The Factor Structure of the Externalizing Spectrum in Adolescence and the Role of GABRA2

by

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ABSTRACT

The present study tested the factor structure of the externalizing disorders (e.g. attention-deficit hyperactivity disorder (ADHD), conduct disorder (SE), and substance experimentation (SE)) in adolescence. In addition, this study tested the influence of the GABRA2 gene on the factors of the externalizing spectrum. Confirmatory factor analyses were used to test the factor structure of the externalizing spectrum. Specifically, three competing alternate confirmatory factor analytic models were tested: a one-factor model where all disorders loaded onto a single externalizing factor, a two-factor model where CD and SE loaded onto one factor and ADHD loaded onto another, and a three-factor model, where all three disorders loaded onto separate factors. Structural equation modeling was used to test the effect of a GABRA2 SNP, rs279858, on the factors of the externalizing spectrum. Analyses revealed that a three-factor model of externalizing disorders with correlated factors fit the data best. Additionally, GABRA2 had a significant effect on the SE factor in adolescence, but not on the CD or ADHD factors. These findings demonstrate that the externalizing disorders in adolescence share commonalities but also have separate sources of systematic variance. Furthermore, biological mechanisms may act as a unique etiological factor in the development of adolescent substance experimentation.

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INTRODUCTION

Overview

Comorbidity among psychiatric disorders is a common phenomenon that occurs in both epidemiological and clinical samples (Clark, Watson, & Reynolds, 1995). Results from the Epidemiological Catchment Survey (ECA; Robins et al., 1991) showed that 60% of respondents with at least one lifetime DSM disorder also had at least one comorbid disorder. Also, the National Comorbidity Survey (NCS; Kessler et al., 1994) indicated that the vast majority (79%) of all lifetime disorders in a sample of 8098 respondents were comorbid disorders.

Data also indicate that comorbidity between disorders is not random; in fact, most disorders systematically co-occur with certain diagnostic classes or disorders (Clark, Watson, & Reynolds, 1995). Many possible explanations exist for the occurrence of comorbidity. For example, formal models for comorbidity between multifactorial disorders proposed by Neale and Kendler (1995) include the possibilities that two disorders share the same underlying continuum of liability, that one disorder sharply increases risk for developing a second disorder, that only extreme cases of one disorder increase risk for developing the second, that two disorders are caused by a third, separate disorder, that the risk factors for the two disorders are correlated, or that liability for one disorder directly causes the second. Understanding and developing these broader conceptualizations of psychological disorders can help identify the common etiological or maintaining

factors among subsets of disorders and can have important implications for clinical diagnosis and treatment.

The Externalizing Spectrum

Recently, confirmatory factor analytic (CFA) methods have been used to test competing hierarchical models of psychiatric disorders in order to better understand comorbidity. This research operates under the assumption that psychiatric disorders may be manifestations of latent liabilities that underlie putatively unique disorders and this, in turn, may help account for diagnostic comorbidity (i.e. shared continuum of liability; Farmer et al, 2009; Krueger et al., 2002). Findings from such studies have consistently demonstrated that psychiatric disorders fall into a hierarchical organizational structure consisting of two higher-order latent factors, internalizing and externalizing. Moreover, much research has attempted to identify the factor structure of these two higher-order factors. The current study focuses on the structure of the DSM-defined externalizing spectrum in adolescence. Broadly, the externalizing spectrum has been conceptualized as a general vulnerability dimension underlying and connecting the psychological syndromes and personality traits of antisocial behavior, substance dependence, impulsivity, and disinhibition (Patrick, Curtin, & Krueger, in press). In terms of DSM-IV diagnostic categories, previous research has generally considered the externalizing spectrum in adolescence to consist of attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD),

alcohol dependence (AD), and drug dependence (DD) (Farmer et al., 2009; Krueger & Markon, 2006; Lahey et al., 2008).

These externalizing disorders in adolescence are a focus of the current study for several reasons. Adolescence is a particularly interesting developmental period when disruptive behavior disorders and substance use are highly comorbid (Lewinsohn et al., 1995), a variety of externalizing problems emerge, and the trajectory of individual externalizing behaviors varies considerably (Bongers et al., 2004). Additionally, the initiation of certain externalizing behaviors in adolescence, such as cigarette smoking and alcohol use, has been shown to significantly raise the risk for smoking, alcohol and marijuana use, antisocial personality symptoms, and criminality in adulthood (Chassin et al., 1990; Flory et al., 2004). Gaining a better understanding of the latent factors that may characterize these disorders in adolescence can give us more insight into the nosology, etiology, and clinical issues surrounding the externalizing disorders and can inform early prevention efforts.

Evidence for a One-Factor Model of Externalizing Disorders

Many studies have attempted to model the externalizing spectrum in adulthood and adolescence. One well-replicated finding among these studies is that a single latent factor best represents the externalizing disorders (Krueger, 1999; Krueger, Caspi, Moffitt, & Silva, 1998; Vollebergh et al., 2001). It is important to note that heterogeneous age ranges were assessed in the studies presented here. One such study demonstrated that a hierarchical three-factor

structure, characterized by two-lower order factors of a broader internalizing factor and a single externalizing factor including AD and DD had the most parsimonious fit for data provided by adults in the community (Slade & Watson, 2006). Krueger and Markon (2006) performed a meta-analysis on published multivariate comorbidity models and tested competing alternative models that included more than one externalizing factor. The meta-analysis included individuals from the ages of 15 into adulthood. Similarly, they found that two superordinate factors, internalizing and externalizing, fit the data best. The externalizing factor consisted of AD, DD, APD, and CD, and the higher-order internalizing factor further bifurcated into two-lower order internalizing factors. Vollebergh et al. (2001) replicated these findings in a sample of adults between the ages of 18-64 and confirmed that a hierarchical three-factor model fit the data best, with one externalizing factor consisting of AD and DD and two internalizing factors. Interestingly, Beesdo-Baum et al. (2009) attempted to replicate this hierarchical three-factor model in a sample of adolescents and young adults (14-34 years) and found that although a three-factor model fit the data, the higher-order 'internalizing' factor had to be omitted; thus this study confirms a one-factor model of externalizing comprised of AD, DD, and APD as well.

A two-factor model consisting of internalizing and externalizing disorders has also been supported in the literature. These studies found that a single externalizing factor consisting of AD, DD, and APD in a sample of 15-54 year olds (Krueger, 1999), CD, marijuana dependence, and AD at ages 18 and 21

(Krueger et al., 1998), and AD, DD, APD, and CD in a sample of adults (Kendler et al., 2003) fit the data the best.

Other studies have attempted to model the externalizing disorders in isolation from the internalizing disorders. Young, Stallings, Corley, Krauter, and Hewitt (2000) found that the covariation among CD, ADHD, early substance experimentation, and novelty seeking in 12-18 year olds were best characterized by a single latent factor. A genetically informative modeling study by Hicks, Krueger, Iacono, McGue, and Patrick (2004) using symptom counts of CD, adult antisocial personality disorder (APD), AD, and DD was suggestive of a single underlying externalizing trait in those aged 16-18. Krueger et al. (2002) also used symptom counts of CD, adolescent antisocial behavior, AD, DD, and disinhibitory personality traits to model the externalizing spectrum with a sample of 17 year old twins. They found that a general factor linked the externalizing syndromes, but distinct etiologic factors also differentiated between each externalizing syndrome. Furthermore, Krueger et al. (2005) used latent class and latent trait models to examine the underlying dimensional structure associated with CD, APD, alcohol dependence, and drug dependence in adults. They demonstrated that a continuous and normally distributed latent continuum of risk best described the externalizing disorders.

One-Factor Models: Methodological Limitations

Although a one-factor model of externalizing disorders is a well-replicated finding, it is noteworthy that many of the modeling studies reporting a one-factor

model of DSM-defined externalizing disorders only examined limited sets of externalizing disorders (Krueger et al. 2003; Kendler, Prescott, Myers, & Neale, 2003). For instance, several studies only included AD and DD in their models (Slade & Watson, 2006; Vollebergh et al. 2001) and across other studies, inconsistencies emerged in whether marijuana dependence, CD, disinhibition, novelty-seeking, and/or APD were included in the models (Krueger et al., 1998; Kendler et al., 2003; Young et al., 2000).

Most of the studies reporting a one-factor model also did not include important childhood externalizing disorders such as ADHD. More specifically, in all the studies noted above only Young et al. (2000) included ADHD in their factor model. This is a major oversight as studies have reported prevalence rates of ADHD at 12.8% in preschoolers and between and 8.8-9.0% throughout adolescence using diagnoses based on the DSM-IV (Lavigne et al., 2009; Merikangas et al, 2010). More importantly, research has identified ADHD without symptoms of CD as a risk factor for CD and APD, and consequently, for substance use disorders (Biederman et al., 1996; Barkley et al., 2004; Mannuzza et al., 2008). ADHD is also highly comorbid with CD (Burt et al., 2001). In order to accurately characterize the externalizing disorders, it is important to include ADHD in modeling studies.

The exclusion of these important childhood and adulthood externalizing diagnoses is also problematic because evidence has demonstrated that the factor structure of common DSM mental disorders may not be stable with the addition

of diagnoses (Wittchen et al., 2009). As mentioned earlier, one consistently replicated finding is that a hierarchical three-factor model, with one broad internalizing factor which bifurcates into two lower-order factors and one externalizing factor, best fits data comprised of ten common DSM mental disorders (Slade & Watson, 2006; Krueger & Markon, 2006; Vollebergh et al., 2001; Kessler et al., 1994). Wittchen et al. (2009) discovered that this hierarchical three-factor model no longer provided a robust fit when tested with the addition of previously excluded disorders (i.e. ADHD). Therefore, it stands to reason that previous studies reporting a one-factor model of externalizing disorders may not be entirely accurate due to the exclusion of important childhood and adulthood externalizing disorders.

Although much work has been done to model the externalizing spectrum, its structure specifically in adolescence has been less studied. Indeed, a couple of the aforementioned studies did include adolescents in their sample (e.g. Young et al., 2000; Beesdo-Baum et al., 2009), but these did not include the full range of possible externalizing disorders. Thus, further research that accounts for the methodological and conceptual limitations present in many of the studies reporting a one-factor model and that examines the factor structure of the externalizing disorders in adolescence is warranted.

Evidence for a Two-Factor Model of Externalizing Disorders

Although much evidence exists to support one common externalizing factor, other studies have shown that there may be distinctions among these

disorders as well. Specifically, researchers have found evidence to support a model of externalizing disorders where CD and substance use have some common liability that is unique from that of ADHD. For example, Farmer et al. (2009) evaluated four competing alternative models of disorders from the externalizing domain which included the DSM-III-R and DSM-IV defined disorders of ADHD, ODD, CD, APD, AD, cannabis use disorder (CAN), and hard drug use (HD). Importantly, this modeling study included substantially more putative childhood and adulthood externalizing disorders in comparison with other similar studies. Farmer and colleagues found that a two-factor model fit the data the best, with the first factor characterized by ADHD and ODD symptoms like inattention and intrusion and the second factor characterized by a general tendency to break rules that included CD, APD, AD, CAN, and HD symptoms (coined the 'social norm violation disorders'). Moreover, a plethora of studies have suggested that the relation between ADHD and substance abuse disappears once comorbid CD is taken into account, while CD remains a significant predictor of substance use (Lynskey & Fergusson, 1995; Disney et al., 1999; Flory & Lynam, 2003; August et al., 2006). Along the same vein, research indicates that CD, APD, alcohol, cannabis, and/or drug diagnoses are best accounted for by a single latent factor (e.g. Krueger et al., 2005; Young et al., 2000). A recent article by Beauchaine et al. (2010) summarized the potential for protective and high-risk environments to differentiate between the development of ADHD-only diagnosis and the development of comorbid ADHD, CD, and more severe antisocial personality

traits in adolescence. Thus, this review suggests that environmental factors may distinguish between ADHD and CD diagnoses. Recent work also suggests that ADHD and CD result from distinct primary deficits, with deficits in executive inhibition acting as the primary deficit in those with ADHD and reactive disinhibitory processes acting as the primary deficit in those with CD (Nigg, 2003). Taken together, these findings suggest that substance use and conduct disorder may share a common liability that is unique from the vulnerability for ADHD.

Need for Replication with Adolescents

As mentioned previously, adolescence is a particularly important and understudied period during which to examine the structure of the externalizing disorders. However, the question still remains as to whether a one-factor model of the externalizing spectrum would hold with the addition of more putative childhood externalizing diagnoses as well as with a sample of adolescents. Additionally, although Farmer and colleagues included substantially more externalizing diagnoses, no studies have yet looked at whether a two-factor model distinguishing ADHD from CD and substance use would hold for a sample of adolescents only. Certainly this is an important distinction as Wittchen et al. (2009) discovered that the hierarchical three-factor model of disorders described above (with a single externalizing factor) did not fit the data robustly when tested with more putative disorders and within four age bands of participants aged 1-34 years. This suggests that, not only might the factor structure of the externalizing

disorders vary across ages, but potentially important developmental differences may emerge when examined across different age bands. For example, distinct substance use factors may not emerge at younger ages due to the lower rates of substance use in youth compared to adults. Similarly, factor analyses that include ADHD would likely yield different results when assessing different age groups because this disorder appears at a higher rate in childhood/adolescence than in adulthood (Faraone & Biederman, 2005).

Genetic Differences Between the 'Social Norm Violation Disorders' and ADHD

Evidence from twin studies and studies using measured genes also suggests that genetic differences may exist between ADHD and the 'social norm violation disorders', providing further substantiation for a two-factor model of putative externalizing disorders. For example, Hicks et al. (2004) and Kendler et al. (2003) both reported a highly heritable general vulnerability for the social norm violation disorders of CD, APD, AD, and DD in two independent twin studies. A genome-wide scan also identified a chromosomal region that demonstrated linkage to both conduct disorder and adult alcohol dependence (Dick et al., 2003). Furthermore, Comings et al. (2000a; 200b) demonstrated that CD may be genetically distinct from ADHD.

Taken together, these findings suggest that genetic distinctions exist between these two factors. However, no studies have yet looked at which particular genes might account for this difference. Taking this next step will be

crucial in order to further understand the comorbidity between and etiology of the externalizing disorders.

