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Genome wide association studies in heterogeneous stock rats identify links between cue-reactivity and cocaine motivation.

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Understanding the genetic factors that contribute to the transition from recreational to problematic drug use is vital for uncovering neurogenetic targets that can aid in preventing and treating substance use disorder (SUD). In our laboratory, we have used an intermittent-access self-administration procedure in rats that triggers increased cocaine motivation (i.e., incentive sensitization) after only limited amounts of drug exposure. This models the transition to early stages of SUD and, when compared to long-access procedures, can be used to dissociate total drug intake from increases in motivation. To uncover the genetic factors behind incentive sensitization during intermittent-access, we conducted a genome-wide association study (GWAS) in a sample of heterogeneous stock rats and identified multiple genomic regions that influence cocaine motivation and contain several candidate genes. In a separate project, we integrated multi-level 'omics' data, including GWAS results, phenome-wide association studies, and transcriptomics to identify understudied genetic variants underlying cue-reactivity, a trait that that is phenotypically and genetically correlated with measures of cocaine and nicotine motivation. Several candidates were identified, including the understudied genes *Tenm4* and *Wnt11*. We then established that intracranial administration of a *Tenm4*-associated protein reduced several measures of cocaine motivation, confirming a pleiotropic effect on cocaine motivation and cue-reactivity. Ongoing work includes increasing sample size to detect additional loci underlying other heritable measures of cocaine self-administration, and investigation of additional candidate genes. Thus, these studies demonstrate the utility of using HS rats to identify genes associated with complex vulnerability traits related to SUD.