Name: Yanning Zuo
PI Name: Francesca Telese
Email: y3zuo@health.ucsd.edu
PI Email: ftelese@health.ucsd.edu

From Rats to Humans: Revealing Conserved Molecular Networks in Addiction through Gene Expression and GWAS Integration

Yanning Zuo[1], Yeji Shin[1], Daimeng Sun[1], Numaan Formoli[1], Thiago Sanchez[1], Benjamin Johnson[1], Brad Balderson[2], Graham McVicker[2], Abraham Palmer[1], Francesca Telese[1]

[1]Department of Psychiatry, University of California San Diego, La Jolla, CA, USA
[2]Integrative Biology Laboratory, Salk Institute, La Jolla, CA, USA

Genetics alone cannot fully explain the biological basis of addiction. We applied network modeling of gene expression integrated with genetic data to identify conserved biological networks underlying addiction vulnerability in humans and rats. Using RNA-seq profiles from ratGTEx based on genetically diverse outbred heterogeneous stock (HS) rats, we constructed gene co-expression networks across 1,082 tissue samples from 673 HS rats. Module preservation analysis showed that these networks were highly conserved with those constructed from corresponding human tissues in GTEx.

We then incorporated 13 human and 1,425 rat addiction-related trait GWAS summary statistics from the Center for Genetics, Genomics, and Epigenetics of Substance Use Disorders in Outbred Rats. Addiction-associated gene mapping was achieved based on rat or human genome coordinates and for human, brain region-specific expression and splicing quantitive trait loci from GTEx. Using Mergeomics, we identified gene modules enriched for addiction-associated genes, indicating that addiction vulnerability influences gene expression in a sex- and tissue-specific manner.

To examine cross-species convergence of addiction-related molecular networks, we performed hierarchical clustering of addiction-associated modules, identifying four conserved meta-modules with distinct functions: (1) neuronal processes, addiction, and chromatin remodeling; (2) cellular stress and oxidative phosphorylation; (3) extracellular matrix, splicing, and metabolism; and (4) immune processes. These findings demonstrate the utility of biological network analysis in uncovering conserved molecular mechanisms of addiction shared between humans and rats.