The Role of the GABA System in Externalizing Disorders

A multitude of genes and their associated neurotransmitter systems have been associated with externalizing disorders. One particularly promising avenue to explore in differentiating between the social norm violation and ADHD is the GABA system. GABA acts as the vertebrate brain's main inhibitory neurotransmitter (Barnard et al. 1998), and $GABA_A$ receptors undergo allosteric modulation by a variety of drugs such as ethanol, benzodiazepines, barbituates, and anesthetics (Enoch, 2008). Studies have suggested that GABA plays a mediating role in the relationships between ethanol consumption and anxiolysis, sedation, motor coordination, and ethanol tolerance and dependence (Buck, 1996; Grobin et al. 1998; Korpi, Makela & Uusi-Oukari, 1998). Animal studies have also demonstrated that $GABA_A$ agonists increase ethanol intake in rats and $GABA_A$ antagonists decrease ethanol intake in rats (Boyle et al. 1993; Tomkins & Fletcher 1996; Nowak et al. 1998). GABAergic interneurons within the ventral tegmental area (VTA) are also primarily responsible for the inhibitory regulation of dopamine neurons (Johnson and North, 1992; Steffensen et al., 1998). Importantly, the dopamine system has long been identified as the "reward" pathway which influences a variety of compulsive, impulsive, and addictive behaviors. Thus, via its regulatory functions over the dopamine system, the

GABA system is also thought play a role in compulsive and addictive behaviors such as substance use, CD, and ASPD (Comings & Blum, 2000).

Candidate gene family studies have also found associations between chromosome 4p (region where some GABA genes are encoded) and alcoholism (Reich, 1996; Reich et al., 1998; Song et al., 2003). Moreover, chromosome 4p displayed linkage to brain oscillations in the β frequency band of the electroencephalogram (13–28 Hz; EEG-β), which is a biological endophenotype that has been found to have increased power in alcoholics compared to controls (Costa and Bauer 1997; Rangaswamy et al. 2002) and in the offspring of male alcoholics (Bauer and Hesselbrock 1993; Rangaswamy et al. 2004). Another biological endophenotype, P300 response, is an event-related potential that is highly heritable and also showed evidence of linkage with chromosome 4 (Dick et al., 2006). Notably, reduced P300 amplitude has been associated with conduct problems in adolescents (Bauer & Hesselbrock, 1999), antisocial personality disorder and alcohol dependence (Costa et al., 2000) and later substance use disorders (Habeych et al., 2005). Through associations with these biological endophenotypes, researchers have posited that the genes on chromosome 4 play a role in the general externalizing spectrum of disorders.

Evidence linking GABRA2 to the Externalizing Spectrum

Of the four genes found on chromosome 4p, Edenberg et al. (2004) discovered that only the GABRA2 gene was significantly associated with alcoholism in a sample of families with multiple alcoholic members assessed in

the Collaborative Study on the Genetics of Alcoholism (COGA). Furthermore, 31 of the 49 single-nucleotide polymorpisms (SNPs) in GABRA2 were significantly associated with alcoholism, while only 1 of the 20 SNPs in the other three genes on chromosome 4p were significantly associated, which is a level that reflects chance. Further analyses showed that the region extending from intron 3 past the 3' end of the GABRA2 gene had the strongest associations with alcoholism.

Using different samples and study designs, several studies have since replicated the initial finding from the COGA study demonstrating that GABRA2 is associated with alcoholism. Covault et al. (2004) found significant associations between alcoholism and seven adjacent SNPs on the GABRA2 gene, many of which were the same SNPs reported by Edenberg and colleagues. This group also detected the strongest associations with alcohol dependence in the 3' region of the GABRA2 gene. Two case-control studies by Lappalainen et al. (2005) and Fehr et al. (2006) examined this effect in Russian alcoholic men and controls and German alcoholics and controls, respectively. They both found significant associations of SNPs in the 3' region of the GABRA2 gene with alcohol dependence.

In addition to associations with alcohol dependence, GABRA2 has also been linked to a spectrum of externalizing disorders such as drug dependence, nicotine dependence, conduct disorder and antisocial personality disorder. Agrawal et al. (2006) reported associations between SNPs in the GABRA2 gene and marijuana and illicit drug dependence in the COGA sample. Interestingly, their results showed that GABRA2 was most strongly associated with comorbid

alcohol and drug dependence. The association between GABRA2 and illicit drug dependence was also replicated by Dick et al. (2006) with a sample of individuals from control families in the COGA study. Despite the lower rates of drug dependence in this sample, the magnitude of the genotype effect was similar to that found with the entire COGA sample. Drgon et al. (2006) found evidence of association between SNPs in the GABRA2 gene and polysubstance abuse in a sample of European American polysubstance abusers and controls. They also found that a haplotype of GABRA2 was present at significantly different allelic frequencies in African American polysubstance abusers compared to controls. Additionally, a case-control study consisting of nicotine-dependent cases and non-dependent smoking controls found that haplotypes of GABRA2 were associated with nicotine dependence (Agrawal et al., 2008).

Dick et al. (2006) also reported a significant association between the rs279871 SNP in GABRA2 and conduct disorder in a sample of children and adolescents. Specifically, those homozygous for the risk allele (A), which was also associated with alcohol dependence in the adult COGA sample, were significantly more likely to meet for a diagnosis of conduct disorder than those who were not homozygous for the A allele. Findings from the COGA study also revealed a higher rate of antisocial personality disorder in those with the high-risk GABRA2 genotype compared to those with the low-risk genotype; this finding was later replicated in an independent control sample as well (Dick et al., 2006). Clearly, GABRA2 is a strong contender to consider in elucidating the genetic

underpinnings of the externalizing spectrum, and more specifically, the social norm violation disorders of CD and substance use.

Developmental Considerations for the Influence of GABRA2

Recent evidence has emerged to suggest that GABRA2 may influence the 'social norm violation disorders', such as CD, AD, and DD, differentially across development. Dick et al. (2006) discovered that having one copy of the risk allele (A) in the rs279871 SNP of GABRA2 conferred risk for conduct disorder in those aged 7-17. Between the ages of 15-20, individuals possessing one copy of the risk allele had consistently elevated rates of alcohol dependence. Before the age of 15 and between the ages of 20-mid-20's individuals possessing the risk allele did not evidence significantly higher rates of alcohol dependence compared to those without the risk allele. The researchers posited that GABRA2 may not have been associated with alcohol dependence before the age of 15 because evidence suggests that the environment has a much greater influence than genetic factors on initiation of alcohol use in early adolescence and not many individuals had alcohol dependence at that time (Rhee et al., 2003; Rose et al., 2001). Additionally, the relation between GABRA2 and alcohol dependence may have been obscured, or diminished, between the ages of 20-mid-20's by the rise in alcohol use and/or dependence as individuals reached legal drinking age. Consistent with previous findings, as these participants reached their mid-20s the GABRA2 risk allele was again associated with increased incidence of alcohol dependence.

In the same study, GABRA2 was found to be associated with illicit drug dependence in adolescents after the age of 15 and through adulthood, which stands in contrast to the observed developmental trajectory between GABRA2 and alcohol dependence. This could be due to the fact that drug experimentation is a less normative behavior and may not be influenced by environmental factors, such as legal age of initiation, as may be the case with alcohol use (Dick et al., 2006).

Taken together, this evidence suggests that adolescence may be a developmental period during which GABRA2 has a distinct effect on all the "social norm violation disorders" of AD, DD, and CD. In other words, GABRA2 may have a particularly robust influence on the latent factor of the social norm violation disorders in adolescence. Yet, this is not to say that GABRA2 does not have important effects on this latent factor at other developmental stages. Note that, because the current study will assess the externalizing spectrum in adolescence, APD has not been included in this discussion as it is a disorder that can only be diagnosed in adulthood (after the age of 18 years).

The Potential Distinct Role of GABRA2 with the Social Norm Violation Disorders vs. ADHD

Thus far, all the work with the GABRA2 polymorphism has focused on associations with the social norm violation disorders. Given the proliferation of candidate gene studies, particularly with GABRA2, and the high heritability of a single externalizing factor, it is surprising that a paucity of research has been

published examining the relation between GABRA2 and ADHD. That the relation between GABRA2 and ADHD has not been established yet warrants further research. This, in combination with recent evidence for a two-factor model and the association between GABRA2 and the social norm violation disorders, could suggest that GABRA2 plays a role in distinguishing the social norm violation disorders and ADHD in adolescence. However, it is important to recognize that GABRA2 could represent just one of multiple genes that may distinctly underlie the social norm violation disorders. Moreover, ADHD and the social norm violation disorders may well share common, as well as distinct, genetic underpinnings. Thus, although GABRA2 may be a good candidate with which to examine the distinct genetic bases of some externalizing disorders, by no means is it the only important gene to consider or would it provide evidence for the complete differentiation between the two hypothesized factors.

The Current Study

Thus, the current study sought to test a two-factor model of externalizing disorders where substance use and conduct disorders load onto the same factor (social norm violation disorders) and ADHD loads onto a separate factor in adolescence. This model will be tested against two competing alternate hypotheses: that a one-factor model including all three disorders fits the data best, and that a three-factor model, where each disorder loads onto its own factor, fits the data best. Additionally, this study aimed to extend the current literature by testing whether a SNP in the GABRA2 gene significantly predicts the

hypothesized 'social norm violation' factor, and does not significantly predict the ADHD factor in adolescence. Furthermore, if the competing alternate models fit the data better, this research sought to examine the relation of the GABRA2 SNP to the factors in each model.

This study is the first, to our knowledge, to test and replicate the two-factor model of externalizing disorders with a sample of adolescents. Although previous studies have suggested that the social norm violation and ADHD may have distinct genetic underpinnings, this study will take the novel approach of examining whether a specific gene, GABRA2, accounts for these differences in adolescence. Importantly, this research draws on previous literature that shows that the effects of GABRA2 may be developmentally sensitive and thus, may have a distinct effect on the latent factor of the social norm violation disorders in adolescence. The findings will expand our understanding of the factor structure of the externalizing disorders in adolescence. Moreover, identifying the genes that influence the latent factors inherent in the externalizing disorders may prove helpful in uncovering the etiology of this class of disorders during the critical developmental period of adolescence.

METHOD

The Original Study

Participants

Participants for the current study are drawn from a longitudinal study of familial alcoholism (Chassin, Flora, & King, 2004; Chassin, Pillow, Curran,

Molina, & Barrera, 1993; Chassin, Pitts, DeLucia, & Todd, 1999). To date, six waves of data have been collected. Wave 1 began in 1988, Wave 2 in 1989, Wave 3 in 1990, Wave 4 in 1995, Wave 5 in 2000, and Wave 6 in 2006.

The total sample at Wave 1 consisted of 454 adolescents and their parents. In this study, the original adolescents are referred to as G2s and the parents are referred to as G1s. Of these G2 adolescents 246 were children of alcoholics (COAs), which means that at least one of their G1 biological parents, who was also a custodial caregiver, was an alcoholic. The remaining 208 G2 adolescents were demographically matched controls who did not have any G1 biological, custodial parents who were alcoholics. These adolescents (G2s) and their parents (G1s) were interviewed for three consecutive years (Waves 1, 2, and 3) after initial contact.

Waves 4, 5, and 6 were long-term follow-ups that began when the G2 adolescents reached emerging adulthood. In addition to the original 454 G2 adolescents, full biological siblings of both COAs and non-COAs were interviewed in Waves 4, 5, and 6. The added siblings are also referred to as G2s. Specifically, 327 G2 siblings were added at Wave 4 and 50 more siblings were added at Wave 5. Sample retention was excellent, with 407 (90%) of the original 454 G2 participants remaining in Wave 4, and 412 (91%) remaining in Wave 5. Of the 327 G2 siblings added in Wave 4, 300 (92%) were retained in the study at Wave 5. At Wave 6, 816 (90%) of the G2s were retained in the study and 745

G3s, or children of G2s, were added to the study. Currently, an 18-month follow-up data collection is being conducted with the G3 participants.

Recruitment

COA families

Several recruitment methods were utilized to obtain the participants in this study. Initially, court records, health maintenance organization wellness questionnaires, and community telephone surveys were used to recruit COA families. Records obtained from seven different court systems identified individuals who were convicted of driving while intoxicated between the years of 1984 and 1988. Inclusion criteria were non-Hispanic Caucasian or Hispanic ethnicity, Arizona residency, and a birth-date between 1927 and 1960. These court records were also used to determine indicators of alcoholism, which varied by court system. Depending on the court system, indicators of alcoholism included a blood alcohol content of at least .15 at the time of arrest, past alcohol-related arrests, a score of seven or higher on the Michigan Alcohol Screening Test (MAST; Selzer, 1971), or a diagnosis of probable alcoholism by a court substance abuse screening center. Using these records, the study recruited 103 COA families.

In addition to records from the court system, participants were recruited by examining HMO wellness questionnaire responses of those who joined a large HMO between 1986 and 1988. These new members who were arrested between 1984 and 1988 and met the previously mentioned inclusion criteria were then

assessed for multiple indicators of alcoholism including consuming 26 or more alcoholic drinks per week, reporting three or more alcohol-related social consequences, or self-labeling as an alcoholic. An additional 22 COA families were recruited using this method. Community telephone surveys were also used to recruit participants. Individuals who endorsed the aforementioned demographic criterion were then screened for alcoholism with the following indicators: being hospitalized for a drinking problem, reporting that their spouse was an alcoholic, or attending an Alcoholic Anonymous meeting. One-hundred twenty additional COA families were recruited with these telephone surveys. In addition, one COA family was recruited at the Veteran's Administration outpatient treatment program. Finally, 80 families who had initially been recruited as demographically matched controls were re-categorized as COA families after in-person interviews revealed the presence of parent alcoholism.

Following these initial screening and recruitment efforts, parental alcoholism diagnoses were verified face-to-face with the DIS-III, which is a structured diagnostic interview that allows for DSM-III diagnoses of lifetime alcohol abuse or dependence (Robins, Helzer, Croughan & Ratcliff, 1981). These interviews were conducted with the identified alcoholic parent unless he/she refused to participate; if so the refusing parent was diagnosed using their spouse's report on the Family History-Research Diagnostic Criteria (FH-RDC; Endicott, Andreason, & Spitzer, 1975). These structured interviews revealed that 219 biological fathers and 59 biological mothers met criteria for DSM-III alcoholism.

Non-alcoholic demographically matched control families

Recruitment of matched controls was achieved by using reverse directories to identify families who lived in the same neighborhood as COA families. Control families were matched on several variables including the original adolescent's age (within one year), family composition (one- vs. two-parent household), ethnicity, and socioeconomic status (based on property value codes or parental income). In order to be in the control group, neither the biological or custodial parents could meet DSM-III or FH-RDC lifetime diagnosis of alcohol abuse or dependence. However, the control group was not screened for any other DSM diagnoses in order to participate. Seventeen control families were eliminated from the study because they reported indicators of alcohol problems that were approaching the diagnostic threshold. This measure was taken in order to decrease the chances that a control parent would be diagnosed as an alcoholic at a later point in the project.

