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Presentation Abstract

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Presentation Title: Delayed cortical maturation, enhanced fear conditioning and social deficits in mice exposed to perinatal ketamine

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Abstract: There is increasing evidence that disruptions in cortical inhibitory networks contribute to negative symptoms and anxiety associated with schizophrenia. These symptoms are extremely debilitating and remain under-treated with current antipsychotic medications. GABAergic interneurons are dysfunctional in a number of brain regions in schizophrenia, including the frontal cortex and hippocampus. Converging evidence from developmental animal models indicates that parvalbumin-positive (PV+) interneurons are particularly critical to disrupted behavior in these models. PV+ fast spiking interneurons modulate the activity of pyramidal neurons and are a key regulatory of the excitatory-inhibitory balance in cortex. We have previously shown that perinatal exposure of mice to the NMDA receptor antagonist ketamine (pNK) results in loss of PV+ immunoreactivity in the prelimbic cortex, in decreased inhibitory drive from fast-spiking interneurons. We

have also shown that pNK produces long term alterations in transcriptional activity suggestive of delayed maturation. Among the differentially expressed genes, we have found several schizophrenia-related genes such as *Reln*, *ErbB4*, *Grin2a*, *Grin2b*, or *Cit*, some of which are expressed preferentially in GABAergic neurons. To further test for delayed development we analyzed whether other maturational features of PV+ neurons showed long term alterations. We have found that perineuronal nets, which are dense extracellular matrix structures that surround the soma and dendrites of many neurons in the mature CNS, in particular PV+ interneurons, are reduced in pNK animals. Furthermore, ketamine administration during the neonatal period produced enduring behavioral deficits. Mice exposed to ketamine during the perinatal period showed decreased social approach behavior and enhanced contextual and cued fear conditioning compared to saline-injected mice. These data indicate that the loss of PV+ interneurons associated with perinatal ketamine administration leads to sustained disinhibition of prefrontal cortex, to enhanced fear expression, and social deficits in mice. Increased fear learning is consistent with the hypothesis that cortical disinhibition in pNK mice leads to increased excitatory output from prelimbic cortex (PL) to the basolateral amygdala (BLA). This circuit has been shown to be important for the fear learning and emotional memory.

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