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RESEARCH HIGHLIGHT

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Crossing diagnostic boundaries to understand the genetic etiology of addiction

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Substance use disorders are complex psychiatric conditions that impose a significant burden on affected individuals, their families, and communities broadly. They are highly prevalent worldwide, influenced by a tangled constellation of interrelated environmental and biological factors. Notably, individuals struggling with substance use problems often use more than one substance, complicating efforts to understand, prevent, and treat these conditions.

Advances in psychiatric genetics suggest that high rates of comorbidity among substance use disorders may be partly explained by a shared genetic etiology. That is, while some genetic influences may be fairly specific to a particular substance (e.g., *ADH1B* and alcohol), research suggests a considerable proportion of genetic risk operates via more general pathways to addiction. Such pleiotropic effects may be more the norm than the exception in psychopathology, as studies routinely find that genetic influences on psychiatric disorders cross diagnostic boundaries [1].

In this issue of *Neuropsychopharmacology*, Hatoum et al. [2] report an ambitious study that interrogates the genetic influences that cut across substance use disorders. To do so, they use Genomic Structural Equation Modeling (Genomic SEM), a statistical framework and software for applying structural equation modeling techniques to genome-wide association study (GWAS) summary statistics, to model the joint genetic architecture of several substances use disorder phenotypes. This approach enabled the authors to conduct a series of analyses that addressed the following questions:

- Can the genetic covariance among substance use disorders be explained by a shared genetic liability?
- How does the shared genetic liability of substance use disorders relate to phenotypes that approximate the three-stage model of addiction?
- How does the shared genetic liability of substance use disorders relate to psychopathology not defined by substance use?

Hatoum and colleagues began by collating some of the largest GWAS results available for substance use disorder phenotypes ($N =$ 82,707–435,563). Specifically, GWAS summary statistics of problematic alcohol use (combination of quantitative trait and case-control designs; $N = 435{,}563$), problematic tobacco use (quantitative trait design; effective $N = 270{,}120$), cannabis use disorder (case-control design; $N = 357{,}806$), and opioid use disorder (case-control design; $N = 82{,}707$) were selected. While not exhaustive, these phenotypes represent a broad array of disorders characterized by addiction, and each dataset had a sufficient sample size for the primary analyses.

Consistent with prior research, the authors found that these phenotypes were all positively "genetically correlated" with one another [ranging from 0.19 to 0.78]. Briefly, genetic correlations are parameter estimates that quantify the degree to which genetic influences on two phenotypes are shared. They range from −1 to 1, with 0 implying that the genetic influences on the phenotypes are independent of one another. Here, the ubiquitously positive genetic correlations reported by the authors suggest that there is a notable degree of genetic overlap among disorders.

The authors then conducted a confirmatory factor analysis, which tested and compared different theoretical models regarding the genetic factor structure of substance use disorders, such as a common factor model (i.e., one dimension of liability) versus a correlated factors model (i.e., two correlated-but-distinct dimensions of liability). Briefly, the patterns of genetic covariance among the four substance use disorder phenotypes were most parsimoniously represented by a single latent genetic factor. This finding parallels those of previous twin- and family-based studies, as well as those from other studies using Genomic SEM to study similar phenotypes [3, 4].

Notably, the authors critically extend this prior work by conditioning the substance use disorder phenotypes on indices of more normative substance use: measures of drinks per week, lifetime tobacco use, and lifetime cannabis use. This allowed the authors to characterize genetic overlap between substance use problems independent of consumption. The factor structure of these clinical phenotypes was markedly similar after accounting for the genetics of normative substance use—with one exception. The factor loading for problematic alcohol use was substantially lower in this conditional model, which may be due to the strong genetic correlation between alcohol consumption and problematic alcohol use [5].

Next, the authors fit structural regression models in which the latent genetic factor of addiction was simultaneously regressed onto the genetic components of theoretically relevant phenotypes. In one model, addiction was simultaneously regressed onto risk-taking, executive functioning, and neuroticism (corresponding to the stages of binge/intoxication, preoccupation/anticipation, and withdrawal/negative affect purported to underlie addiction), and significant genetic associations with all predictors were found

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in the expected direction. Although these associations remained significant after covarying for indices of normative substance use, they did not fully explain the latent genetic factor of addiction in either model. The results therefore provide partial support for the three-stage model of addiction while highlighting that a significant proportion of the genetic etiology of addiction is not explained by these constructs.

The latent genetic factor of addiction was also regressed onto three latent genetic factors of psychopathology—compulsive disorders, psychotic/mood disorders, and neurodevelopmental disorders—as previously modeled in the literature [1]. Here, significant genetic associations between addiction and all predictors were again observed, where neurodevelopmental and compulsive disorders represented the strongest and weakest predictors, respectively. Interestingly, the genetic association between the addiction and compulsive disorders factors was negative, and after accounting for normative substance use, it was non-significant. This suggests that disorders characterized by addiction and compulsivity may be influenced by distinct genetic factors—at least as currently modeled.

Overall, Hatoum et al. generate novel insights into the shared genetic etiology of substance use disorders and their interplay with other complex traits. While questions about the specific nature of this etiological overlap remain, these findings complement contemporary studies, such as a large multivariate GWAS of the "externalizing" spectrum [3] and an examination of how substance use disorders fit into the broader factor structure of psychopathology [4].

Findings from these recent genome-wide studies compel us to take a broader view of substance use disorders. While substance-specific pathways remain important to study, a growing literature now implicates diverse, developmentally-relevant pathways in the etiology of multiple substance use disorders. Results like those reported in this issue shed new light on the genetic correlates of addiction, and they have great potential to usher in a new age of biomedical investigation for one of society's most devastating problems.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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