Recruitment biases

Two main sources of potential recruitment bias exist for this study: not all the potential COA participants were contacted and some individuals contacted refused to participate (Chassin, Barrera, Bech, & Kossak-Fuller, 1992). The potential bias of selective contact with potential COA participants was addressed by comparing the HMO and court archival records of the participants who were and were not contacted. Chi-square and t-test analyses demonstrated no significant differences between these two groups on blood alcohol level at the

time of arrest, self-labeling as an alcoholic, the number of prior alcohol-related arrests, or MAST scores. However, these analyses revealed that the non-contacted potential participants were more likely than contacted participants to be younger (37 vs. 39 years old), from court sources (90% vs. 87%), of Hispanic ethnicity (22% vs. 39 %), unmarried (64% vs. 48%), and to have a lower SES rating associated with their residence (t-tests and chi-square comparisons significant at $p<.05$).

Refusal to participate was the second source of recruitment bias. Of the potential COA families who were contacted through telephone surveys, 73% of the COA families and 77% of the control families participated. The remaining families who refused to participate did not differ from the non-refusers on alcoholism indicators, age, sex, or SES ratings. However, refusers were more likely to be Hispanic (24% vs. 18%) and married at the time of their arrest (69% vs. 50%). Of the potential matched control families, 91 families provided demographic information during the initial phone screen but ultimately refused to participate. Therefore, refusal bias in the matched control sample was assessed by comparing the control families who agreed to participate against those who refused. No significant differences emerged between the two groups in family composition or SES ratings of their residences. However, significant differences were found between the two groups with respect to ethnicity. Specifically, both mothers and fathers who refused to participate were more likely than non-refuser mothers and fathers to be Hispanic (41% vs. 18% and 40% vs. 22%, respectively).

Procedure

At each wave, consent and assent to participate were provided by parents and children. Subsequently, the families were interviewed either at the family's residence or at the Arizona State University campus. Trained staff members conducted all interviews by reading items verbally from a laptop computer. The participants had a choice between entering their responses directly into the laptop computer or responding verbally and allowing interviewers to enter their data. Family members who arrived to the session together were interviewed in separate rooms in order to increase the privacy and confidentiality of their responses. These interview sessions lasted between 1-2 hours and each family was paid $50 for their participation. Additionally, at Wave 6 G2s and G3s were given the option to participate in DNA testing. Participants could decline participation in this portion without consequences. G2s who agreed to participate provided consent and G3s who agreed to participate provided assent and received consent from the G2 guardian. They then provided a cheek brushing sample or saliva sample and were paid an additional $15 for their participation.

The Current Study

Participants

Two subsets of participants were used in the study. The first subsample of participants was used for the modeling of the externalizing spectrum and include those G2s who were between the ages of 12-18 years at waves 1, 2, and 3, were either of non-Hispanic Caucasian or Hispanic ethnicity, and had no missing data

on self-reported ADHD, CD, and substance use at all three waves (N=302). The second subsample of participants was used to determine whether there were genetic effects on the externalizing spectrum and include those G2s who were between the ages of 12-18 years at waves 1, 2, and 3, were successfully genotyped, were either of non-Hispanic Caucasian or Hispanic ethnicity, and had complete data on self-reported externalizing behaviors and substance use (N=138). A small percentage of the original sample (4.9%) self-reported as an ethnicity other than non-Hispanic Caucasian or Hispanic. These participants were dropped in order to avoid problems relating to population stratification. Descriptive data for the first subsample follow. The mean age was 13.80 years (SD=1.03) at wave 1, 14.74 years (SD=1.03) at wave 2, and 15.74 years (SD=1.04) at wave 3. The total mother-reported family mean income in the first subsample over the three waves ranged from approximately $39,423 - $39,679, 47% were female, 73.5% self-identified as non-Hispanic Caucasian, and 26.5% self-identified as Hispanic. More than half of the G2's mothers' (56%) and fathers' (57.8%) had at least some college education at wave 3 and 52.6% of the G2s were identified as children of alcoholics (COAs). Descriptive data for the second subsample (those who were also genotyped) follows. The mean age was 13.77 years (SD=1.04) at wave 1, 14.70 years (SD=1.05) at wave 2, and 15.70 years (SD=1.06) at wave 3. The total mother-reported family mean income in the first subsample over the three waves ranged from approximately $37,766 - $39,7570, 50.7% were female, 72.5% self-identified as non-Hispanic Caucasian,

and 27.5% self-identified as Hispanic. More than half of the G2's mothers' (56.4%) and fathers' (54.5%) had at least some college education at wave 3 and 52.9% of the G2s were identified as children of alcoholics (COAs).

A series of analyses were conducted to determine if any differences were evident between the G2s at Wave 3 who were included in the first and second subsamples versus those who were excluded. The participants were compared on all proposed variables in the model including gender, age, ethnicity, COA status, highest level of parent education, child report of externalizing behaviors, and child-report of own substance use. The first subsample (N=302) had significantly higher CD symptoms at waves 1 ($t(447)=-3.29$, $p=.001$, Cohen's $d=.33$), 2 ($t(444)=-3.57$, $p<.001$, Cohen's $d=.36$) and 3 ($t(432)=-2.6$, $p=.01$, Cohen's $d=.27$), ADHD symptoms at wave 1 ($t(450)=-2.21$, $p=.028$, Cohen's $d=.22$), number of substances used at wave 3 ($t(307.6)=-2.42$, $p=.016$, Cohen's $d=.24$), and age at waves 1 ($t(230.7)=-13.11$, $p<.001$, Cohen's $d=1.45$), 2($t(219.6)=-12.94$, $p<.001$, Cohen's $d=1.46$), and 3 ($t(214.3)=-13.29$, $p<.001$, Cohen's $d=1.51$) compared to excluded participants. The two groups also differed significantly on ethnicity ($\chi^2(4)=49.41$, $p<.001$, Cohen's Omega=.40). These differences are likely due to the age and ethnicity exclusion criteria that defined the first subsample. The second subsample (N=138) did not differ significantly from the excluded participants on the aforementioned variables except the second subsample had significantly higher age at waves 1 ($t(371.3)=-6.36$, $p=.001$, Cohen's $d=.56$), 2 ($t(370)=-6.18$, $p=.001$, Cohen's $d=.55$), and 3 ($t(369.3)=-6.24$, $p=.001$, Cohen's

d=.56) compared to excluded participants, and the two groups differed significantly on ethnicity ($\chi^2(4)=11.25$, p=.024, Cohen's Omega=.29). See Tables 1 and 2 for further details.

Measures

The measures used in the current study were administered as part of a larger interview battery administered in the longitudinal study described above. Descriptive statistics for the variables in the first and second G2 subsamples are presented in Tables 3 and 4.

Adolescent Demographics

Adolescents self-reported their gender and age. Gender was dummy coded, with females coded 0 and males coded 1. A continuous age variable was computed for each adolescent as the number of years between their date of birth and their interview date. Age at wave 3 was used for the analyses because there was greater variability compared to age reports at wave 1. Adolescents self-reported on their ethnicity using the following options: Non-Hispanic Caucasian; Hispanic; Asian, Oriental, or Pacific Islander; American Indian; Black or Afro-American; or Other.

Parental Education and Total Family Income

Mothers and fathers reported on the highest level of education they received. The response options were as follows: 1 (grade school), 2 (some high school), 3 (high school graduate), 4 (technical school), 5 (some college), 6 (college graduate), and 7 (graduate school/professional school). The highest level

of education obtained by either mother or father at wave 3 was used as an indicator of socioeconomic status (SES). If this indicator of SES was missing at wave 3, then wave 2 or wave 1 SES was used. Mothers and fathers were also asked to report their total family income; there were no response options for this item.

Adolescent ADHD and CD

Adolescent ADHD and CD symptom counts during the past 3 months were assessed using the Child Behavior Checklist (CBCL; Achenbach, 1978) at all three waves. The CBCL was administered to adolescents and consisted of 40 items. This measure contains four subscales of adolescent symptomatology: internalizing, externalizing, aggression, and hyperactivity. The externalizing and aggression subscales also included Achenbach youth-self report items that were modified to match the CBCL item formats. The adolescents rated how often each item has been true of them in the past three months (e.g. "I argued a lot," "I disobeyed at school" "I stole things at home," "I threatened to hurt people"). These items were scored on a three-point Likert scale: 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true). However, in the original longitudinal study the response scale for the adolescent self-report was modified to a five-point Likert scale in order to increase the variance of the adolescent's scores and to eliminate the confounding effects of frequency and intensity in a single response scale. Each item in the modified adolescent self-report battery was

scaled accordingly: 0 (almost never), 1 (once in a while), 2 (sometimes), 3 (often), or 4 (almost always).

For the purposes of the current study, each item in the adolescent-version was re-scaled to the original three-point scale. The modified options of '1' (once in a while) and '2' (sometimes) were collapsed to represent the original scale option of '1' (somewhat or sometimes true) and the modified options of '3' (often) and '4' (almost always) were collapsed to represent the original scale option of '2' (very true or often true). The response option '0' (almost never) remained the same.

Selected items from the CBCL can be scored according to DSM-oriented subscales, which were constructed by panels of expert psychiatrists and psychologists who identified the CBCL items that closely reflected DSM-IV criteria. In the current study, we used these criteria to construct DSM-oriented symptom scales of ADHD and CD. Seven of the 22 items could not be assessed because they were not included in the 1978 version of the CBCL. To compute symptom scales, items from each subscale (response options from 0-2) were summed. Thus in this study, child-report of ADHD consisted of 4 items and scores ranged from 0-8 and CD consisted of 12 items and scores ranged from 0-24.

The CBCL is one of the most widely used measures of behavioral/emotional problems in children with established reliability and predictive validity (Runyan et al., 1998). Good internal consistencies have been

reported for the adolescent's self-report (Cronbach's Alpha ranging from .70-.86), and the measure has been demonstrated as a reliable indicator of child conduct, oppositional defiant, and aggressive behaviors (Achenbach & Rescorla, 2001). Good test-retest correlations have also been established for the subscales of the adolescent's self-report (.82-.88 over 8 days). In the current study, internal consistencies for the subscales of ADHD and CD ranged from .65-.79 for adolescent-report across the three waves and two subsamples. Only one reporter was chosen in order to maintain consistency (substance use was only reported by adolescents, see below) and to retain a sufficient sample size for the analyses.

Adolescent Substance Experimentation

Adolescents self-reported their substance experimentation by responding to items from a questionnaire adapted from a previous measure by Sher et al. (1987). The measure by Sher et al. (1987) was originally adapted from questionnaires by Blane (1987) and Jessor & Jessor (1973). Nine items assessed how often in the past year the adolescent typically: got drunk on alcohol, used marijuana, amphetamines, quaaludes or barbituates, tranquilizers, hallucinogens, cocaine or crack, opiates, or inhalants. Responses were scaled on an 8-point Likert scale (0=never to 7=everyday). Alcohol use was defined as whether the adolescent had "gotten drunk" in order to capture a more severe group of substance-users.

Adolescent substance experimentation for each wave was defined as the number of substances the adolescent used (at least one time) in the past year.

Their responses were then categorized into three groups with 0 indicating never having tried any substances in the past year, 1 indicating having tried 1 substance in the past year, and 2 indicating having tried 2 or more substances in the past year. There were no overlapping items between the items on the DSM-oriented subscales from the CBCL and the substance use items, so no items were deleted.

GABRA2

Genotyping was done through the Washington University Genome Sequencing Center of the Midwest Alcohol Research Center (MARC) with assistance from a bioinformatician from the Division of Human Genetics. The SNPS were scored using Illumina's Assay Design Tool to ensure designability. After genotyping was complete, the following quality control analyses were conducted: (1) cluster plots were examined to rule out ambiguous genotype calls; (2) checks for Mendelian inconsistencies, incorrect gender assignments and sample swaps, and cryptic relatedness were conducted and appropriate corrections were made; (3) SNPs with low call rates (< 95%) and deviations from Hardy-Weinberg equilibrium ($p < 10^{-6}$) were flagged. A SNP from the GABRA2 gene was used in the analysis. This SNP, rs279858, encodes a silent polymorphism in exon 5 of the GABRA2 gene and has two alleles, G and A. The GABRA2 SNP was coded with a series of dummy codes. These dummy codes compared the AA homozygote genotype to the AA and GG genotypes. Another series of dummy codes was used to compare the AA and GG genotypes. The SNP was in Hardy-Weinberg equilibrium (p=.64) and had excellent call rates (98.385%). Among

self-identified non-Hispanic Caucasians, 68.0% (N=68) possessed at least one copy of the G allele and the minor allele frequency (MAF) was 40%. Among self-identified Hispanics, 65.8% (N=25) possessed at least one copy of the G allele and the minor allele frequency (MAF) was 36%.

Population stratification occurs when non-random mating among sub-groups results in systematic differences in allele frequencies between sub-groups in the sample. This phenomenon poses a threat to the internal validity of genetic association studies (Cardon & Palmer, 2003). Based on the non-significant correlation between ethnicity and the GABRA2 SNP (r=-.034, p=.70), we concluded that population stratification was not a threat to the internal validity of the study.

DATA ANALYTIC STRATEGY

Confirmatory Factor Analyses

Three competing alternative models (one-, two-, and three-factor models) of the externalizing spectrum were tested using CFA. The hypothesized model bifurcates into two correlated factors. The first factor consists of six indicators: conduct disorder symptom counts and substance experimentation at waves 1, 2, and 3. The second factor consists of three indicators: ADHD symptom counts at waves 1, 2, and 3. The next model that was tested was the one-factor model of externalizing. This single latent factor was indicated by ADHD and CD symptom counts and substance experimentation at waves 1, 2, and 3. The last model tested was a three-factor model of externalizing. This model had three correlated latent

factors of CD (indicated by CD symptom counts at waves 1, 2, and 3), ADHD (indicated by ADHD symptom counts and waves 1, 2, and 3), and substance experimentation (indicated by substance experimentation at waves 1, 2, and 3). See Figures 1 and 2 for a pictorial summary of the three competing models.

