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Naturally occurring variation in cocaine self-administration among high-diversity mouse populations

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Background/Rationale
Numerous factors determine an individual's response to addictive drugs. Genetic, psychological, and environmental factors interact and influence the progression from substance use to dependence. Understanding the genetic basis of volitional drug use requires drug seeking and taking behaviors to be modeled beyond the initial exposures. Here, we utilize advanced, high diversity mouse populations to characterize the phenotypic range of addiction-related traits using cocaine intravenous self-administration (IVSA).
Methods
Using a multi-stage, longitudinal study design, mice from the Collaborative Cross (CC) reference panel, Diversity Outbred (J:DO) mouse population, and their eight founder strains were tested on the cocaine IVSA paradigm. Following acquisition, individuals completed a full dose-response curve (0.032 – 1.8 mg/kg/infusion). Next, the extinction of drug-paired responses was recorded. Relapse propensity was modeled using cue-induced reinstatement.
Results
Prominent strain differences in addiction-relevant phenotypes were observed among the founders and amplified in the CC strains that display an expansive range for these traits. The DO mice are characterized by wide-ranging individual values and population mean that lies centered in the phenotypic range of the CC and founder strains. Heritability estimates of addiction-relevant traits were also computed.
Conclusions
We identified extreme strains for traits that confer individual vulnerability to addiction and estimate the genetic influences on these traits through heritability measures. Using high-diversity advanced mouse populations, we identify genetically influenced addiction-relevant traits, examine the relationships between these traits and lay the groundwork for studies that aim at identification of genetic mechanisms underlying these traits.