From rats to humans: revealing conserved molecular networks of addiction through gene expression and GWAS integration

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Genetics alone cannot fully dissect the biological basis of addiction. Here, we applied network modeling of gene expression in combination with genetic data to identify conserved biological networks underpinning addiction vulnerability between humans and rats. We leveraged the genetically diverse outbred heterogeneous stock (HS) rats and the available RNA-seq transcriptional profiles from ratGTEx. We constructed gene co-expression networks, termed modules, across 1082 tissue samples from 673 unique HS rats. Conservation analysis showed that modules are well conserved between rats and humans when we compared modules constructed from corresponding human tissues in GTEx. Next, we inferred polygenic risk scores (PRSs) for each rat for 6 cocaine addiction traits and 4 heroin addiction traits collected by the *Center for Genetics, Genomics, and Epigenetics of Substance Use Disorders in Outbred Rats*. This allowed us to identify “rat addiction-PRS modules” that were correlated ($p<0.05$) with PRSs. These results indicated that addiction vulnerability influences gene expression variation in a sex and tissue-specific manner. To further investigate the convergence of addiction molecular networks between rats and humans, we identified rat and human modules that were enriched for human addiction-associated genes using Mergeomics. Addiction-associated gene mapping was achieved by integrating human GWAS summary statistics for 13 addiction-related traits with human gene coordination and brain region-specific expression and splicing quantitive trait loci from GTEx. Hierarchical clustering of the rat addiction-PRS modules and human addiction-associated modules revealed 5 conserved clusters of modules termed meta-modules (MMs), which function in 1) neuronal processes, addiction, splicing, and chromatin remodeling (MM5); 2) Metabolism (MM2); 3) immune processes (MM1); 4) and 5) cellular stress processes (MM3 and MM4). Overall, these results indicated that leveraging biological knowledge networks is valuable in identifying conserved addiction-related molecular underpinnings shared between humans and rats.