The WLSMV estimator was used because the dependent variables were continuous and ordered categorical. The WLSMV estimator produces weighted least square parameter estimates using a diagonal weight matrix with standard errors and mean-and variance- adjusted chi-square test statistic that use a full weight matrix (Muthén & Muthén, 1998-2007). The models were evaluated using an omnibus chi-square test of global model fit. This is used to test the null hypothesis that the model fits exactly in the population. Researchers typically consider an acceptable chi-square goodness of fit test statistic to be one whose p-value is above .05 (Saris, Satorra, & van der Veld, 2009). In addition, the models were assessed for goodness of fit based on whether the values of the following fit indices were in line with recommendations made by Hu & Bentler (1999): Comparative Fit Index (CFI): ≥.95, and Root Mean Square Error of Approximation (RMSEA) ≤ .06, and by Muthén & Muthén (2006): Weighted Root Mean Square Residual (WRMR) <.90. Furthermore, to study sources of lack of fit in case of an overall misfit, model residuals and model modification indices were examined.

Structural Equation Modeling

Depending on the best-fitting model, structural equation modeling was used to determine the effect of GABRA2 on the externalizing spectrum. Thus, if the hypothesized two-factor model fit the data better than the one-or three- factor models of externalizing disorders, both latent factors were regressed on the GABRA2 SNP in the structural equation modeling framework to test the hypothesis that GABRA2 significantly predicted one factor (indicated by CD and substance experimentation) in the two-factor model and not the second factor (indicated by ADHD). However, if the one- factor model of externalizing disorders fit the data better than a two-or three factor model, the effect of GABRA2 on the single latent externalizing factor was tested by regressing the externalizing latent factor on the GABRA2 SNP. Lastly, if the three-factor model fit the data best, the effect of GABRA2 on each of the three latent factors was tested by regressing each latent factor on the GABRA2 SNP. Paths were considered significant at $p<.05$.

Covariates and Covariate by Predictor Interactions

In addition to testing the effect of the GABRA2 SNP, the structural equation models also tested the effects of covariates and covariate-by-predictor interactions. Covariates were included to increase the power and sensitivity of the test by minimizing uncontrolled variability, and therefore to account for some variance that would otherwise be considered error (Cohen et al., 2003). Preliminary analyses were conducted to determine which covariates to include in

the final models. The continuous predictors were centered in order to reduce non-essential multicollinearity in analyses that include interaction terms (Cohen, Cohen, West, & Aiken, 2003). Covariate-by-predictor interactions were entered as the product of the covariate of interest and the GABRA2 SNP. Before estimating the final models, a preliminary model was estimated to test covariate effects of age, SES, ethnicity, gender, and parental alcoholism. Those significant at $p<.05$ were retained. Then, a preliminary model was estimated to test the covariate by predictor interaction effects by entering them with all the covariates in a separate model because the large number of independent variables made it unfeasible to test all the covariates and covariate-by-predictor interactions in a single model. Interaction terms (along with their corresponding covariate terms, regardless of their significance levels) were retained at $p<.05$.

RESULTS

Descriptive Statistics and Correlations

Descriptive statistics for the first and second subsamples are displayed in Tables 3 and 4, respectively. All continuous and ordered categorical variables are coded such that high scores indicate high levels of the variable. In the first subsample note the low correlations between ADHD and substance use at all three waves, and the comparatively higher correlations between CD and substance use at all three waves (Table A1). Also note that across all waves, parental alcoholism is significantly correlated with ADHD symptoms, CD symptoms, and substance use experimentation (COAs reported more), age is significantly correlated with

substance experimentation (older adolescents more likely to use), and gender is significantly correlated with CD symptoms, such that males reported more CD symptoms than did females. In the second subsample, note the significant correlation between the GABRA2 SNP (where AA is the reference group compared against the GG genotype) and substance use at wave 2 (Table B1). Also note the similar pattern of association compared to the first subsample with the covariates: age is significantly correlated with substance use at all waves, gender is significantly correlated with CD symptoms at wave 3, and parental alcoholism is significantly correlated with ADHD symptoms at all waves and CD symptoms at waves 1 and 2. Additionally at all waves, ADHD has comparatively lower correlations with substance experimentation than those between CD symptoms and substance experimentation, which is consistent with the current hypotheses. Surprisingly, parental alcoholism was not significantly correlated with the GABRA2 SNP despite the significant correlation between GABRA2 and substance experimentation at wave 2.

Confirmatory Factor Analyses

Confirmatory factor analyses were conducted using MPlus version 5.0 (Muthén & Muthén, 1998-2007). Table 5 presents the fit indicators for each of the models evaluated. Both the one factor and two factor models did not fit the data adequately. For the one factor model, the model fit information follow: χ^2=258.56, df=27, p<.001; RMSEA=0.169; CFI=0.704; WRMR=1.68. For the two factor model, χ^2=194.176, df=26, p<.001; RMSEA=0.146; CFI=0.785;

WRMR=1.439. Thus, neither of these models met the cut-off values suggested by Hu & Bentler (1999) and Muthén & Muthén (2006) to indicate good model fit. However, the fit indices of the three-factor model suggested that this model provided a good fit to the data: χ^2=53.794, df= 24, p<.001; RMSEA=0.064; CFI=0.962; WRMR=0.684. Each indicator (CD, ADHD, and substance experimentation at each wave) loaded significantly onto their respective factors (p<.001).

Despite the adequate model fit of the three-factor model, modification indices suggested that there was shared time-specific variance between the ADHD and CD indicators at the same wave. Indeed, both measures of ADHD and CD were derived from the same questionnaire. Thus, method and occasion-specific variance between these two indicators at each wave may explain the need for time-specific correlations to be modeled (Steyer, Ferring, & Schmitt, 1992). In the final three-factor model, this variance was modeled by allowing for the residuals of the ADHD and CD measures at the same time-points to be correlated. Correlations between the substance use and other indicators were not modeled.[1] Accounting for this method variance improved model fit indices, which are also presented below in Table 5: χ^2=29.694, df=21, p=0.098; RMSEA=0.037; CFI=0.989; WRMR=0.684. Each indicator (CD, ADHD, and substance experimentation at each wave) loaded significantly onto their respective factors. Additionally, all three residual correlations were substantial and significant (See Figure 3). This three-factor model with correlated factors of ADHD, CD, and

substance use was used in all subsequent analyses. See Figure 3 for a pictorial summary of the model as well as the standardized factor loadings.

Regression diagnostics

Mplus does not yield regression diagnostics, thus the models were run in OLS Regression using SPSS to examine the potential influence of outliers on regression models. No abnormalities were detected and therefore no outliers were deleted from the subsequent analyses.

Structural Equation Modeling: Covariate and Covariate-by-Predictor Interaction Effects

Preliminary analyses were conducted to determine which covariates and covariate-by-predictor interaction terms to include in the final analysis. Of note, all of the following analyses are done with the second subsample (N=138) who were genotyped. Different covariates for each latent outcome variable (ADHD, CD, and substance experimentation) were allowed because each of these outcomes may be differentially affected by the covariates and interactions. All continuous variables were centered. For each latent outcome variable, all of the covariates (age, gender, SES, ethnicity, and parent alcoholism) were tested as main effects. Parental alcoholism significantly predicted all three latent outcome variables, gender significantly predicted CD, and age significantly predicted substance use. Covariate-by-predictor interactions were not included in the final models[2]. The final model retained parental alcoholism and gender as covariates

predicting CD, parental alcoholism predicting ADHD, and parental alcoholism and age predicting substance use.

Structural Equation Modeling: Effect of GABRA2

The main effect of the GABRA2 SNP, rs279858, on each of the three latent outcome variables was tested using structural equation modeling. A total of 4, 3 and 4 independent variables were included in the models predicting CD, ADHD, and substance use, respectively. The factor loadings of each indicator on the three factors in this model (N=138) were similar to those from the previous model (N=302). See Figure 4. The model fit the data well: χ^2= 49.836, df=55, p=0.67; RMSEA=0.00; CFI=1.00; WRMR=0.553. The results of these analyses are shown in Table 6. The beta regression coefficients reported below are unstandardized. Gender significantly predicted the CD latent factor (*B*=1.075, *p* =.016) such that boys were higher in CD. There was also a significant relation between parental alcoholism and CD (*B*=1.22, *p* =.003), such that COAs were higher in CD. The GABRA2 SNP did not have a significant main effect on CD: there were no significant differences between the AA and AG groups (*B*=-0.021, p=.964) or the AA and GG groups (*B*=-.247, *p* =.710). Parental alcoholism also significantly predicted the ADHD latent factor (*B*= 0.839, *p* =.003), such that COAs were higher on the ADHD factor. There were no significant differences between the AA and AG groups (*B*=-0.130, *p* =.661) or AA and GG groups (*B*=-0.17, *p* =.714) on ADHD. Finally, both parental alcoholism and age were significant predictors of the substance experimentation factor, with COAs (*B*= 0.

592, p =.006) and older adolescents (B= 0.403, p =.001), reporting more substance experimentation. Interestingly, the GABRA2 SNP did have a main effect on the substance experimentation factor. The AA and AG groups (B= -0. 431, p =.047) and AA and GG groups (B= -0. 774, p =.028) were significantly different on the substance experimentation factor. Those with the AA genotype reported significantly more substance experimentation compared to those with the AG or GG genotypes. Post-hoc analyses revealed no significant differences between the AG and GG genotypes (B= -0.367, p =.269). See Figure 4 for a pictorial summary of these results. In the final model, the predictors accounted for 12.6% of the variance in the CD latent factor, 33.4% of the variance in the SE latent factor, and 8.7% of the variance in the ADHD latent factor. The incremental contribution of the GABRA2 SNP over and above the other predictors was .18% for the CD factor, 9.5% for the SE factor, and .2% for the ADHD factor.

DISCUSSION

The first goal of the present study was to compare different factor models of youth externalizing behavior. Confirmatory factor analyses demonstrated that, out of a one-, two-, and three-factor model, the three-factor model fit the data best. In this model, each of the three correlated latent factors were represented by ADHD, CD, and SE indicators. The second goal of the study was to evaluate the influence of the GABRA2 SNP, rs279858, on externalizing behaviors. Structural equation modeling showed that this GABRA2 SNP had a significant main effect

on the SE factor over and above parental alcoholism and age, but did not have an effect on the ADHD or CD factors.

The results from confirmatory factor analyses are contrary to the initially hypothesized two-factor model, where CD and SE comprise one factor and ADHD comprises another. Although previous studies have provided support for the distinction between ADHD and CD in childhood (e.g. Nigg, 2003; Beauchaine et al., 2010) and have tested and supported a two-factor model where CD and substance use are distinct from ADHD in adulthood (e.g. Farmer et al., 2009), no modeling studies to date have tested this two-factor model in adolescence. Interestingly, taking into consideration the unique developmental issues experienced in adolescence can help us understand why the factor structure of externalizing disorders in adolescence may look different from that in adulthood. Adolescence is a stage characterized by experimental substance use (Petraitis, Flay, & Miller, 1995), and the severity of adolescent substance use often must be measured by the level and/or frequency of use rather than the categorical or dimensional scales of abuse or dependence that are used in adult studies (e.g. Young et al., 2000; Verona et al., 2011; Castellanos-Ryan et al., 2011). Although adolescent substance experimentation is a risk factor for future substance abuse and dependence (Chassin, Pitts, & Prost, 2002), not all adolescents who experiment with alcohol or drugs will go on to develop a substance use disorder. The common one-factor model of externalizing behaviors in adulthood may be reflective of a stronger common cause between substance use disorders and

conduct and antisocial behaviors than between substance experimentation and conduct problems. Thus, in adolescence substance experimentation may represent a meaningfully distinct, but correlated, factor with CD and ADHD that describes a subset of adolescents who experiment with alcohol and drugs but may not necessarily develop a substance-use disorder later in life. It is likely that CD and ADHD symptoms overlap with substance experimentation in adolescence, which is explained in our data by the significant correlations between the three factors, but there may be some distinct underlying processes that drive *experimentation* with substances and not externalizing symptomatology. Accordingly, two recent adolescent modeling studies used measures of substance use frequency and both found that substance use formed a factor that was distinct from CD and/or ADHD (Verona et al., 2011; Castellanos-Ryan et al., 2011). Further research specifically examining the differentiation between substance experimentation in adolescence and substance use disorder in adulthood may be helpful in gaining a better understanding of why the factor structure of externalizing disorders varies across development. Moreover, our results are not consistent with the one-factor model found in adult data (Kendler et al., 2003; Hicks et al., 2004; Vollebergh et al., 2001).

Although our results are not consistent with the previous literature that found evidence for one- and two- factor models, our findings are not inconsistent with the common notion that both general and specific etiologic factors exist within the externalizing disorders. For example, Krueger et al. (2002) found that a

single hierarchical externalizing factor characterized the co-occurrence among alcohol dependence, drug dependence, conduct disorder, antisocial behavior, and a disinhibitory personality style. However, after accounting for this single factor there were still specific etiological factors attributable to each syndrome. Furthermore, recent studies modeling adolescent psychopathology found that CD and substance use shared some common variance but also shared specific sources of variance (Castellanos-Ryan & Conrod, 2011; Verona et al., 2011). Researchers have also suggested that ADHD and CD share a common diathesis but may be distinguished by parenting influences (see Beauchaine et al., 2010) and that ADHD and CD both result from reactive and executive disinhibition processes, but that ADHD primarily results from executive disinhibitory deficits while CD primarily results from reactive disinhibitory deficits (Nigg, 2003). These studies show that similarities exist among these disorders but that each disorder is also influenced by unique processes. Indeed, while three separate factors had the best fit to our data, there were also substantial intercorrelations between ADHD, CD, and SE in the final model. Thus, the findings from our competing alternate models of externalizing psychopathology in adolescence suggest that ADHD, CD, and SE have unique sources of significant specific sources variance but also may share common variance. However this study did not model a hierarchical single externalizing factor because, theoretically, modeling a higher order factor would not provide any additional information and would fit the same as our model with three correlated factors. Even though we did not model a higher order factor, the

significant and substantial correlations between the three factors provides evidence that they share common variance.

Our original hypothesis that the GABRA2 SNP, rs279858, would significantly predict the social norm violation disorders (CD and SE) and would not significantly predict the ADHD factor was not supported. Using the three latent factors from our best-fitting model as outcome variables, we found that GABRA2 significantly predicted the SE factor, but not the CD and ADHD factors. Specifically, we found that A allele homozygotes were more likely to experiment with substances (alcohol and other illicit drugs) than those with the A/G or G/G genotypes after controlling for adolescent age and parental alcoholism. A/G and G/G carriers did not differ in their substance experimentation.

Previous studies have identified two GABRA2 haplotype blocks in Caucasians, American Indians, and Asians, with significant association signals with alcoholism detected within the haplotype block extending downstream from intron 3 (Enoch et al., 2008). Numerous studies have found two major yin-yang haplotypes within this block, both of which account for a vast majority of the haplotype diversity in Caucasian and Asian samples. The haplotype tagged by the A allele of rs279858 is found to be of slightly higher frequency (‘major’ haplotype) than the haplotype tagged by the G allele of rs279858 (‘minor’ haplotype). While many previous studies have found a relation between GABRA2

and substance use and dependence, not all are in agreement regarding which allele or haplotype confers risk for such disorders.

