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Prospective Effects of Adolescent Indicators of Behavioral Disinhibition on DSM-IV Alcohol, Tobacco, and Illicit Drug Dependence in Young Adulthood

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Abstract

Objective—To identify robust predictors of drug dependence.

Methods—This longitudinal study included 2361 male and female twins from an ongoing longitudinal study at the Center for Antisocial Drug Dependence (CADD) at the University of Colorado Boulder and Denver campuses. Twins were recruited for the CADD project while they were between the ages of 12 and 18. Participants in the current study were on average approximately 15 years of age during the first wave of assessment and approximately 20 years of age at the second wave of assessment. The average time between assessments was five years. A structured interview was administered at each assessment to determine patterns of substance use and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; Fourth Edition) attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and drug dependence symptoms. Cloninger's Tridimensional Personality Questionnaire was also used to assess novelty seeking tendencies (NS). At the second wave of assessment, DSM-IV dependence symptoms were reassessed using the same interview. Path analyses were used to examine direct and indirect mechanisms linking psychopathology and drug outcomes.

Results—Adolescent substance use, CD, and NS predicted young adult substance dependence, whereas the predictive effects of ADHD were few and inconsistent. Furthermore, CD and NS effects were partially mediated by adolescent substance use.

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Contributors

Authors John Hewitt, Susan Young, Michael Stallings, Soo Rhee, Robin Corley, and Christian Hopfer designed the CADD study and wrote the protocol. Author Rohan Palmer conducted literature searches and provided summaries of previous research studies, as well as conducted the statistical analysis under the guidance of Dr. Valerie Knopik. Author Rohan Palmer wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Conflict of Interest

All of the listed authors declare that they have no conflicts of interests.

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Conclusions—Adolescent conduct problems, novelty seeking, and drug use are important indices of future drug problems. The strongest predictor was novelty seeking.

Keywords

Attention Deficit Hyperactivity Disorder; Conduct Disorder; Behavioral Disinhibition; Drug Dependence; Alcohol Dependence; Tobacco Dependence

1. Introduction

Difficulty in inhibition of behavioral impulses results in an increased risk for the development of substance use and substance use disorders (SUD; consisting of DSM-IV abuse or dependence) (American Psychiatric Association, 2000). Individuals diagnosed with conduct disorder (CD) or attention problems (i.e., deficits in attention or hyperactivity-impulsivity – as defined by DSM-IV ADHD) are more likely to use substances during adolescence and develop a SUD during young adulthood (Charach, Yeung, Climans, & Lillie, 2011). Likewise, high novelty seeking (NS; a tendency for high levels of exploratory behavior, novel experiences, and immediate rewards), low harm avoidance, and low reward dependence tendencies have been associated with the development of SUD (Wills, Vaccaro, & McNamara, 1994). Further, early use of alcohol, tobacco, and illicit drugs increases the likelihood of future drug problems (Grant & Dawson, 1997).

A growing number of studies (Iacono, Malone, & McGue, 2008) indicate that ADHD, CD, and NS frequently co-occur and that the covariance among these traits can be best explained by an underlying latent trait referred to as Behavioral Disinhibition (BD; i.e., “the inability to inhibit behavior despite its social undesirability, and cascade of familial, educational, psychological, and legal consequences”) (Young, Stallings, Corley, Krauter, & Hewitt, 2000). The high comorbidity among these disorders has prompted the need for more studies that can clarify the relationship between early assessments of ADHD, CD, NS, and SU and future drug problems. For instance, several reports have suggested that CD mediates the association between the inattention and hyperactivity subscales of ADHD and young adult drug problems (Brook, Duan, Zhang, Cohen, & Brook, 2008; Disney, Elkins, McGue, & Iacono, 1999; Fergusson, Horwood, & Ridder, 2007). Of these studies, those that have managed to adjust for the co-occurrence of CD and ADHD have concluded that ADHD effects could be attributed to the fact that CD was not accounted for in the model. Still, it remains unclear if any or all of these associations are due to their direct relationship with substance dependence or with the early stages of substance initiation and use.

