic transmission though prolonged exposure to NMDA-R antagonists leads to a reversible loss of phenotype of PV-interneurons in cultured cortical neurons as well as in adult rodents. This loss becomes permanent when the treatment is performed early during postnatal development, supporting the idea that disruption of the normal postnatal development of inhibitory circuits, by either genetic predisposition and/or environmental insults, can lead to persistent network changes in adulthood. How alteration of glutamatergic transmission during critical periods of postnatal development leads to the loss of PV-interneurons in adulthood is, however, not known.

Activation of the metabotropic glutamate receptor mGluR5 was previously shown to exacerbate the pro-psychotic effects of NMDA-R antagonists, and mGluR5 knockout animals show profound alterations in prepulse inhibition of the startle response, which is considered a behavioral hallmark in schizophrenia. Cross-talk
between NMDA-Rs and mGluR5 occur at glutamatergic synapses, and mGluR5 receptors are necessary for the development of PV-interneuron synaptic plasticity. We previously showed that activation of mGluR5 was able to prevent the NMDA-R antagonist-mediated loss of phenotype of PV-interneurons in culture, suggesting that the cross-talk between these two glutamate receptors is important for the maintenance of the GABAergic phenotype of PV-interneurons. Here, using the Cre/LoxP system, we created a mouse line in which mGluR5 receptors were deleted exclusively from PV-interneurons at the time of the initiation of their postnatal maturation. Analysis of the PV-interneuronal population showed profound alterations in the development of their characteristic perisomatic synaptic contacts on pyramidal cells as well as substantial loss of PV-positive neurons when animals reached adulthood. These results suggest that mGluR5 receptors are involved in the postnatal maturation of PV-interneurons.

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**T.J. Sejnowski:** None.  
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**M.M. Behrens:** None.

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