For example Agrawal et al. (2006) found that the major, or more abundant, haplotype was associated most strongly with alcoholics with co-occurring drug dependence in a mostly Caucasian sample saturated for alcoholism (from the Collaborative Studies on Genetics of Alcoholism; COGA). From the same COGA sample, Dick et al. (2006b) also found that the major haplotype-tagging allele, A, on SNP rs279871 was associated with elevated rates of drug dependence and conduct disorder in adolescents from control or alcoholic families. Furthermore, Lind et al. (2008) found that GABRA2 SNPs tagging the major allele were associated with alcohol dependence symptoms and age at first alcohol symptom in an adult Australian population sample and, in a case-control study of German treatment-seeking alcoholics, Soyka et al. (2008) demonstrated that the major haplotype was associated with alcoholism.

On the other hand, several other case-control studies found the less frequent "minor" haplotype to be significantly more frequent among U.S. Caucasian (Covault et al., 2004), Russian (Lappalainen et al., 2005), and German (Fehr et al., 2006) treatment-seeking alcoholics than among controls. Interestingly, Covault et al. (2004) found that this minor haplotype was most strongly associated with alcoholics who were not drug dependent. Furthermore, the minor haplotype-tagging G allele of rs279858 was related to decreased unpleasurable effects of alcohol (e.g. dizziness, ringing, nausea, stomach bloating)

in a group of social drinkers (Pierucci-Lagha et al., 2005). Bauer et al. (2007) found that this same allele was associated with a higher daily probability of drinking and heavy drinking in alcoholics from the Project MATCH study, and Villafuerte et al. (2011) found evidence that this allele, and its associated minor haplotype, was related to alcohol dependence symptoms and NEO-PI-R Impulsiveness scores.

Although seemingly contradictory, the literature appears to indicate that both of the yin-yang haplotypes can increase the risk for substance use disorders. In support of this notion are findings from Enoch et al. (2006) who demonstrated that in a sample of Finnish male alcoholic criminal offenders and controls, those with high trait anxiety (as measured by harm avoidance) and alcoholism had the highest frequency of the major haplotype, those with low trait anxiety and alcoholism had the highest frequency of the minor haplotype, and non-alcoholics (whose mean levels of trait anxiety were intermediate between the two alcohol groups) had intermediate frequencies of the major and minor haplotypes. Thus, both major and minor haplotypes were over-represented in alcoholics in this study. The authors propose that trait anxiety may play a role in explaining some of the discrepancies in the identification of a risk haplotype or allele in the GABRA2 gene. Namely, Enoch and colleagues hypothesize that studies where the minor haplotype was associated with increased risk for alcoholism may have sampled alcoholics who had lower trait anxiety, while those where the major haplotype was associated with risk may have studied alcoholics who had higher

trait anxiety. The failure to account for these variables may help explain some of the variability in the literature.

Interestingly, Haughey et al., (2008) also found that both major and minor alleles of the rs279858 SNP conferred risk for an endophenotype of alcoholism. They found that those with the major haplotype-associated AA and minor haplotype-associated GG genotypes of SNP rs279858 reported greater alcohol-induced positive mood and feelings of vigor after an alcohol infusion challenge as compared to AG heterozygotes. These findings are consistent with the notion that greater frequencies of both the major and minor alleles can increase the risk for alcoholism. Based on the findings from Enoch et al. (2006), it would be interesting to test whether the association between GABRA2 and substance use disorders is moderated by measures of anxiety and whether this could elucidate the nature of the risk conferring alleles in the GABRA2 gene.

The lack of association between GABRA2 and ADHD is consistent with the original hypotheses and consistent with the current status of the literature. Indeed, to our knowledge this is the first study to examine the relationship between the GABRA2 gene and ADHD. Contrary to one of our initial hypotheses, the GABRA2 SNP was not associated with conduct disorder. These hypotheses were based on a study by Dick et al. (2006) who established a relation between self-reported CD and GABRA2 in children of treatment-seeking alcoholics and controls. Our results are consistent with a more recent replication study of 13-18 year old adolescent patients from a university substance abuse treatment program

and controls, which did not find evidence for an association between the GABRA2 rs279871 SNP and self-reported CD in both case-control and family-based association tests (Sakai et al., 2010).

However, the lack of association between CD and GABRA2 in both our study and the study by Sakai and colleagues can potentially be explained by findings from Dick et al. (2007) who outlined the importance of environmental and developmental influences in studies of genetic association. In this study, growth mixture modeling was used to identify trajectories of externalizing behavior characterized by self-reports of aggression and delinquency in adolescents/young adults from 12-22 years and to examine the effect of SNPS in the GABRA2 gene and of parental monitoring on these externalizing behaviors. They revealed two classes of externalizing behaviors, one characterized by elevated and persistent behaviors into adulthood (elevated persistent) and the other characterized by a decrease in behavior from adolescence to adulthood (developmentally limited). They found that multiple SNPs in the GABRA2 gene had a main effect on class membership, with each additional copy of the major allele (e.g. SNPs rs279858, rs279871), that tag the major haplotype, increasing the odds of membership in the elevated persistent externalizing trajectory. Moreover, although no main effect of parental monitoring was present, parental monitoring moderated the effect of GABRA2 such that GABRA2 had a stronger influence on externalizing class membership under conditions of low monitoring compared to conditions of high monitoring. Thus, these findings highlight the need to consider

environmental influences, such as parental monitoring, in studies of genetic association. It might be that in our data, the presence of interactive environmental effects (e.g. parental monitoring) precluded the detection of a significant main effect of GABRA2 on CD. Indeed, an important avenue for future research includes examining the effect of environmental factors in order to gain a better understanding of how genes affect behavior. Moreover, these results underscore the importance of considering developmental trajectories of problem behavior and highlight the possibility that GABRA2 actually plays a larger role in influencing pathways of problem behavior rather than behaviors observed at single time points. Although we did use three different time points to define the CD factor, this method does not capture the pattern and course of problem behaviors over time. While it is important to consider environmental and developmental factors, our study also differed methodologically from the study by Dick et al. (2006) because they used child-reported DSM-III-R CD diagnoses whereas we used child-reported Achenbach symptom scales of CD. The discrete versus categorical approach to classifying problem behaviors may well explain the discrepancies in our results as well. Finally, our DSM-oriented symptom scale of CD was missing three out of fifteen items (i.e. lacks guilt, breaks rules, sets fires). It could be that the accuracy of our CD measure was compromised due to missing these items.

One unanticipated finding from our study was the non-significant correlation between parental alcoholism and GABRA2. This is especially surprising because there was a significant relation between GABRA2 and

adolescent substance experimentation. However, given that our measure of substance experimentation included both alcohol and illicit drugs, and given that some studies have shown the major haplotype of GABRA2 to have the strongest association with co-occurring alcohol and drug dependence (Agrawal et al., 2006), it might be that GABRA2 would be significantly correlated with a measure of parental alcoholism and co-occurring drug dependence. Another interesting possibility to explain this finding is that parent trait anxiety may play a moderating role in the relation between parental alcoholism and GABRA2. Similarly, we were surprised that gender was not a significant predictor of the ADHD factor because prevalence rates consistently show that ADHD is more common in males than in females (Faraone et al., 2003). A potential explanation for the lack of gender differences in ADHD symptomatology is that youth self-report was utilized. Perhaps if parent- or teacher-reported ADHD measures were used we would have seen this difference. This finding could also be due to the fact that our DSM-oriented ADHD scale was missing three of the seven items that comprise the scale (i.e. fails to finish, talks too much, loud). Perhaps these items discriminate between boys and girls' self-reports of ADHD.

Strengths, Limitations, and Future Directions

This study extends the literature on the unique and shared liabilities to externalizing disorders by investigating these phenomena in adolescents and by demonstrating that specific etiological differences in substance experimentation can be explained, in part, by genetic influences. Indeed, this study is one of few to

examine multiple competing factor structures of externalizing disorders in adolescents while also including substance use measures (Verona et al., 2011). This study also adds to the currently limited research on the influence of measured genetics on adolescent substance use. Furthermore, latent measures of CD, ADHD, and SE symptomatology were constructed in this study by using indicators of each disorder at three waves. Thus, our externalizing behavior outcomes represent somewhat of a trait-like measurement, which implies that we captured externalizing behaviors that were more stable across adolescence rather than limited to one specific stage of adolescence (e.g. pre-adolescence).

Although the current study contributes to the literature on the structure of adolescent externalizing disorders and the genetics of substance use, there are also limitations that should be considered as avenues for future research. Because the ADHD and CD items were taken from an older version of the Achenbach CBCL, we were not able to construct complete DSM-oriented scales. The ADHD scale was missing three out of seven items and the CD scale was missing three out of fifteen items. Thus, although the internal consistency for each scale was still good, this could mean that our definitions of ADHD and CD were not as accurate as possible. Additionally because single-reporter models may lead to bias, a limitation of our study was that we only utilized adolescent self-reports of ADHD, CD, and SE. In the future, multiple-reporter models should be examined to see if the same factor structure and relations hold.

It is important to consider that these analyses used a single SNP to predict adolescent outcomes. In future analyses it will be important to utilize more robust genetic measures such as estimating haplotypes or diplotypes of the GABRA2 gene. As single-gene associations are often of small effect size, it will also be important to investigate how environmental factors influence the relation between genes and adolescent externalizing behaviors. For example, interactions between parental monitoring and GABRA2 might yield significant effects on adolescent CD in our sample (Dick et al., 2007). Similarly, examining the effect of gene-by-gene interactions may lead to a better understanding of the biological mechanisms that influence externalizing behaviors.

Another important question that stems from these analyses concerns the mechanisms through which GABRA2 influences substance experimentation in adolescence. Indeed, understanding how GABRA2 influences substance use may give us greater insight into the functional role of the gene. Interestingly, multiple facets of disinhibition may differentiate between externalizing disorders and GABRA2 has also been hypothesized to affect SUDs through disinhibitory processes. It would be interesting to investigate whether certain facets of disinhibition mediate the relation between GABRA2 and SE. Finally, this study awaits replication with broader samples including those with more diverse ethnic groups.

Summary and Conclusions

In conclusion, this study confirmed findings from previous research demonstrating that ADHD, CD, and SE each have unique sources of significant unique sources of variance. Due to the significant intercorrelations between the three problem behaviors, this study also partially supports the notion of a broader externalizing factor that accounts for commonalities among externalizing disorders. However, this conclusion should be viewed with caution because we did not actually model a hierarchical externalizing factor due to sample size limitations. Our study also extends previous research by showing that biological mechanisms act as a unique etiological factor in the development of substance experimentation in adolescence. Specifically, possession of the homozygous major allele genotype of the GABRA2 SNP, rs279858, may be one unique risk factor for substance use experimentation in adolescence.

Table 1.
Comparing First Subsample to Excluded Participants

	Included		Excluded			
Covariates, Outcome Variables	***N***	***Mean (SD)***	***N***	***Mean (SD)***	***t***	***p-value***
G2 Age						
Wave 1	302	13.80(1.03)	152	12.07(1.45)	-13.112	**<.001***
Wave 2	302	14.74(1.03)	147	13.00(1.46)	-12.936	**<.001***
Wave 3	302	15.74(1.04)	143	13.95(1.44)	-13.289	**<.001***
G2 report of own ADHD[a]						
Wave 1	302	3.96(1.90)	150	3.54(1.93)	-2.207	**.028***
Wave 2	302	3.67(1.83)	146	3.51(1.91)	-.850	.396
Wave 3	302	3.71(1.89)	141	3.52(1.88)	-.956	.339
G2 report of own CD[b]						
Wave 1	302	3.34(3.12)	147	2.32(3.00)	-3.292	**.001***
Wave 2	302	3.60(3.16)	144	2.50(2.78)	-3.570	**<.001***
Wave 3	302	4.05(3.36)	132	3.13(3.44)	-2.600	**.010***
G2 report of own substance experimentation[c]						
Wave 1	302	0.22(0.55)	152	0.19(0.55)	-.570	.569
Wave 2	302	0.35(0.67)	147	0.27(0.63)	-1.266	.207
Wave 3	302	0.44(0.72)	143	0.28(0.64)	-2.419	**.016***
Covariates	***N***	***%***	***N***	***%***	***Chi-Square***	***p-value***
G2 COA Status Non-COA=0 COA=1	302	47.4% non-COA 52.6% COA	152	42.8% non-COA 57.2% COA	.857	.355
G1 SES (highest-reported education)[d]	302	Mean=4.86	147	Mean=4.88	.778	.993
G2 Gender 0=Female 1=Male	302	47.0% Female 53.0% Male	152	47.4% Female 52.6% Male	.005	.944
G2 Ethnicity 0=Non-Hispanic Caucasian 1=Hispanic 2= Other Ethnicity [e]	302	73.5% Caucasian 26.5% Hispanic	147	68% Caucasian 17.0% Hispanic 15% Other	49.41	**<001***

*statistical significance. [a] 4 items (CBCL), 0-8. [b]12 items (CBCL), 0-24. [c]9 substance use items truncated: ordinal categorical variable, range: 0-2. [d]1 (grade school), 2 (some high school (HS)), 3 (HS graduate), 4 (technical school), 5 (some college), 6 (college graduate), and 7 (graduate school/professional school). [e]not used in final analyses, used for comparing between groups.

