

## A Developmental Perspective on the Role of Genes on Substance Use Disorder

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Despite recent technological advances in genotyping, understanding how specific genes contribute to risk for addiction remains challenging. Maximizing the utility of these advances requires interdisciplinary research to identify etiological pathways to substance use disorders (SUD) using a developmental framework. The focus also needs to continue to shift away from diagnoses, and toward understanding the genetics of intermediate behavioral phenotypes that play a major role in guiding and directing behavior. In a series of studies, the role of intermediate phenotypes that may be critical in linking genetic vulnerabilities to SUD are examined. This includes various levels of analyses (neurobiological, temperamental, behavioral) using multiple-mediator modeling. It is hypothesized that this strategy would offer a more articulated pathway for the unfolding of genetic risk than has been possible with cross-sectional direct effect models.

This work is based on a sample of adolescents recruited from the Michigan Longitudinal Study, an ongoing prospective study of youth from families with high levels of SUD and a contrast sample of families without SUD. Parents and children completed extensive assessments starting from early childhood into early adulthood. A portion of the participants were genotyped and a subset completed functional magnetic resonance imaging (fMRI).

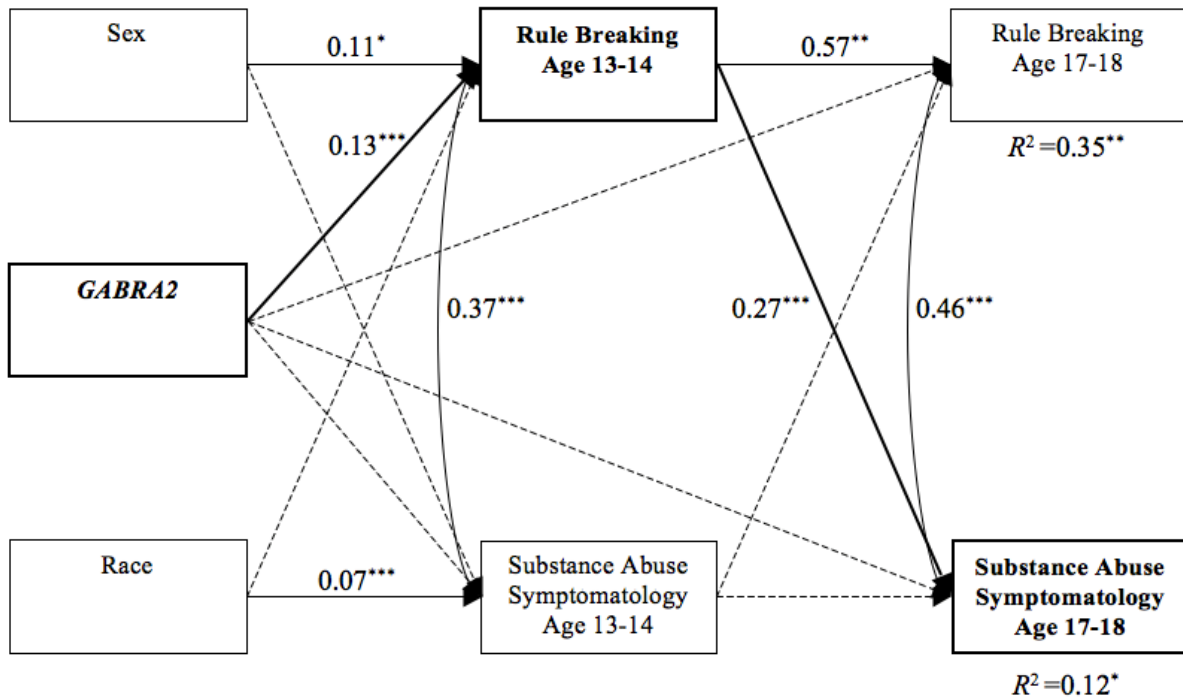
Study 1 ( $n = 518$ ) focused on GABA receptor subunit alpha-2 (*GABRA2*) variants (rs279858, rs279826, and rs279827), given evidence for their role in increasing SUD risk in adults. We examined age-specific associations between *GABRA2* and a developmental precursor to SUD (i.e., rule breaking/externalizing behavior), problematic alcohol use, and substance abuse symptomatology. We also examined whether rule breaking mediated the *GABRA2*-substance abuse relationship. G-allele carriers reported higher levels of rule breaking in mid- to late-adolescence, while *GABRA2* did not predict substance use outcomes across adolescence. Rule breaking mediated the association between *GABRA2* on substance use outcomes supporting an externalizing pathway to the development of alcohol use disorder and drug abuse (see Figure 1).

