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Characterizing the Genetic Overlap between Externalizing Phenotypes and Substance Use Disorders

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Substance use disorders (SUDs) are phenotypically and genetically correlated with each other and with other psychological traits characterized by behavioral undercontrol, termed externalizing phenotypes. In this study, we used Genomic Structural Equation Modeling to explore the shared genetic architecture among six externalizing phenotypes and four SUDs used in previous multivariate GWAS of externalizing (N = 1,373,240) and an addiction risk factor (N = 1,019,521), respectively.

Using a preregistered set of criteria, we first evaluated the performance of five confirmatory factor analytic models and used a combination of model fit, factor reliability, and model characteristics to adjudicate among the models. Our results suggest that both one- and two-factor models fit the data, although dimensions in the two-factor models were very highly correlated with each other (r_gs > .87). To further explore this covariance, we characterized the degree of shared and unique genetic influences on externalizing phenotypes and SUDs by 1) estimating their genetic correlations with external criteria; 2) quantifying the number of causal variants that influence both sets of phenotypes; and 3) comparing the specific genetic variants that influence them. Results from this study can be used to inform future efforts to characterize genetic liability for broad externalizing as well as specific externalizing and SUD phenotypes.