Table 2.
Comparing Second Subsample to Excluded Participants

	Included		Excluded			
Covariates, Outcome Variables	***N***	***Mean (SD)***	***N***	***Mean (SD)***	***t***	***p-value***
G2 Age						
Wave 1	138	13.77(1.04)	316	12.98(1.52)	-6.355	**<.001***
Wave 2	138	14.70(1.05)	311	13.93(1.53)	-6.178	**<.001***
Wave 3	138	15.70(1.06)	307	14.92(1.53)	-6.243	**<.001***
G2 report of own ADHD[a]	138					
Wave 1	138	3.83(1.97)	314	3.82(1.89)	-.092	.927
Wave 2	138	3.62(1.85)	310	3.61(1.86)	-.016	.987
Wave 3	138	3.59(1.84)	305	3.68(1.91)	.420	.675
G2 report of own CD[b]	138					
Wave 1	138	2.67(2.85)	311	3.15(3.22)	1.508	.132
Wave 2	138	3.27(3.05)	308	3.23(3.10)	-.109	.913
Wave 3	138	3.70(3.23)	296	3.80(3.49)	.269	.788
G2 report of own substance experimentation[c]	138					
Wave 1	138	.17(.48)	316	.23(.57)	1.240	.216
Wave 2	138	.33(.68)	311	.32(.66)	-.269	.788
Wave 3	138	.40(.68)	307	.39(.71)	-.153	.879
Covariates	***N***	***%***	***N***	***%***	***Chi-Square***	***p-value***
G2 COA Status Non-COA=0 COA=1	138	47.1% non-COA 52.9% COA	316	45.3% non-COA 54.7% COA	.132	.716
G1 SES (highest-reported education)[d]	138	Mean=4.78	147	Mean=4.73	2.779	.836
G2 Gender 0=Female 1=Male	138	50.7% Female 49.3% Male	316	45.6% Female 54.3% Male	1.024	.311
G2 Ethnicity 0=Non-Hispanic Caucasian 1=Hispanic 2= Other Ethnicity [e]	138	72.5% Caucasian 27.5% Hispanic	311	71.4% Caucasian 21.5% Hispanic 7.1% Other	11.246	**.024***

*statistical significance. [a]4 items (CBCL), 0-8. [b]12 items (CBCL), 0-24. [c] 9 substance use items truncated to form an ordinal categorical variable ranging from 0-2. [d]1 (grade school), 2 (some high school), 3 (high school graduate), 4 (technical school), 5 (some college), 6 (college graduate), and 7 (graduate school/professional school). [e]This code was not used in the final analyses, but was just used for the purposes of comparing between groups.

Table 3.
Descriptive Statistics for First Subsample.

	N	Min.	Max.	Mean(SD)	Skewness(SE)	Kurtosis (SE)
G2 Age						
Wave 1	302	12.00	16.61	13.80(1.03)	.24(.14)	-.71(.28)
Wave 2	302	12.90	17.60	14.74(1.03)	.24(.14)	-.69(.28)
Wave 3	302	13.84	18.63	15.74(1.04)	.21(.14)	-.67(.28)
G2 SES [g]	302	1.00	7.00	4.768(1.49)	-.53(.14)	-.28(.28)
G2 report of own ADHD[a]						
Wave 1	302	.00	8.00	3.960(1.90)	.02(.14)	-.45(.28)
Wave 2	302	.00	8.00	3.67(1.83)	-.06(.14)	-.36(.28)
Wave 3	302	.00	8.00	3.71(1.89)	.09(.14)	-.29(.28)
G2 report of own CD[b]						
Wave 1	302	.00	17.00	3.34(3.12)	1.17(.14)	1.40(.28)
Wave 2	302	.00	17.00	3.60(3.16)	1.29(.14)	2.01(.28)
Wave 3	302	.00	16.00	4.05(3.36)	1.05(.14)	.77(.28)
G2 report of own substance experimentation[c]						
Wave 1	302	.00	2.00	.22(.55)	2.40(.14)	4.57(.28)
Wave 2	302	.00	2.00	.35(.67)	1.69(.14)	1.31(.28)
Wave 3	302	.00	2.00	.44(.72)	1.29(.14)	.16(.28)

	N	%
G2 Gender[d]	302	47.0% (N=142) Female
G2 Ethnicity[e]	302	73.5% (N=222) Non-Hispanic Caucasian
G2 COA Status[f]	302	52.6% (N=159) COA

Note. All continuous variables are coded such that high scores indicate high levels of the variable. [a]Consists of four items from the CBCL, scores range from 0-8. [b]Consists of twelve items from the CBCL, scores range from 0-24. [c]Consists of nine substance use items that were truncated to form an ordinal categorical variable ranging from 0-2.[d]0=Female, 1=Male. [e]1=Caucasian, 2=Hispanic, 3=Other Ethnicity. [f]0=non-COA, 1=COA. [g]1 (grade school), 2 (some high school), 3 (high school graduate), 4 (technical school), 5 (some college), 6 (college graduate), and 7 (graduate school/professional school).

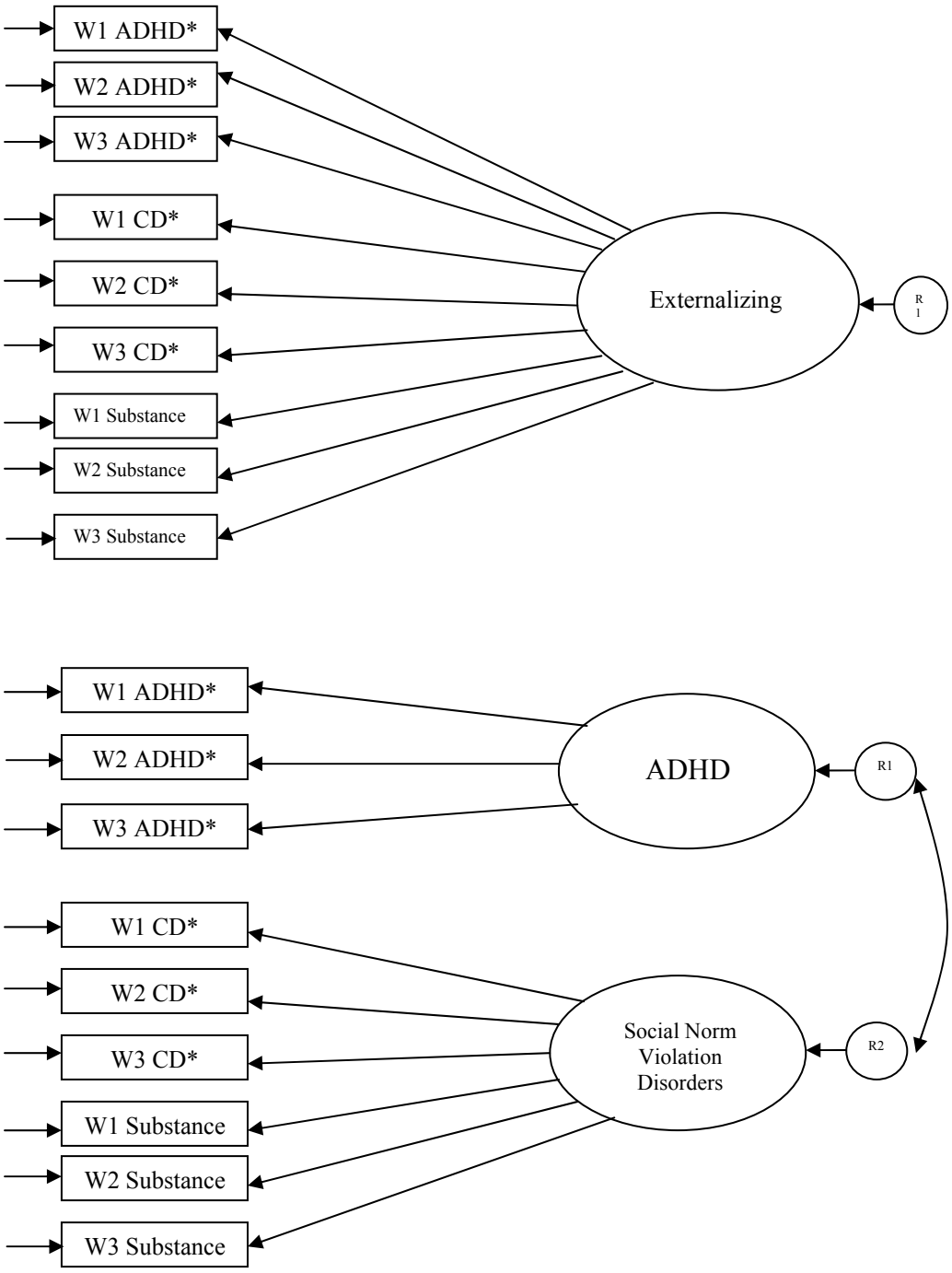
Table 4.
Descriptive Statistics for Second Subsample.

	N	Min.	Max.	Mean(SD)	Skewness (SE)	Kurtosis (SE)
G2 Age						
Wave 1	138	12.00	15.89	13.77(1.04)	.16(.21)	-.93 (.41)
Wave 2	138	12.96	16.84	14.70(1.05)	.14(.21)	-.92(.41)
Wave 3	138	13.89	17.86	15.70(1.06)	.12(.21)	-.90(.41)
G2 SES [g]	138	1.00	7.00	4.78(1.48)	-.56(.21)	-.13(.41)
G2 report of own ADHD[a]						
Wave 1	138	.00	8.00	3.83(1.97)	-.03(.21)	-.58(.41)
Wave 2	138	.00	8.00	3.62(1.85)	-.14(.21)	-.46(.41)
Wave 3	138	.00	8.00	3.59(1.84)	.04(.21)	-.05(.41)
G2 report of own CD[b]						
Wave 1	138	.00	17.00	2.67(2.85)	1.70(.21)	4.07(.41)
Wave 2	138	.00	16.00	3.27(3.05)	1.35(.21)	2.28(.41)
Wave 3	138	.00	16.00	3.70(3.23)	1.25(.21)	1.57(.41)
G2 report of own substance experimentation[c]						
Wave 1	138	.00	2.00	.17(.48)	2.92(.21)	7.72(.41)
Wave 2	138	.00	2.00	.33(.68)	1.78(.21)	1.58(.41)
Wave 3	138	.00	2.00	.40(.68)	1.44(.21)	.69(.41)

	N	%
G2 Gender[d]	138	50.7% (N=70) Female
G2 GABRA2 rs279858	138	67.4% (N=93) AA/AG genotype; 32.6% (N=45) AA genotype
G2 Ethnicity[e]	138	72.5% (N=100) Non-Hispanic Caucasian
G2 COA Status[f]	138	52.9% (N=73) COA

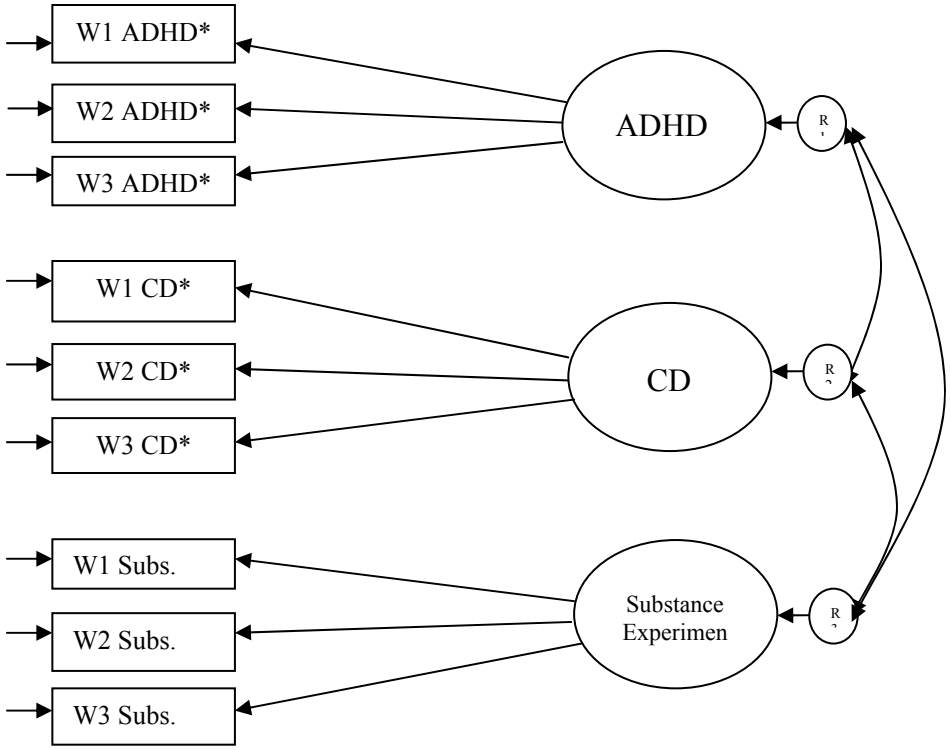
Note. All continuous variables coded so high scores are high levels of variable. [a]4 items (CBCL), 0-8. [b]12 items (CBCL), 0-24. [c]9 substance use items to form ordinal categorical variable, 0-2.[d]0=Female, 1=Male. [e]1=Caucasian, 2=Hispanic, 3=Other Ethnicity. [f]0=non-COA, 1=COA. [g]1 (grade school), 2 (some high school), 3 (high school graduate), 4 (technical school), 5 (some college), 6 (college graduate), and 7 (graduate school/professional school).

Figure 1.
Competing Confirmatory Factor Analytic Models with First Subsample
One-Factor and Two-Factor Models of Externalizing Disorders



*Note. ADHD: Attention-Deficit Hyperactivity Disorder. CD: Conduct Disorder.