In Study 2 ( $n = 487$ ), this model was expanded to include relevant temperamental traits of resiliency and reactive control during childhood, as they represent strong precursors to externalizing behavior. Multiple genetic risk factors associated with adult SUD were also included: *SLC6A4*, 5-HTTLPR; *DRD4*, u-VNTR; *SLC6A2*, rs36021; *GABRA2*, rs279858; and *GABRA6*, rs3811995. Findings indicate that differences in emotional coping and behavioral regulation in childhood and externalizing behavior in early adolescence represent mechanisms through which specific genetic factors impact alcohol, cigarette, and marijuana use. For some youth, genetic risk may be expressed as early difficulties modulating distress. For other youth, genetic risk may be expressed as difficulties controlling impulses (see Figure 2).

In Study 3 ( $n = 80$ ), the utility of integrating genetics, imaging, and measures of temperament to identify mechanisms of genetic effects on problem behavior is demonstrated. It was expected that brain activation to emotional words would differ across *GABRA2* (rs279858) genotypes, which would lead to differences in childhood temperament. In turn, temperament would predict early adolescent externalizing behavior. Findings indicate that those with the GG genotype had reduced arousal to both positive and negative words. Blunted activation to positive words predicted higher negative emotionality in childhood, leading to higher externalizing problems in adolescence (Figure 3A). Blunted activation to negative words predicted higher resiliency in childhood, leading to lower externalizing problems in adolescence (Figure 3B). This suggests a potential tradeoff of emotional hyporesponsivity among youth with the GG genotype.

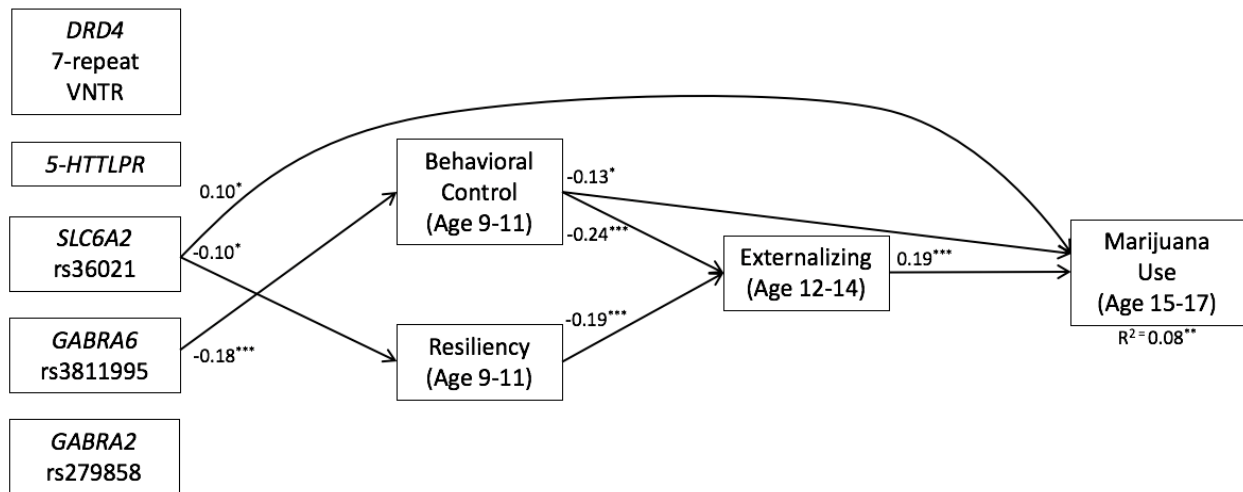
Improving prevention programming requires a better understanding of development precursors of health risk and age-relevant intermediate phenotypes that lead to addiction. Risk for abuse and dependence occurs well before the onset of actual use. Testing for prospective genetic pathways to addiction via the operation of non-specific risk behaviors across development is innovative because it articulates the mechanistic structure of the process, and in so doing identifies specific behavioral operations taking place at specific ages.

