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Genetic dissection of initial drug sensitivity and behavioral sensitization using the Collaborative Cross and Diversity Outbred mouse populations

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Recent data suggests that cocaine use is increasing and the number of overdose deaths involving cocaine has risen appreciably in the last several years in the US. However, effective treatment options for cocaine use remain extremely limited. Human twin studies support a high heritability for the development of cocaine dependence (h2~0.65) indicating a significant role for genetics. The Center for Systems Neurogenetics of Addiction (CSNA) was formed with the goal of identifying genetic and biological relationships between the stages and patterns of cocaine addiction and behaviors that predict drug abuse. The CSNA uses a systems genetics approach that takes advantage of genetically diverse yet tractable rodent populations, the Collaborative Cross (CC) and Diversity Outbred (DO). These strains were designed to more accurately model the heterogeneous genetic background present in the human population. Genetic diversity is expanded in these populations compared to traditional mouse resources, thereby enhancing the ability to capture a broader range of phenotypes and identify causal genetic variants. As part of the CSNA, we are examining initial locomotor sensitivity and behavioral sensitization to cocaine. We will present preliminary QTL mapping data generated from the DO population in which we identified regions on Chrs 2, 6, 14 and 18 that are associated with initial sensitivity and behavioral sensitization to cocaine. We will also highlight several CC strains with extreme behavioral phenotypes and discuss work we are doing to examine underlying mechanisms, including pharmacokinetics and the monoaminergic systems, that may contribute to the unique cocaine behavioral phenotypes in these strains.