Figure 2.
Competing Confirmatory Factor Analytic Models with First Subsample: Three-Factor Model of Externalizing Disorders

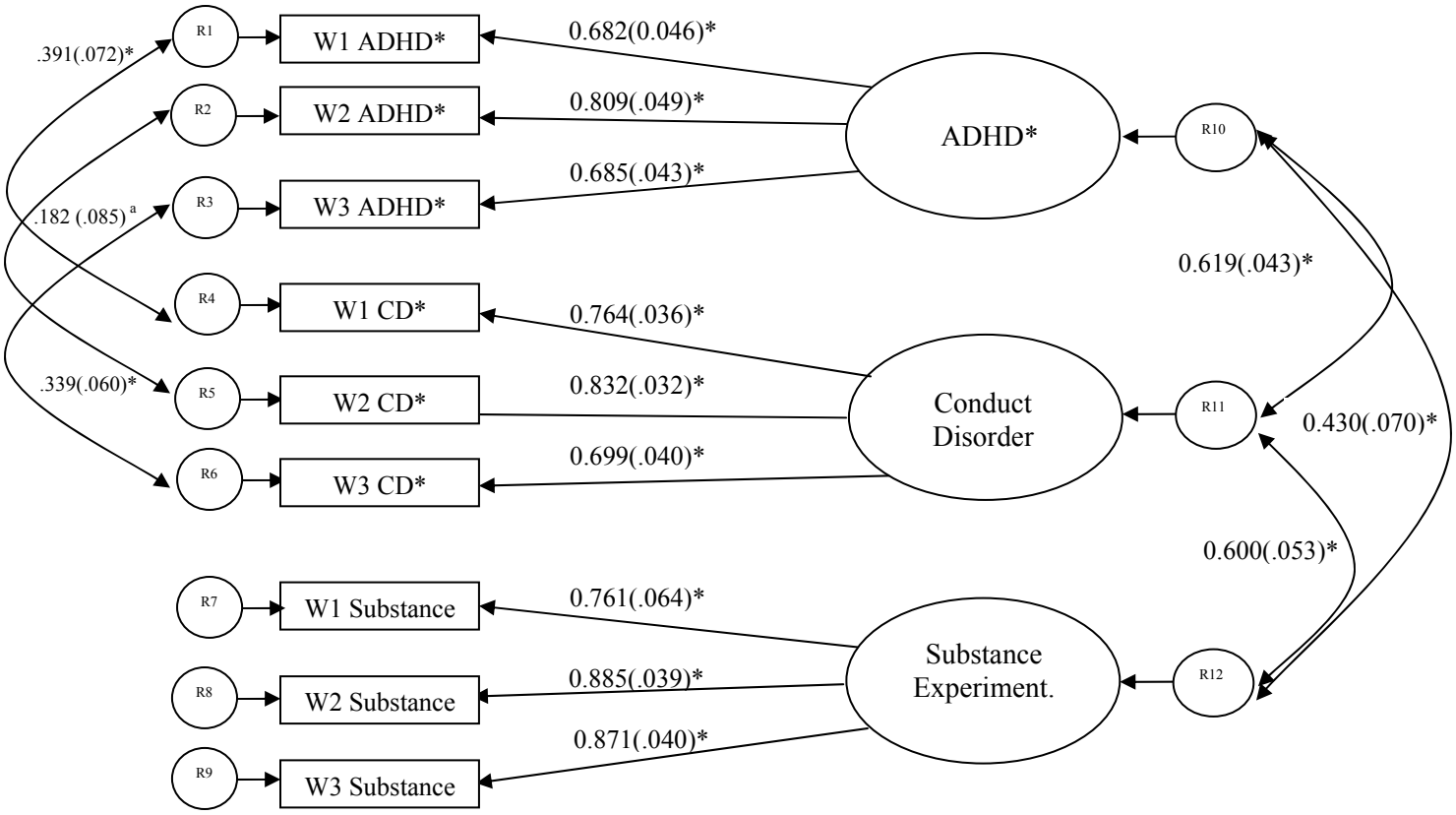


*Note. ADHD: Attention-Deficit Hyperactivity Disorder. CD: Conduct Disorder. Subs: Substance Experimentation.

Table 5.
Model Fit Indices for One-, Two-, and Three-Factor Models of Externalizing Behaviors in First Subsample.

Indicators of Model Fit						
	χ^2					
Model	**Value**	***df***	***p* value**	**CFI**	**RMSEA**	**WRMR**
One-Factor	258.555	27	<.0001	0.704	0.169	1.683
Two-Factor	194.176	36	<.0001	0.785	0.146	1.439
Three-Factor	53.794	24	0.0005	0.962	0.064	0.684
Three-Factor with time-specific correlations	29.694	21	0.0983	0.989	0.037	0.499

Figure 3.
Path Diagram for Three-Factor Model with time-specific correlations: First Subsample



*Note. Standardized parameter estimates and standard errors in parentheses are presented here. *$p < .001$. [a]p=.032. ADHD: Attention-Deficit Hyperactivity Disorder. CD: Conduct Disorder.

Table 6.

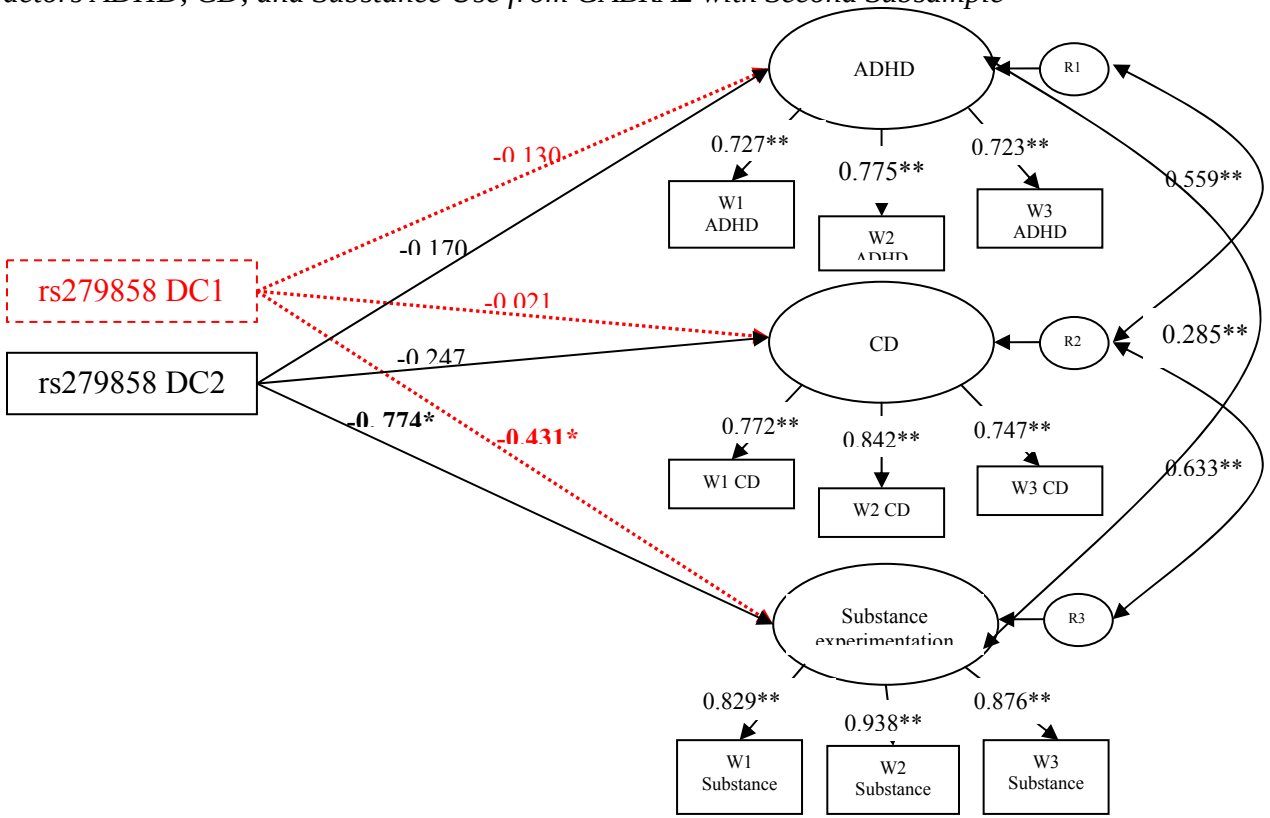
GABRA2 SNP rs279858 and Covariates Predicting Latent Factors of Three-Factor Model: ADHD, CD, and Substance Use in Second Subsample

	ADHD				CD				Substance Experimentation			
Predictor	**B**	**SE B**	**β**	**p**	**B**	**SE B**	**β**	**p**	**B**	**SE B**	**β**	**p**
rs279858 DC1	-0.130	0.296	-0.046	0.661	-0.021	0.462	-0.005	0.964	**-0. 431***	0.218	-0.229	0.047
rs279858 DC2	-0.17	0.465	-0.043	0.714	-.247	0.663	-0.040	0.710	**-0. 774***	0.352	-0.295	0.028
Age	--	--	--	--	--	--	--	--	**0.403****	0.124	0.451	0.001
COA	**0.839****	0.286	0.294	0.003	**1.22****	0.409	0.277	0.003	**0. 592****	0.215	0.314	0.006
Gender	--	--	--	--	**1.075***	0.445	0.244	0.016	--	--	--	--

**p<.01 *p<.05. ADHD: Attention Deficit Hyperactivity Disorder. CD: Conduct Disorder. DC1= dummy code of GABRA2 genotype (AG=1, AA=reference group) DC2= dummy code of GABRA2 genotype (GG=1, AA=reference group). Gender: 0=Female, 1=Male. COA: 0=non-COA, 1=COA. Higher levels of age represent older age. As each factor was allowed to have unique covariates, the '- -' are covariates that were not included in the prediction of each latent factor.

Figure 4.

Predicting Latent Factors ADHD, CD, and Substance Use from GABRA2 with Second Subsample



Note. Bold font indicates statistical significance. *p<.05, p<.001**. The covariates were not included in this model for ease of presentation. See Table 8 for the effect of covariates on the three latent factors. For correlations among the exogenous variables (DC1, DC2, gender, parent alcoholism, and age) refer to Table B1. Three factor model is not wholly depicted for ease of presentation (e.g. time-specific correlations): See Figure 2. Parameter estimates are standardized. DC1= dummy code of GABRA2 genotype (AG=1, AA=reference group) DC2= dummy code of GABRA2 genotype (GG=1, AA=reference group). ADHD: Attention-Deficit Hyperactivity Disorder. CD: Conduct Disorder.

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APPENDIX A

ADOLESCENT REPORT OF EXTERNALIZING SYMPTOMS: THE CHILD BEHAVIOR CHECKLIST

These are items that describe people. Please use them to describe the way that you have been during the past three months. In the past three months, how often have much of these things been true of you?

1. Easily distractible.

    2. Very true or often true

    1. Somewhat or sometimes true

    0. Not true

2. Fidgety, has difficulty sitting still.

3. Runs away from home.

4. Truant, skips school.

5. Steals outside of the home, e.g. shoplifting.

6. Mean or cruel to others.

7. Destroys things belonging to others.

8. Starts fights.

9. Hangs around with kids who get in trouble.

10. Acts without stopping to think.

11. Lies or cheats.

12. Physically attacks people.

13. Steals things at home.

14. Swearing or obscene language.

15. Threatens people.

16. Can't concentrate.

APPENDIX B

ADOLESCENT REPORT OF OWN SUBSTANCE USE

These questions are about alcohol and drug use. When we ask you about drug use we do NOT mean medicines that were given to you by your doctor. We want to know about your use of drugs that were NOT PRESCRIBED BY YOUR DOCTOR.

1. In the past year, how many times have you gotten drunk on alcohol? (not just light-headed)

    0. Never

    1. 1-2 times in my life

    2. 3-5 times in my life

    3. More than 5 times, but less than once a month

    4. 1-3 times a month

    5. 1-2 times a week

    6. 3-5 times a week

    7. Every day.

2. In the past year, how many times did you use marijuana (grass, pot) or hashish (hash, hash oil)?

3. In the past year, how many times did you use amphetamines (uppers, speed, meth, dex, pep pills, ice)?

4. In the past year, how many times did you use quaaludes (quads, sopers, methaqualone) or barbituates (downs, downers)?

5. In the past year, how many times did you use tranquilizers (valium, librium)?

6. In the past year, how many times did you use hallucinogens (LSD, PCP, ANGEL DUST, MESCALINE, PSILOCYBIN, PEYOTE, DMT, MUSHROOMS, SHROOMS)?

7. In the past year, how many times did you use cocaine (coke) or crack?

8. In the past year, how many times did you use opiate drugs (These include codeine, demerol, morphine, darvon, opium, percodan, percocet, and heroin (horse, skag, smack))?

9. In the past year, how many times did you use inhalant drugs?

APPENDIX C

TABLES REPORTING CORRELATIONS FOR FIRST SUBSAMPLE

Table C1.

Correlations Between Covariates and Indicators of Latent Factors for First Subsample

		G2 Age [d]	G2 Gender [b]	G2 COA [c]	G2 SES	G2 Ethnicity [a]	G2 ADHD Wave 1	G2 ADHD Wave 2
G2 Age[d]	Pearson Correlation	1	-.010	-.089	.026	.086	.066	.114*
	Sig. (2-tailed)		.857	.125	.650	.136	.254	.048
	N	302	302	302	302	302	302	302
G2 Gender [b]	Pearson Correlation	-.010	1	.037	.103	-.066	.015	-.056
	Sig. (2-tailed)	.857		.525	.073	.253	.791	.329
	N	302	302	302	302	302	302	302
G2 COA Status [c]	Pearson Correlation	-.089	.037	1	-.130*	.133*	.124*	.212**
	Sig. (2-tailed)	.125	.525		.023	.020	.032	.000
	N	302	302	302	302	302	302	302
G2 SES	Pearson Correlation	.026	.103	-.130*	1	-.291**	-.052	-.040
	Sig. (2-tailed)	.650	.073	.023		.000	.371	.492
	N	302	302	302	302	302	302	302
G2 Ethnicity [a]	Pearson Correlation	.086	-.066	.133*	-.291**	1	.009	.020
	Sig. (2-tailed)	.136	.253	.020	.000		.881	.735
	N	302	302	302	302	302	302	302
G2 ADHD Wave 1	Pearson Correlation	.066	.015	.124*	-.052	.009	1	.557**
	Sig. (2-tailed)	.254	.791	.032	.371	.881		.000
	N	302	302	302	302	302	302	302
G2 ADHD Wave 2	Pearson Correlation	.114*	-.056	.212**	-.040	.020	.557**	1
	Sig. (2-tailed)	.048	.329	.000	.492	.735	.000	
	N	302	302	302	302	302	302	302

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability.

Table C2.
Correlations Between Covariates and Indicators of Latent Factors for First Subsample (cont.)

		G2 ADHD W3	G2 CD W1	G2 CD W2	G2 CD W3	G2 Subs. W1[e]	G2 Subs. W2[e]	G2 Subs. W3[e]
G2 Age[d]	Pearson Correlation	.081	.126*	.054	.026	.284**	.216**	.198**
	Sig. (2-tailed)	.158	.029	.352	.652	.000	.000	.001
	N	302	302	302	302	302	302	302
G2 Gender[b]	Pearson Correlation	.013	.116*	.141*	.247**	-.055	-.016	.000
	Sig. (2-tailed)	.825	.044	.014	.000	.344	.781	.999
	N	302	302	302	302	302	302	302
G2 COA Status[c]	Pearson Correlation	.114*	.148**	.222**	.185**	.167**	.165**	.208**
	Sig. (2-tailed)	.048	.010	.000	.001	.004	.004	.000
	N	302	302	302	302	302	302	302
G2 SES	Pearson Correlation	-.014	-.090	-.102	-.047	-.006	.031	-.022
	Sig. (2-tailed)	.815	.117	.076	.414	.917	.591	.708
	N	302	302	302	302	302	302	302
G2 Ethnicity[a]	Pearson Correlation	-.003	.084	.067	.061	.072	.013	.026
	Sig. (2-tailed)	.962	.148	.247	.290	.211	.819	.649
	N	302	302	302	302	302	302	302
G2 ADHD Wave 1	Pearson Correlation	.473**	.507**	.356**	.327**	.114*	.151**	.187**
	Sig. (2-tailed)	.000	.000	.000	.000	.047	.008	.001
	N	302	302	302	302	302	302	302
G2 ADHD Wave 2	Pearson Correlation	.546**	.364**	.476**	.325**	.168**	.276**	.256**
	Sig. (2-tailed)	.000	.000	.000	.000	.003	.000	.000
	N	302	302	302	302	302	302	302

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability. [e]Subs.=Substance Experimentation.