Figure 1.



Note. Cross-lagged model for substance abuse symptomatology. Note. Model fit: RMSEA = .022, CFI = .995, TLI = .979. Values represent standardized path coefficients. Dashed lines represent non-significant paths (\* =  $p < .05$ , \*\* =  $p < .01$ , \*\*\* =  $p < .001$ ). Bold lines represent a significant mediated path.

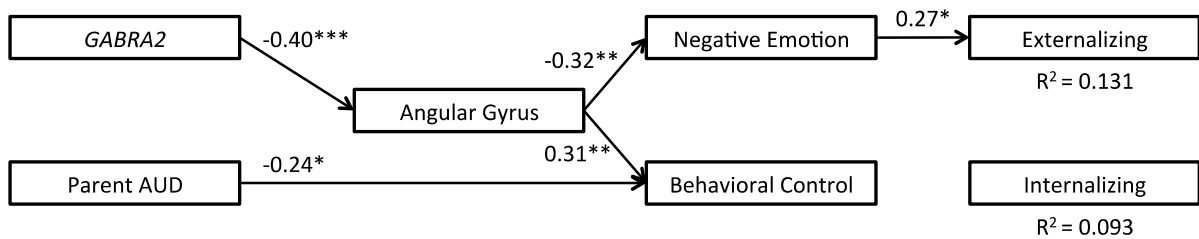
Figure 2.



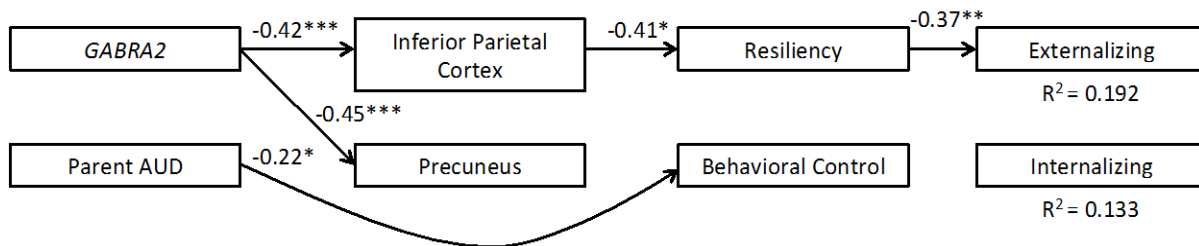
Note. Model for marijuana use. Values represent standardized path coefficients. Only significant paths (\* =  $p < .05$ , \*\* =  $p < .01$ , \*\*\* =  $p < .001$ ) are presented. Covariates and covariances are not depicted. Model fit =  $\chi^2 = 8.92 (10)$ ,  $p = 0.54$ , RMSEA = 0.00, CFI = 1.00. Findings are comparable when predicting problematic alcohol use and frequency of cigarette use.

Figure 3.

Panel A.



Panel B



Note. Estimated standardized path coefficients. Only significant paths are presented (\* =  $p < .05$ , \*\* =  $p < .01$ , \*\*\* =  $p < .001$ ). Panel A. Comparison of positive words versus neutral words (POS). Model fit:  $\chi^2 = 11.46$  (10),  $p = 0.32$ , RMSEA = 0.04, CFI = 0.96, TLI = 0.89. Panel B. Comparison of negative words versus neutral words (NEG). Model fit:  $\chi^2 = 5.11$  (5),  $p = 0.40$ , RMSEA = 0.02, CFI = 1.00, TLI = 0.99.

