Name: Ashley Auth, PSM Email: ashley.olson@jax.org

Behavioral and molecular sub-type specific predictors of cocaine self-administration in the Collaborative Cross using permutation based maximum covariance analysis

The mechanisms underlying individual differences in vulnerability to cocaine use disorder remain largely unknown. Leveraging the genetic and behavioral breadth of the Collaborative Cross (CC) mouse panel, we sought to identify predisposing traits and gene networks that confer phase-specific variation across acquisition, extinction, and cue induced reinstatement phases to cocaine intravenous self-administration (IVSA).

Behavioral measurements (26 cocaine IVSA; 44 predisposing behaviors) and striatal gene expression collected across 32 CC strains by the Center for Systems Neurogenetics of Addiction were analyzed using Permutation-based Maximum Covariance Analysis (PMCA). PMCA is a non-parametric data-driven approach for extracting and prioritizing relations across a multimodal experimental framework. For each relation, PMCA quantifies uncertainty with a permutation-based false positive rate (FPR); it is robust to overfitting and other challenges inherent in noisy, high-dimensional data. Strain scores across these networks revealed phase-specific vulnerability profiles.

Across phases, greater cocaine intake and cocaine-seeking covaried with higher impulsivity and anxiety-like behaviors, and lower risk-taking, novelty seeking, and exploration behaviors. This analysis revealed vulnerability subtypes: impulsivity-driven, anxiety-driven, and mixed. Gene networks covarying with IVSA traits converged on molecular pathways (79 genes and 29 pathways), with strong phase specificity. Notably, gene networks specific to extinction were specifically enriched for proteostasis and ubiquitin–proteasome components, with a proteasome centered subnetwork inversely associated with drug seeking during extinction.

In a genetically diverse and reproducible model, impulsivity and anxiety-like avoidance jointly predict increased cocaine IVSA across phases, consistent with the directional relationships observed in people. We demonstrate that this association is partially driven by shared genetic influences, revealing potentially novel genetic mechanisms underlying vulnerability. Phase-specific gene networks provide mechanistic footholds for interventions that account for subtype heterogeneity, and our PMCA framework yields integrated networks that stratify vulnerability and nominate testable molecular targets to support cessation and prevent relapse.

Authors:
Submitter: Ashley Auth, The Jackson Lab, Bar Harbor, ME
Robyn Ball, PhD, The Jackson Lab
Elissa Chesler, PhD, The Jackson Lab
J. David Jentsch, PhD, Binghamton University
Lisa Tarantino, PhD, UNC Chapel Hill

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