Table C3.
Correlations Between Covariates and Indicators of Latent Factors for First Subsample (cont.)

		G2 Age[d]	G2 Gender[b]	G2 COA[c]	G2 SES	G2 Ethnicity[a]	G2 ADHD W1	G2 ADHD W2
G2 ADHD W3	Pearson Correlation	.081	.013	.114*	-.014	-.003	.473**	.546**
	Sig. (2-tailed)	.158	.825	.048	.815	.962	.000	.000
	N	302	302	302	302	302	302	302
G2 CD W1	Pearson Correlation	.126*	.116*	.148**	-.090	.084	.507**	.364**
	Sig. (2-tailed)	.029	.044	.010	.117	.148	.000	.000
	N	302	302	302	302	302	302	302
G2 CD W2	Pearson Correlation	.054	.141*	.222**	-.102	.067	.356**	.476**
	Sig. (2-tailed)	.352	.014	.000	.076	.247	.000	.000
	N	302	302	302	302	302	302	302
G2 CD W3	Pearson Correlation	.026	.247**	.185**	-.047	.061	.327**	.325**
	Sig. (2-tailed)	.652	.000	.001	.414	.290	.000	.000
	N	302	302	302	302	302	302	302
G2 Subs. W1[e]	Pearson Correlation	.284**	-.055	.167**	-.006	.072	.114*	.168**
	Sig. (2-tailed)	.000	.344	.004	.917	.211	.047	.003
	N	302	302	302	302	302	302	302
G2 Subs. W2[e]	Pearson Correlation	.216**	-.016	.165**	.031	.013	.151**	.276**
	Sig. (2-tailed)	.000	.781	.004	.591	.819	.008	.000
	N	302	302	302	302	302	302	302
G2 Subs. W3[e]	Pearson Correlation	.198**	.000	.208**	-.022	.026	.187**	.256**
	Sig. (2-tailed)	.001	.999	.000	.708	.649	.001	.000
	N	302	302	302	302	302	302	302

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability. [e]Subs.=Substance Experimentation.

Table C4.
Correlations Between Covariates and Indicators of Latent Factors for First Subsample (cont.)

		G2 ADHD W3	G2 CD W1	G2 CD W2	G2 CD W3	G2 Subs. W1[e]	G2 Subs. W2[e]	G2 Subs. W3[e]
G2 ADHD Wave 3	Pearson Correlation	1	.329**	.371**	.473**	.130*	.127*	.261**
	Sig. (2-tailed)		.000	.000	.000	.023	.027	.000
	N	302	302	302	302	302	302	302
G2 CD Wave 1	Pearson Correlation	.329**	1	.609**	.545**	.342**	.315**	.373**
	Sig. (2-tailed)	.000		.000	.000	.000	.000	.000
	N	302	302	302	302	302	302	302
G2 CD Wave 2	Pearson Correlation	.371**	.609**	1	.602**	.265**	.419**	.379**
	Sig. (2-tailed)	.000	.000		.000	.000	.000	.000
	N	302	302	302	302	302	302	302
G2 CD Wave 3	Pearson Correlation	.473**	.545**	.602**	1	.163**	.216**	.403**
	Sig. (2-tailed)	.000	.000	.000		.005	.000	.000
	N	302	302	302	302	302	302	302
G2 Subs. W1[e]	Pearson Correlation	.130*	.342**	.265**	.163**	1	.511**	.417**
	Sig. (2-tailed)	.023	.000	.000	.005		.000	.000
	N	302	302	302	302	302	302	302
G2 Subs. W2[e]	Pearson Correlation	.127*	.315**	.419**	.216**	.511**	1	.595**
	Sig. (2-tailed)	.027	.000	.000	.000	.000		.000
	N	302	302	302	302	302	302	302
G2 Subs. W3[e]	Pearson Correlation	.261**	.373**	.379**	.403**	.417**	.595**	1
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	
	N	302	302	302	302	302	302	302

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability. [e]Subs.=Substance Experimentation.

APPENDIX D

TABLES REPORTING CORRELATIONS FOR SECOND SUBSAMPLE

Table D1. *Correlations Between Covariates and Indicators of Latent Factors for Second Subsample.*

		AG group [e]	GG group [f]	G2 Age [d]	G2 Gender [b]	G2 COA [c]	G2 SES	G2 Ethnic [a]	G2 ADHD W1
AG group [e]	Pearson Correlation	1	-.442**	.053	.044	-.003	.026	.006	-.030
	Sig. (2-tailed)		.000	.538	.607	.977	.762	.948	.731
	N	138	138	138	138	138	138	138	138
GG group [f]	Pearson Correlation	-.442**	1	-.051	-.095	.076	-.061	-.035	.015
	Sig. (2-tailed)	.000		.551	.269	.373	.481	.681	.857
	N	138	138	138	138	138	138	138	138
G2 Age	Pearson Correlation	.053	-.051	1	.076	-.128	-.034	.062	-.047
	Sig. (2-tailed)	.538	.551		.373	.133	.692	.467	.586
	N	138	138	138	138	138	138	138	138
G2 Gender	Pearson Correlation	.044	-.095	.076	1	-.086	.135	-.121	.010
	Sig. (2-tailed)	.607	.269	.373		.314	.114	.158	.909
	N	138	138	138	138	138	138	138	138
G2 COA	Pearson Correlation	-.003	.076	-.128	-.086	1	-.099	.127	.208*
	Sig. (2-tailed)	.977	.373	.133	.314		.246	.139	.014
	N	138	138	138	138	138	138	138	138
G2 SES	Pearson Correlation	.026	-.061	-.034	.135	-.099	1	-.359**	-.067
	Sig. (2-tailed)	.762	.481	.692	.114	.246		.000	.432
	N	138	138	138	138	138	138	138	138
G2 Ethnic	Pearson Correlation	.006	-.035	.062	-.121	.127	-.359**	1	.019
	Sig. (2-tailed)	.948	.681	.467	.158	.139	.000		.822
	N	138	138	138	138	138	138	138	138
G2 ADHD W1	Pearson Correlation	-.030	.015	-.047	.010	.208*	-.067	.019	1
	Sig. (2-tailed)	.731	.857	.586	.909	.014	.432	.822	
	N	138	138	138	138	138	138	138	138

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability. [e]0=AA genotype, reference group 1=AG genotype. [f]0=AA genotype, reference group, 1=GG genotype.

Table D2. *Correlations Between Covariates and Indicators of Latent Factors for Second Subsample (cont.)*

		G2 ADHD W2	G2 ADHD W3	G2 CD W1	G2 CD W2	G2 CD W3	G2 Subs. W1[e]	G2 Subs. W2[e]	G2 Subs. W3[e]
AG group[e]	Pearson Correlation	-.018	.002	.099	-.049	.020	.000	-.086	-.058
	Sig. (2-tailed)	.830	.984	.246	.567	.818	1.000	.315	.500
	N	138	138	138	138	138	138	138	138
GG group[f]	Pearson Correlation	.012	-.049	-.129	-.044	.045	-.106	-.180*	-.041
	Sig. (2-tailed)	.892	.566	.132	.608	.597	.215	.035	.634
	N	138	138	138	138	138	138	138	138
G2 Age	Pearson Correlation	.046	.074	-.005	.021	.033	.202*	.242**	.269**
	Sig. (2-tailed)	.595	.386	.951	.811	.704	.018	.004	.001
	N	138	138	138	138	138	138	138	138
G2 Gender	Pearson Correlation	.025	.044	.113	.151	.289**	-.071	-.036	-.002
	Sig. (2-tailed)	.775	.606	.187	.076	.001	.407	.676	.980
	N	138	138	138	138	138	138	138	138
G2 COA	Pearson Correlation	.229**	.179*	.157	.250**	.166	.148	.144	.127
	Sig. (2-tailed)	.007	.035	.066	.003	.052	.084	.093	.138
	N	138	138	138	138	138	138	138	138
G2 SES	Pearson Correlation	-.076	.088	-.044	-.047	.029	.031	.058	.021
	Sig. (2-tailed)	.376	.306	.605	.586	.735	.719	.498	.803
	N	138	138	138	138	138	138	138	138
G2 Ethnicity	Pearson Correlation	-.083	-.076	.076	.084	.037	.125	.032	.045
	Sig. (2-tailed)	.334	.376	.373	.325	.668	.144	.709	.604
	N	138	138	138	138	138	138	138	138
G2 ADHD W1	Pearson Correlation	.572**	.538**	.459**	.336**	.357**	-.025	.086	.176*
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.774	.317	.039
	N	138	138	138	138	138	138	138	138

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability. [e]0=AA genotype, reference group 1=AG genotype. [f]0=AA genotype, reference group, 1=GG genotype. [e]Subs.=Substance Experimentation.

Table D3.

Correlations Between Covariates and Indicators of Latent Factors for Second Subsample (cont.)

		AG group [e]	GG group [f]	G2 Age [d]	G2 Gender [b]	G2 COA [c]	G2 SES	G2 Ethnic [a]	G2 ADHD W1
G2 ADHD W2	Pearson Correlation	-.018	.012	.046	.025	.229**	-.076	-.083	.572**
	Sig. (2-tailed)	.830	.892	.595	.775	.007	.376	.334	.000
	N	138	138	138	138	138	138	138	138
G2 ADHD W3	Pearson Correlation	.002	-.049	.074	.044	.179*	.088	-.076	.538**
	Sig. (2-tailed)	.984	.566	.386	.606	.035	.306	.376	.000
	N	138	138	138	138	138	138	138	138
G2 CD W1	Pearson Correlation	.099	-.129	-.005	.113	.157	-.044	.076	.459**
	Sig. (2-tailed)	.246	.132	.951	.187	.066	.605	.373	.000
	N	138	138	138	138	138	138	138	138
G2 CD W1	Pearson Correlation	-.049	-.044	.021	.151	.250**	-.047	.084	.336**
	Sig. (2-tailed)	.567	.608	.811	.076	.003	.586	.325	.000
	N	138	138	138	138	138	138	138	138
G2 CD W3	Pearson Correlation	.020	.045	.033	.289**	.166	.029	.037	.357**
	Sig. (2-tailed)	.818	.597	.704	.001	.052	.735	.668	.000
	N	138	138	138	138	138	138	138	138
G2 Subs. W1	Pearson Correlation	.000	-.106	.202*	-.071	.148	.031	.125	-.025
	Sig. (2-tailed)	1.000	.215	.018	.407	.084	.719	.144	.774
	N	138	138	138	138	138	138	138	138
G2 Subs. W2	Pearson Correlation	-.086	-.180*	.242**	-.036	.144	.058	.032	.086
	Sig. (2-tailed)	.315	.035	.004	.676	.093	.498	.709	.317
	N	138	138	138	138	138	138	138	138
G2 Subs. W3	Pearson Correlation	-.058	-.041	.269**	-.002	.127	.021	.045	.176*
	Sig. (2-tailed)	.500	.634	.001	.980	.138	.803	.604	.039
	N	138	138	138	138	138	138	138	138

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability. [e]0=AA genotype, reference group 1=AG genotype. [f]0=AA genotype, reference group, 1=GG genotype.

Table D4.
Correlations Between Covariates and Indicators of Latent Factors for Second Subsample (cont.)

		G2 ADHD W2	G2 ADHD W 3	G2 CD W1	G2 CD W2	G2 CD W3	G2 Subs. W1[e]	G2 Subs. W2[e]	G2 Subs. W3[e]
G2 ADHD W2	Pearson Correlation	1	.535**	.355**	.466**	.271**	.114	.319**	.228**
	Sig. (2-tailed)		.000	.000	.000	.001	.181	.000	.007
	N	138	138	138	138	138	138	138	138
G2 ADHD W3	Pearson Correlation	.535**	1	.378**	.345**	.469**	.094	.145	.207*
	Sig. (2-tailed)	.000		.000	.000	.000	.271	.090	.015
	N	138	138	138	138	138	138	138	138
G2 CD W1	Pearson Correlation	.355**	.378**	1	.625**	.559**	.340**	.295**	.324**
	Sig. (2-tailed)	.000	.000		.000	.000	.000	.000	.000
	N	138	138	138	138	138	138	138	138
G2 CD W1	Pearson Correlation	.466**	.345**	.625**	1	.617**	.350**	.437**	.424**
	Sig. (2-tailed)	.000	.000	.000		.000	.000	.000	.000
	N	138	138	138	138	138	138	138	138
G2 CD W3	Pearson Correlation	.271**	.469**	.559**	.617**	1	.179*	.169*	.368**
	Sig. (2-tailed)	.001	.000	.000	.000		.035	.047	.000
	N	138	138	138	138	138	138	138	138
G2 Subs. W1[e]	Pearson Correlation	.114	.094	.340**	.350**	.179*	1	.573**	.492**
	Sig. (2-tailed)	.181	.271	.000	.000	.035		.000	.000
	N	138	138	138	138	138	138	138	138
G2 Subs. W2[e]	Pearson Correlation	.319**	.145	.295**	.437**	.169*	.573**	1	.647**
	Sig. (2-tailed)	.000	.090	.000	.000	.047	.000		.000
	N	138	138	138	138	138	138	138	138
G2 Subs. W3[e]	Pearson Correlation	.228**	.207*	.324**	.424**	.368**	.492**	.647**	1
	Sig. (2-tailed)	.007	.015	.000	.000	.000	.000	.000	
	N	138	138	138	138	138	138	138	138

*p<.05, **p<.01. For all continuous variables, higher values indicate higher levels of the variable. [a]0=non-Hispanic Caucasian, 1=Hispanic. [b]0=Female, 1=Male. [c]0=non-COA, 1=COA. [d]G2 Age is age at wave 3 because there was increased variability. [e]0=AA genotype, reference group 1=AG genotype. [f]0=AA genotype, reference group, 1=GG genotype. [e]Subs.=Substance Experimentation.

Footnotes

[1]When correlations between the substance use and CD or ADHD indicators were modeled, no improvement in the model fit was observed. For methodological reasons, this lack of improvement is expected. The CD and ADHD indicators were measured with the same questionnaire while the substance use indicators were measured with a different questionnaire. Thus, method variance accounts for the need for correlations between the CD and ADHD indicators but not with the substance use indicators.

[2]All five potential covariates and five covariate-by-predictor interactions were tested as main effects on each latent outcome. None of the covariate-by-predictor interactions were significant, so they were trimmed from the final model.