1.1 Associations between measures of BD and Substance Problems

Population-based studies suggest a more than chance association between adolescent measures of BD and the development of future substance problems (Disney, et al., 1999; Elkins, King, McGue, & Iacono, 2006; Elkins, McGue, & Iacono, 2007; Grekin, Sher, & Wood, 2006; Jenkins, et al., 2011; Zucker, 2008); however, most studies are not prospective in nature and fail to account for the shared liability among adolescent ADHD, CD, NS, substance use, and substance problems (i.e., DSM-IV abuse or dependence) (Lee, Humphreys, Flory, Liu, & Glass, 2011). At the time of this study, we reviewed the literature and identified two longitudinal studies that examined the effect of both childhood/adolescent ADHD and CD on young adult (i.e., 30 > age > 18) SUDs and a third study that also included personality traits. In their study of 506 boys in the Pittsburgh Youth Study, Pardini and colleagues (Pardini, White, & Stouthamer-Loeber, 2007) examined the effects of early adolescent ADHD, CD, anxiety, and depression on young adult alcohol use disorders. The authors concluded that while controlling for the comorbidity amongst all the adolescent psychopathologies, CD was related to young adult alcohol use disorder symptoms but

ADHD was not. Furthermore, there was no interaction between ADHD and CD. Similar findings were obtained by Fergusson and colleagues, who used a 25-year longitudinal study of a New Zealand birth cohort to examine the link between CD and attention problems and young adult substance use, abuse, and dependence (Fergusson, et al., 2007). In a separate study, Tarter and colleagues used a sample of males assessed during adolescence and young adulthood to identify pathways linking childhood hyperactivity to young adult substance use disorder (Tarter, Kirisci, Feske, & Vanyukov, 2007). Tarter and colleagues discovered that childhood hyperactivity is a “diathesis for externalizing disturbances” at young adulthood. Furthermore, the link between childhood hyperactivity and young adult SUDs was mediated by both neuroticism and conduct problems, thus suggesting that NS and CD carry a much greater risk than ADHD.

1.2 Deriving robust estimates of effects in the context of adolescent drug use

Despite the growing number of studies linking childhood/adolescent psychopathology and personality with adult drug outcomes, it is not known whether any of the patterns of association described above are robust longitudinal effects, as most studies have failed to account for the joint effects of adolescent substance use (a robust predictor of future drug problems) (Grant & Dawson, 1997; Guy, Smith, & Bentler, 1994), which has been shown to be elevated among teens with externalizing problems (August, et al., 2006). In order to obtain robust estimates of effect between each of these early traits and young adult drug outcome, it is necessary to analyze longitudinal studies that have assessed all of these traits using a multivariate regression framework. A multivariate framework provides the opportunity to explore two fundamental research questions linking early assessments of ADHD, CD, and NS with future drug problems. Specifically, (1) Are adolescents with a history of ADHD OR CD problems OR an exuberance for novelty at increased risk for future drug problems, and (2) are those risk estimates, specifically related to the drug problems themselves, OR are they driven by their association with other behaviors, especially drug use, which on its own is capable of mimicking the characteristics of ADHD, CD, and NS because it causes neurocognitive (e.g., decreased memory, attention and speeded information processing, and executive functioning) and brain matter volume deficits (e.g., hippocampal, prefrontal cortex, and white matter volume) in the developing brain (Squeglia, Jacobus, & Tapert, 2009). For example, Squeglia and colleagues showed that moderate to heavy alcohol use and high levels of hangover symptoms was associated with reduced sustained attention in males and reduced visuospatial task performance (e.g., visuospatial memory) in females (Squeglia, Spadoni, Infante, Myers, & Tapert, 2009). Overall, studies examining the effects of ADHD, CD, and NS on future drug problems need to account for (1) shared variance between the traits, and (2) the effects of adolescent drug use, as it can produce neural abnormalities that can perpetuate behavioral disadvantages that increase the risk for drug use/problems.

1.3 Purpose of the current study

The purpose of this study was to address the ambiguity surrounding the predictive role of BD indicators, especially since only a few prospective studies have considered their joint effects and underlying comorbidity with early/adolescent substance use. We hypothesized that early externalizing psychopathology (i.e., ADHD and CD symptomatology) and novelty seeking tendencies are indicators of future drug dependence problems, over and above the effects of early adolescent substance use. In addition to direct processes, we further hypothesized that conduct and attention problems and novelty seeking influence the liability to drug dependence by also influencing the level of drug use during adolescence (i.e., indirect mechanisms).

