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Using spatial transcriptomics to characterize the effects of cocaine self-administration on brain gene expression in a selectively bred rat model of individual vulnerability to psychiatric disorders and drug addiction

Background: To better understand individual vulnerability to psychiatric disorders and drug addiction, we have selectively bred rats for many generations to produce two lines with highly divergent behavioral temperaments: bred Low Responders (bLR) are highly inhibited and anxious in a novel environment, whereas bred High Responders (bHR) are highly exploratory, sensation-seeking, and prone to drug-seeking behavior. We used spatial transcriptomics to characterize the differential impact of cocaine self-administration (SA) on brain gene expression in bHR versus bLR rats and relate these findings to known genetic and genomic differences between the two lines.

Methods: bHR/bLR rats (generation F81, N=24: n=3/line/group/sex) were given access to 3 weeks of cocaine SA (0.3 mg/kg/infusion, 2hrs/day for 5 days/week), and then sacrificed 48-72 hrs following SA with matched unhandled controls. One coronal slice per subject was collected for spatial RNA-sequencing (A/P: ~ -3.5 mm, includes hippocampus) using the Visium platform (10x Genomics; 28x151bp sequencing: Illumina NovaSeqXPlus). Data was preprocessed using SpaceRanger (mRatBN7.2), and analyzed using Seurat and Limma-trend pipelines.

Results: Spatial barcodes ("spots") cleanly clustered, mapping to known anatomical regions, including hippocampal subregions. A large number of genes were differentially expressed between the two lines, replicating previous findings related to bioenergetics (Ist1, Pex11a), microglial function (C1qc, Ucp2, Fcrl2), reactive oxygen species (Nqo2), and growth and development (Bmp4). There were much fewer effects of cocaine SA vs controls, but some of these genes were also differentially expressed in association with bred line, including large effects for a gene essential to the electron transport chain, apoptosis, oxidative damage response, and pruning (Cycs).

Conclusion: Multiple levels of evidence now implicate a key set of genes in behavioral temperament, potentially modulating vulnerability to psychostimulant use. By characterizing their expression and regulation by cocaine in specific regions and circuits, we lay the groundwork for mechanistic studies and pharmacological targeting.

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