



Presentation Abstract

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Presentation Title: Hypo-NMDA receptor function leads to altered transcription in frontal cortex

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Abstract: We have previously shown that prolonged N-Methyl-D-Aspartate receptor (NMDAR) blockade during a critical period for the development of parvalbumin-positive (PV+) interneurons, leads to altered electrophysiological properties and reduced PV+ cells in adult animals, resembling alterations observed in schizophrenia models. In this study, we use this NMDAR hypofunction mouse model to monitor transcriptome changes throughout development into early adulthood. mRNA was extracted from the frontal cortex of healthy and ketamine-treated mice at 2, 6, and 10 weeks of age, in order to study the genome-wide transcriptional changes that lead to altered PV(-) phenotype. Whole genome transcript expression was obtained using Illumina 2000 RNAseq methods. Reads were aligned to the NCBI-37 reference genome using Bowtie and Tophat, and transcript quantification was performed using Cufflinks. For differential expression at each time-point we used both Cuffdiff and EdgeR computation analyses. Finally, to uncover functional groups of related genes we employed the Ingenuity IPA system.

This analysis revealed that at P13, two days after the last ketamine injection, 69 genes remained differentially-expressed as compared to the controls. Cuffdiff and EdgeR had a strong overlap in differential expression output between saline and ketamine samples. Gene ontology mapping identified that ketamine treated mice

had altered expression of gene families involved in cell-cell signaling and neural cell development, consistent with an altered trajectory of cell development which may contribute to the phenotype observed in adolescent mice. Surprisingly, we have not observed changes in parvalbumin mRNA at any time point analyzed, suggesting decreased PV immunoreactivity after ketamine may be due to post-transcriptional changes. Cell-type specificity of these transcriptional changes is being assessed using immunohistochemistry, in situ hybridization and cell-type specific quantitative PCR.

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