2. Materials and methods

2.1 Participants

The sample consisted of 2361 individual members of a twin pair (46% male) who were drawn from the Center for Antisocial Drug Dependence (CADD) Study, an ongoing study at the University of Colorado. The twins utilized in the CADD originate from two community-based twin samples at the University of Colorado that are part of the much larger Colorado Twin Registry based at the Institute for Behavioral Genetics at the University of Colorado at Boulder. The two samples consist of the Longitudinal Twin Study (LTS) sample and the Community Twin Sample (CTS). The CTS sample was open to all twins born in the state of Colorado between 1979 and 1990, and additional in-migrating twins in the same age range ascertained through Colorado school districts. The LTS included twins born in Colorado between 1984 and 1990 who were initially tested prior to age 2 and who were followed longitudinally (Rhea, Gross, Haberstick, & Corley, 2006, 2013); inclusion in this sample depended on location and early twin and family characteristics. Twins from both samples were recruited into the CADD while they were between the ages of 12 and 18 years of age. Due to the longitudinal nature of the study, subjects from the LTS and CTS are currently enrolled in five-year follow-ups of the original baseline assessment. Data for the current study were drawn from the first and second waves of the CADD study. At the end of data collection for Wave 2 during the year 2008, 100% of LTS participated at both waves and 93% of CTS twins participated at both waves.

Data for the current study are drawn from the first (Wave 1) and second (Wave 2) waves of data collection. The sample is diverse and largely made up of Caucasians (87.12%) with similar rates of males and females across different ages. At Wave 1, the average age of the participants was 14.87 years ($SD = 2.17$). At Wave 2, the average age of assessment was 19.64 years ($SD = 2.60$). The interval between both waves of assessment was approximately five years (mean = 5.22, $SD = 1.06$). Rates of substance use and abuse and dependence in the CADD are similar to those typically observed in large population samples, such as the Monitoring the Future Study and the National Survey on Drug Use and Health (R. H. Palmer, et al., 2009).

2.2 Procedure

Data for the CADD project were obtained after identifying participants from the CTS and LTS samples. Participants were assessed using diagnostic interviews as part of an entire day of a battery of tests that included cognitive functioning, diagnostic interviews, and self-reports. The University of Colorado Boulder and Denver campuses Institutional Review Boards approved all components of the CADD presented in this study. Additional details on the recruitment and sample description of the twin samples in the CADD are available elsewhere (Rhea, et al., 2006, 2013).

2.3 Psychiatric and Personality Assessments

DSM-IV symptoms of ADHD (i.e., nine symptoms of inattention and nine symptoms of hyperactivity/impulsivity) and CD (15 symptoms) were measured during Wave 1 using the Diagnostic Interview Schedule for Children Version IV (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The DISC-IV was used to assess DSM-IV symptoms and diagnoses. Several ADHD that are part of the DSM-IV criteria were “Fidgets in seat”, “Talks a lot”, “Easily Distracted”, and “Difficulties sustaining attention”. Several of the CD criteria that were included were “Cruelty to animals”, “Bullying”, and “Breaking and entering”. Computer algorithms were used to determine the lifetime symptom counts (i.e., a sum of the criteria met by each respondent) of the hyperactivity-impulsivity (scores could range from 0 to 9 symptoms) and inattention (participants could report no symptoms (i.e., 0)

or up to 9 symptoms) subscales of ADHD, and the total DSM-IV symptoms for CD (participants scores could take on values from 0 to 15 symptoms).

Adolescent levels of NS were assessed using 18 items from Cloninger's Tridimensional Personality Questionnaire-Short Form (Heath, Cloninger, & Martin, 1994). Although the TPQ assesses other measures of personality we decided to utilize only NS for this study because of prior evidence. A sample of items asked by the questionnaire included, "I often try new things just for fun or thrills, even if most people think it is a waste of time" and (reversed) "I hate to make decisions based only on my first impressions". The mean of the NS items endorsed was used for the current analyses.

The Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) was used to obtain information on substance experimentation, repeated use (defined as: use of alcohol more than five times, smoked 20 or more cigarettes or used tobacco-based products such as snuff, tobacco pipe, or cigars, and use of marijuana and the other illicit drugs more than five times), frequency of use, and lifetime problems (i.e., DSM-IV symptoms levels and diagnoses of drug abuse or dependence) during waves 1 and 2. For the purposes of this study, adolescent substance use and problems were defined as the number of substances repeatedly used, and the number of substances with problems, respectively. These measures provided indication of the extent of substance use and problems during adolescence.

Wave 2 (i.e., young adult) levels of lifetime DSM-IV alcohol, tobacco, and illicit (i.e., cannabis, sedative, hallucinogen, amphetamine, opioid, inhalant, phencyclidine, club drugs, and cocaine) drug dependence symptoms endorsed were tallied to create a symptom count variable (with scores ranging from zero to seven per substance). The measure Dependence Vulnerability (DV; which is a polysubstance dependence vulnerability index (Button, et al., 2006), was also constructed ($DV = \text{total number of DSM-IV dependence symptoms across all 11 substances} / \text{total number of substances used}$).

Wave 1 (adolescent) predictors included: (1) the hyperactivity-impulsivity (HI) and (2) Inattention (INATT) subscales of ADHD, (3) CD, (4) substance use (SU) and problems (SP), and (5) NS. Wave 2 (young adult) dependent variables were: alcohol, tobacco, and illicit drug dependence and dependence vulnerability (DV).

2.4 Analysis plan

Data management and descriptive analyses were conducted using SAS (Version 9.2)(SAS, 2002). To correct for departures from normality often seen in count phenotypes, the data were rank normalized after adjusting for age effects within each gender (Young, et al., 2000). Subsequent analyses were conducted in MPlus ® (Muthen & Muthen, 1998–2012) that has the capabilities to handle multiple variables of varying distributions (ordinal, continuous, count, etc.) and complex survey data (e.g., subpopulation analysis, clustering, stratification, etc.).

To test the main research question (Figure 1), path analyses were conducted in MPlus using the rank normalized [mean=0, standard deviation (STD) = 1] scores for the Wave 2 outcome variables and the Wave 1 independent variables. Effect estimates for Figure 1 were derived using path analysis to determine how this set of variables (i.e., ADHD hyperactivity/impulsivity, ADHD attention problems, CD, NS, and SU) is related to future alcohol, tobacco, and illicit drug dependence (i.e., the total effect). In addition, we tested the hypothesis that a portion of the total effect of these variables (i.e., ADHD, CD, and NS) results from an indirect effect through adolescent substance use. Further, because the occurrence of substance use disorders (i.e., DSM-IV substance abuse or dependence) is

common during adolescence, the model also controlled for these effects to account for any bias in our estimates that might result from early and persistent patterns of problematic substance use. Finally the model also controlled for age at time of assessment during Wave 1, the gender [coded as male (1) vs. female (0)] of the participants, and the racial identification of the respondent (coded as Caucasian vs. Other). Age and gender interaction effects were also tested and are reported when detected. MPlus models were estimated while accounting for the fact that participants within the sample are clustered within families (i.e., MPlus computed standard errors that accounted for the non-independent nature of the observations).

3. Results

3.1 Mean-level Gender Differences

Table 1 presents the untransformed means and standard deviations for each trait. Robust Poisson regression was used to determine gender differences in the mean at each assessment. At Wave 1, males reported higher mean levels of ADHD, CD, NS, and alcohol dependence symptoms. At Wave 2, females reported higher mean levels of tobacco dependence symptoms, while males endorsed more alcohol dependence symptoms than females. Males also scored higher on the DV measure. With the exception of NS, most of the observed data were right skewed. Analyses presented in the Results section employed normalized measures for each of these variables.

3.2 Prospective effects of BD indicators on young adult drug dependence

Table 2 shows the effects of ADHD, CD, SU, and NS on young adult alcohol, tobacco, and illicit drug dependence and dependence vulnerability (DV). Details on other covariates in the model are presented for completeness. The first half of Table 2 shows the association of the Wave 1 predictors with adolescent substance use. High levels of ADHD attention problems (ATT), novelty seeking (NS), and conduct disorder (CD) were associated with greater levels of substance involvement at Wave 1. These significant associations suggested that adolescent substance use may provide a mechanism for a part of or all of the association of ATT, CD, and NS with drug dependence.

The pattern of results across the right portion of Table 2, outline the effect of each predictor on drug dependence outcomes at Wave 2. CD, NS, and substance use at Wave 1 were the most consistent predictors of substance problems at Wave 2. Taking into account the effects of all other covariates in the model, increasing levels of ADHD attention problems was associated with higher scores on the DV measure. The hyperactivity/impulsivity (HI) subscale of ADHD was not predictive of alcohol, tobacco, or illicit drug dependence symptoms at Wave 2. There was an association between symptom levels on the ADHD attention problems subscale and Wave 2 illicit drug dependence and DV. Higher levels of CD were associated with alcohol, and illicit drug dependence and DV. Further, the increase in illicit drug dependence problems due to higher CD levels further increased with higher levels of age. NS predicted increased symptom levels for all Wave 2 outcomes. Being male or Caucasian did not have any effect on drug dependence at Wave 2.

Table 3 presents the partitioning of the total effect of each Wave 1 predictor (HI, ATT, CD, and NS) into indirect effects via substance use (as indicated in Figure 1) and direct effects. In regards to alcohol problems at Wave 2, the total effect for both subscales of ADHD suggested no overall effect; however, there was an indirect effect of ATT on alcohol dependence mediated by substance use. Notably, due to the lack of a total main effect for ATT it is difficult to interpret its indirect relationship on alcohol dependence other than to say that it may operate via adolescent substance use. Substance use also mediated a part of

CD's and NS's effect on alcohol problems, although there were also direct effects, suggesting only partial mediation.

For Tobacco dependence, there was limited evidence to suggest that either ADHD subscale influenced the level of tobacco problems. Similar to alcohol, the specific indirect effect for ATT on tobacco via substance use was significant suggesting that such associations may be operating via adolescent substance use. CD and NS had significant total effects on tobacco dependence. Further, all of CD's total effect was mediated by the level of substance use during adolescence. The significant effect of NS on tobacco dependence was only partially mediated by substance use, as there was evidence to suggest direct effects linking NS and tobacco dependence.

In the model for Illicit drug dependence, ATT, CD, and NS were significant predictors. However, unlike the results for alcohol and tobacco, the coefficients for specific indirect effects suggested no mediation via substance use. Consequently, direct effects of each predictor drove almost all of the total effects.

Lastly, ATT, CD, and NS significantly predicted DV, such that higher scores were associated with higher DV scores. For this general liability index for drug dependence, ATT, CD, and NS have specific indirect and direct effects on the liability for drug dependence, suggesting partial mediation.

Overall, these results suggest that CD and NS are the most robust predictors of alcohol, tobacco, and illicit DSM-IV dependence symptoms and DV. Further, their effect on substance dependence (except illicit drug dependence) is partially mediated by adolescent substance use.

4. Discussion

This study is a unique attempt to examine the prospective relationship between adolescent psychopathology (i.e., ADHD and CD) and personality (i.e., NS) and young adult drug dependence in the context of adolescent substance use. It also explores the mediating effects of adolescent substance use, thus providing a useful mechanism for how early externalizing psychopathology is related to later drug dependence. Regression analyses in our community-based sample of twins showed that after accounting for the overlap among the adolescent measures, the indicators of BD were differentially predictive of young adult substance dependence. Moreover, in addition to effects mediated by substance use there are unique and independent effects of CD and NS on drug dependence.

4.1 Consistency with previous research

Our results were similar to those of Pardini and colleagues' study, which showed that conduct disorder symptoms during late adolescence were predictive of alcohol dependence (Pardini, et al., 2007). The results are also consistent with the aforementioned longitudinal studies that also suggest that CD and NS mediate the associations between childhood/adolescent measures of inattention, hyperactivity-impulsivity and ADHD and later substance problems. This paper adds to the literature by demonstrating the effects of CD and NS on DSM-IV drug dependence while also accounting for the mediating effects of early drug use. Our results were similar to the results presented by Elkins and colleagues (Elkins, et al., 2007), whose adjusted models showed no effect of either subscale of ADHD on alcohol abuse/dependence, but a significant effect of CD. On the other hand, Elkins and colleagues were able to detect strong positive associations between HI and tobacco dependence, whereas our study did not. It is important to note, however, that Elkins and colleagues did not account for the effects of early drug use and problems or their mediating effects.

4.2 Implications of findings for alcohol and other drug studies

To put the results of this study into perspective, behavioral problems in childhood (in particular conduct disorder) increase the risk of developing problems with multiple substances and future drug dependence. The results of this study suggest that treatment of conduct problems during childhood or early adolescence or the management of novelty seeking tendencies may help to reduce the risk of substance use during adolescence and problematic substance use. The fact that these effects are only partially mediated by drug use suggests that drug use is not the sole cause of later dependence symptoms. This supports the findings of conditioning in the brain due to repeated substance use (Volkow, Wang, Fowler, & Tomasi, 2012), as well as the hypothesis that individuals who present with early externalizing psychopathology are more susceptible to the effects of substances of abuse. Consequently, these findings have serious implications for the development of treatment and prevention efforts, as well as future molecular genetics research. Behavioral or pharmacological treatment of disruptive disorders in children and adolescents is likely to have lasting effects across multiple disruptive psychopathologies due to the common thread that underlies ADHD, CD, and NS - the inability to plan out actions, inhibit actions, and consider the implications of actions (impulsivity) (Miller, Stephen, & Tudway, 2004). For instance, preliminary findings from our lab recently determined that higher levels of CD and ADHD symptoms are associated with higher levels of initial sensitivity (e.g., subjective and autonomic experiences, such as reports of pleasure, liking the taste, nausea, heart rate, etc.) to alcohol and tobacco during adolescence, which suggests that these individuals may be primed to be more responsive to substances of abuse (Bidwell, et al., 2012; R.H. Palmer, et al., 2012; Wills, et al., 1994).

Though clinically defined traits, our strongest predictors, CD and NS, represent an early indication of neurobiological profiles that may be more susceptible to the effects of substances of abuse (e.g., poor inhibitory control as evidenced by impulsive decision making and poor executive control as evidenced by low response inhibition). This is suggested by the fact that drug addicted individuals and individuals with a family history of drug addiction present with similar cognitive and neuropsychological deficits (Iacono, et al., 2008). Among the many neurological domains that influence drug addiction (Volkow, et al., 2012), the prefrontal cortex (PFC) is a common structure that links ADHD, CD, NS, and SUDs (Arnsten, 2009). The PFC is necessary for event planning, emotional regulation, attention, and regulating behavior. Variation in PFC functioning, as manifested by these childhood/adolescent disorders represents a singular component of a larger network of factors that contribute to the liability to substance addiction. It is clear from the findings of this study, that understanding and identifying these associations will help to build this network and generate new hypotheses for addiction research. These findings also have important implications for building genetic models of addiction liability. To date, a number of twin studies have demonstrated an evidence of unique and shared genetic mechanisms between externalizing behavior and substance problems (Button, et al., 2006; Edwards & Kendler, 2012; Knopik, Heath, Bucholz, Madden, & Waldron, 2009). For instance, several studies have suggested that both novelty seeking and drug seeking behaviors are mediated by the mesolimbic dopamine system making it an ideal starting point for genetic studies. A testament of the validity of this hypothesis has been evidence from pharmacological studies which have shown that blockage of dopamine receptors using dopamine antagonists, such as haloperidol, blocks/reduces both drug seeking and novelty seeking behaviors (Bardo, Donohew, & Harrington, 1996). Recent studies also suggest that females with the Catechol-O-methyltransferase (COMT; a protein responsible for the degradation of dopamine in the synapse) Met/Met genotypes have a higher mean-level of NS symptoms compared to females with the Val/Val or Val/Met genotypes (Golimbet, Alifimova, Gritsenko, & Ebstein, 2007), although these relationships may be sample dependent and should be replicated

across larger samples and similar measures. NS has also been shown to mediate the association between DRD4 and drinking (Laucht, Becker, Blomeyer, & Schmidt, 2007) and smoking behaviors (Laucht, Becker, El-Faddagh, Hohm, & Schmidt, 2005), as well as the association between COMT and the age of onset of drug use (Li, et al., 2011). Further, the Val 158 Met polymorphism in the COMT gene also influences the level of CD and ADHD symptoms in males (DeYoung, et al., 2010). Overall, the evidence suggests that variation within the mesolimbic dopamine system influences the liability to drug use, CD, ADHD, and novelty seeking tendencies, however, further research with larger samples and using multiple measures is necessary to obtain robust estimates of association as many studies have been unable to conduct multivariate analyses of the type presented in this manuscript. Such investigations are becoming increasingly possible with the developmental research projects, such as the Genes Environment Development Initiative (Minnesota Center for Twin and Family Research) and the Center for Antisocial Drug Dependence, which combine whole genome genotyping with extensive behavioral assessments.

4.3 Limitations of research

A notable limitation, that is not unique to this type of study, is that not everyone in the study has passed through the “age of risk” (i.e., ages 21–25) (Substance Abuse and Mental Health Services Administration, 2011) for developing a substance use disorder; however, most of our subjects are within the age range where the highest levels of substance use and disorders have been observed. In the future, we plan to overcome this limitation by using data collected from the third wave of assessment of respondents at the Center for Antisocial Drug Dependence, and similar longitudinal studies. Despite this limitation, the current findings support previous work highlighting NS tendencies as a powerful early indicator of future SUDs. In addition, it suggests that understanding the mechanisms underlying ADHD and CD may help to inform our understanding of the shared mechanisms underlying substances of abuse, as well as unique mechanisms for some substances. Another limiting factor is the limited inclusion of socio-demographic variables other than race, such as socioeconomic, and peer and family substance use. Additional research in samples with detailed environmental variables is still needed to better estimate these effects in such contexts.

5. Conclusions

In summary, this investigation indicates that in a model including CD, adolescent substance use and problems, ADHD subscales, and NS, levels of adolescent conduct problems, substance use, and an innate tendency to seek out novel stimuli (i.e., NS) are the most robust indicators of young adult substance dependence. In conclusion, the characterization of personality and psychopathology via prospective longitudinal studies is an integral component in our understanding of the liabilities to alcohol and drug addiction.

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Highlights

- The predictive effects of adolescent indicators of Behavioral Disinhibition varied by substance.
- ADHD subscales were positive associated with illicit drug dependence.
- Conduct disorder and novelty seeking were predictive of alcohol, tobacco, and cannabis dependence. These effects were partially mediated by adolescent substance use.
- The strongest predictor of future drug problems was novelty seeking.

Figure 1.

Path diagram depicting direct (solid lines) and indirect (dashed lines) relationships tested in the current study. For simplicity, indirect pathways via substance use are only shown for alcohol dependence symptoms at Wave 2. Other covariates included in the model were age at Wave 1, gender, and race (none of which are shown for simplicity). Abbreviations: ATT, ADHD attention problems, HI – ADHD hyperactivity/impulsivity, CD – DSM-IV conduct disorder symptoms, DV – Dependence vulnerability, NS – novelty seeking.

Table 1

Mean level of untransformed scores for each phenotype by gender

Behavior	Females				Males				Means Test	
	N	Mean (STD)	Skew	Kurtosis	N	Mean (STD)	Skew	Kurtosis	Z-value	
<i>Wave 1 independent variables (adolescence)</i>										
ADHD - Hyperactivity/Impulsivity	1268	.18 (.91)	5.51	30.15	1093	.35 (1.25)	3.78	13.00		3.43 <i>b</i>
ADHD - Inattention	1268	.21 (.98)	5.04	24.87	1093	.43 (1.40)	3.27	9.32		4.16 <i>b</i>
Conduct Disorder	1268	.59 (.95)	2.42	8.50	1093	1.00 (1.37)	2.25	8.08		7.41 <i>c</i>
Novelty Seeking	1249	.43 (.19)	.32	-.28	1080	.47 (.19)	0.11	-.37		5.03 <i>c</i>
# of substances used	1268	.53 (1.11)	2.71	8.31	1093	.48 (.98)	2.99	12.13		-0.82
# of substances with problems	1268	.17 (.57)	4.21	20.24	1093	.16 (.60)	5.68	40.46		-0.39
<i>Wave 2 (young adulthood)dependent variables</i>										
Alcohol Dependence Sx	984	1.01 (1.54)	1.91	3.55	901	1.34 (1.63)	1.30	1.11		3.92 <i>c</i>
Tobacco Dependence Sx	379	2.65 (1.94)	.18	-1.13	529	2.24 (2.03)	0.47	-1.03		-2.80 <i>b</i>
Illicit Drug Dependence Sx	379	1.95 (3.02)	2.32	6.57	452	1.97 (3.23)	3.59	22.28		.10
DV	1268	1.02 (1.23)	1.29	1.37	904	1.19 (1.21)	1.07	.95		2.78 <i>b</i>

Note: For gender difference tests using the transformed scores.

^a p<.05,

^b p<.01,

^c p<.001.

STD - standard deviation, Sx - Symptoms.

Table 2
Standardized regression coefficients (standard error) from the models predicting young adult drug dependence

<i>Wave 1 (adolescent) variables</i>	Wave 1 (Adolescence)				Wave 2 (Young Adult) Outcomes			
	Substance Use	Alcohol	Tobacco	Illicit	DV			
ADHD - Hyperactivity/Impulsivity	.000 (.024)	-.0228 (.024)	.002 (.037)	-.024 (.035)	-.009 (.024)			
ADHD - Inattention	.118 (.044) <i>b</i>	.023 (.039)	.049 (.041)	.123 (.048) <i>b</i>	.077 (.034) <i>a</i>			
Conduct disorder	.350 (.026) <i>c</i>	.096 (.027) <i>c</i>	.032 (.033)	.135 (.036) <i>a</i>	.093 (.026) <i>c</i>			
Novelty seeking	.123 (.020) <i>c</i>	.141 (.022) <i>c</i>	.129 (.033) <i>a</i>	.110 (.033) <i>b</i>	.164 (.022) <i>c</i>			
Substance use	-	.131 (.031) <i>c</i>	.128 (.038) <i>b</i>	.057 (.043)	.160 (.032) <i>c</i>			
Substance problems	-	.078 (.037) <i>a</i>	.117 (.037) <i>b</i>	.125 (.044) <i>b</i>	.141 (.033) <i>c</i>			
Age	-.074 (.045)	-.093 (.040) <i>a</i>	-.121 (.044) <i>b</i>	-.139 (.050) <i>b</i>	.056 (.034)			
Gender	-.004 (.021)	-.014 (.022)	.029 (.036)	-.013 (.031)	-.007 (.022)			
Race	.002 (.023)	.023 (.022)	.010 (.029)	.017 (.027)	-.013 (.020)			

Note: ADHD: Attention Deficit Hyperactivity Disorder. Standardized coefficients are given with standard errors in parentheses. - indicates parameters that were not estimated in the model.

a $p < .05$,

b $p < .01$,

c $p < .001$.

Table 3

Standardized total, indirect, and direct effects on wave 2 outcomes

Models	Standardized Effects on Wave 2 (Young Adulthood) Outcomes							
	Total Effect			Specific Indirect Effect (via Use)			Direct Effect	
	Estimate	S.E.	P-Value	Estimate	S.E.	P-Value	Estimate	P-Value
<i>Alcohol</i>								
ADHD - Hyperactivity/Impulsivity	-.028	.025	.240	.000	.003	1.000	-.028	.250
ADHD - Inattention	.038	.040	.339	.015	.007	.021	.023	.558
Conduct Disorder	.142	.027	<.001	.046	.012	<.001	.096	<.001
Novelty Seeking	.157	.022	<.001	.016	.005	.001	.141	<.001
<i>Tobacco</i>								
ADHD - Hyperactivity/Impulsivity	.002	.037	.983	.000	.003	1.000	.002	.960
ADHD - Inattention	.064	.043	.134	.015	.007	.037	.049	.233
Conduct Disorder	.077	.033	.019	.045	.014	.001	.032	.329
Novelty Seeking	.145	.033	<.001	.016	.005	.003	.129	<.001
<i>Illicit</i>								
ADHD - Hyperactivity/Impulsivity	-.024	.035	.491	.000	.001	1.000	-.024	.489
ADHD - Inattention	.130	.049	.008	.007	.006	.235	.123	.011
Conduct Disorder	.155	.034	<.001	.020	.015	.191	.135	<.001
Novelty Seeking	.117	.033	<.001	.007	.005	.197	.110	.001
<i>DV</i>								
ADHD - Hyperactivity/Impulsivity	-.009	.025	.717	.000	.004	1.000	-.009	.712
ADHD - Inattention	.096	.035	.006	.019	.008	.016	.077	.021
Conduct Disorder	.149	.026	<.001	.056	.012	<.001	.093	<.001
Novelty Seeking	.184	.022	<.001	.020	.005	<.001	.164	<.001

Standardized parameter estimates are shown along with their standard error and corresponding p-value for each model predicting the Wave 2 dependent variables.