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Presentation Abstract

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Presentation Title: Perinatal disruption of NMDA receptor function results in life-long transcriptional changes in frontal cortex

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Abstract: Repetitive perinatal exposure to the NMDAR antagonist ketamine leads to the permanent loss of parvalbumin-positive (PV+) immunoreactivity in mouse prefrontal cortex (PFC), in close similarity to what is observed in schizophrenia postmortem samples. Decreased expression of parvalbumin is accompanied by long-term changes in spontaneous postsynaptic currents in this subpopulation of neurons (Pinto-Duarte et al., 2011). We have previously shown that the loss of PV+ phenotype occurs in the absence of increased neuronal death (Powell et al., 2011). We propose that NMDAR antagonism during this critical period of development alters the trajectory of normal postnatal maturation by modifying the developmentally-regulated transcriptional profile of cortical neurons. In order to test this hypothesis we treated C57BL/6 mice with ketamine (30 mg/kg) at P7, P9 and P11. Subsequently, the frontal cortex of ketamine- and saline-treated mice was collected at four developmental time points; 2 weeks, 4 weeks, 6 weeks and 10 weeks. Total RNA was extracted and samples were analyzed by RNA-Seq. Reads were obtained for each time point and mapped to the mouse genome. RNA abundance and differences between treatments were determined using quartile normalized data. Large scale transcriptional changes were observed in both saline and ketamine-treated groups throughout development, with pronounced changes appearing during the adolescent period. Perinatal ketamine exposures lead to substantial changes in gene expression at each developmental stage. Using the online

resource Database for Annotation, Visualization and Integration Discovery (DAVID), families of genes were identified as selectively enriched or depleted after ketamine treatment throughout the course of development. These include genes involved in synaptic integration and function such as the sodium channels, potassium channels and neurotransmitter receptors. These observations will provide insight into potential mechanisms upstream of electrophysiological and behavioral alterations that are responsible for executing the potent and persistent effects of perinatal ketamine exposure.

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