The effects of prenatal stress on distinct dorsal striatal cell types and autism spectrum disorder-relevant behaviors in mice

Maya M. Evans, Benjamin W. Q. Hing, Sara V. Maurer, Matthew A. Weber, Kartik Sivakumar, Nandakumar S. Narayanan, Hanna E. Stevens

Dept. of Psychiatry, Dept. of Neurology, University of Iowa

Background
- Prenatal stress (PS) is linked to increased risk for neuropsychiatric disorders in offspring, including autism spectrum disorder (ASD).
- Many with ASD show alterations in hyperconnectivity of the dorsal striatum.
- Medium spiny neurons (MSNs) are the principal neurons of the striatum, with Drd1 & Drd2 subtypes.
- Drd2 antagonists can ameliorate some ASD-like behaviors in mouse models.
- Pharmacological manipulation of MSNs during interval timing results in delayed response times and altered time-related neural activity.

Hypothesis: PS will lead to:
1. Changes in striatal gene expression, especially in the domain of synapse function.
2. Striatum-dependent behavioral deficits, including in procedural learning and interval timing.
3. Altered physiological activity of MSNs during interval timing.

Methods
Prenatal stress (PS): 45-min sessions of restraint & bright light, 3x daily, from embryonic day 12 through birth in CD-1 mice.

Offspring Outcomes:
1. Single-cell RNA sequencing (scRNAseq): Dorsal striatum
2. Recording: Multielectrode array recordings from the dorsomedial striatum during interval timing

Results: scRNAseq

Cell Clustering

Overview with SFARI Genes

Drd1 MSNs

Drd2 MSNs

ASD-associated genes from the SFARI Gene database were highly overexpressed among genes that were differentially expressed after PS in Drd1 and Drd2 MSNs.

Pathway enrichment analysis was run on the overlapping genes using both DAVID and PANTHER, revealing synaptoc-related pathways.

Conclusions
1. Transcriptional changes that were consistent across distinct striatal cell types
   - Synaptic-related pathways were enriched among upregulated DEGs
   - Translation-related pathways were enriched among downregulated DEGs
   - Significant overrepresentation of ASD-associated genes among DEGs in Drd1 and Drd2 MSNs
2. Enhanced procedural learning on Rotarod and earlier switch times in the interval timing task
3. Changes in striatal MSN physiology (more ramping neurons and faster ramping) that may contribute to earlier switch times

Acknowledgements

Project Funding: K23 DA037430 to B.W.Q.H. and K23 MH111192 to M.M.E.

References: