

Name: Holly Poore, Ph.D.

Email: holly.poore@rutgers.edu

Substance use disorders exhibit unique and disorder specific genetic associations with externalizing and internalizing psychopathology

Substance use disorders (SUDs) are heritable and share genetic variance with externalizing and internalizing psychopathology. Although recent gene identification efforts have demonstrated the value of modeling the shared genetic architecture among SUDs and externalizing, most research has thus far failed to account for overlap with internalizing. In this study, we aim to characterize the genetic relationships of both externalizing and internalizing with SUDs. We used genome-wide association study (GWAS) summary statistics derived from previously published studies of externalizing, internalizing, and SUD outcomes to quantify the genetic overlap between these phenotypes. We characterize this overlap using omnibus, partial, and local genetic correlations, estimates of their shared polygenic effects, genetic causality models, polygenic score (PGS) analyses, and estimates of each SUDs residual variance derived from models in Genomic SEM. We found strong genetic relationships of externalizing and, to a lesser extent, internalizing with all SUDs across methods. Despite their more modest associations, internalizing emerged as an important genetic correlate of SUDs. After accounting for variance shared with externalizing, partial genetic correlations between internalizing and SUDs were attenuated but, with the exception of TUD, still significant. Similarly, the PGSINT accounted for a statistically significant increase in variance over and above PGSEXT. Two SUD specific patterns emerged such that TUD was least associated with both psychopathology spectra and OUD was most strongly related to internalizing relative to other SUDs. From these findings we conclude that shared genetic influences may explain comorbidity observed between SUDs and internalizing disorders and suggest that genetic risk for internalizing should be incorporated into SUD identification and prevention efforts. Future gene identification efforts should study SUDs in the context of both externalizing and internalizing psychopathology.

Authors:

Submitter: Holly Poore, Faculty Instructor/Early Career, Rutgers Addiction Research Center, Robert Wood Johnson Medical School, Piscataway, NJ

Peter Barr, Ph.D., Department of Psychiatry & Behavioral Sciences, SUNY Downstate Health Sciences University; Veteran's Affairs New York Harbor Healthcare System

Maia Choi, Ph.D., Department of Psychiatry, Robert Wood Johnson Medical School, Rutgers University; Rutgers Addiction Research Center, Brain Health Institute, Rutgers Health

Denise Hien, Ph.D., Rutgers University Center of Alcohol & Substance Use Studies

David Zald, Ph.D., Center for Advanced Human Brain Imaging Research, Rutgers University