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Genes Identified in Rodent Studies of Alcohol and Nicotine Intake Are Enriched in GWASs of Human Substance Use

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Rodent studies of drug use provide a rich and expansive biological catalogue for specific aspects of substance use and addiction. Human genome-wide association studies (GWASs) have identified numerous loci that are associated with drug use and substance use disorder phenotypes. We hypothesized that genes identified in rodent paradigms of drug use would overlap with human gene variants and would contribute to specific heritable components for substance use and SUD traits. To address this, we examined gene-sets from 19 neurobiological gene expression studies of rodent alcohol and nicotine use and human GWASs of alcoholic drinks per week, problematic alcohol use, cigarettes per day and smoking cessation. Using partitioned linkage disequilibrium score regression, we tested whether rodent gene-sets were enriched for the heritability of a trait and benchmarked our findings using KEGG nicotine and alcohol addiction pathways, as well as non-substance gene-sets (from rodents) and human GWASs. We found that genes identified using rodent paradigms of alcohol use – especially binge drinking paradigms - were enriched for heritability for human drinks per week, cigarettes per day and cigarette cessation (p_{adj} < 0.05), but not problematic alcohol use. No KEGG pathway or non-substance related gene-set were significant and rodent drug use gene-sets demonstrated more enrichment for substance use GWASs than non-substance use GWASs with similar heritabilities. Further cross-species genomic research integrating a wide array of experimental paradigms with human GWASs may help elucidate the genetic, neurobiological and behavioral mechanisms of complex traits.