Genetic and Environmental Risks Predicting Patterns of Alcohol Use and Abuse from Adolescence Through Early Adulthood

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Introduction

Alcohol and substance use are primary public health concerns in the U.S. Initiation of alcohol use often begins during adolescence, and earlier use can be a predictor of related risk behaviors as well as later abuse and dependence (SAMHSA, 2011). Extant research suggests the importance of both genetic and environmental risk factors as influential in the initiation and growth of alcohol use and potential progression to problematic use during adolescence. This literature demonstrates that genetic and environmental factors are likely to have an additive effect – with the risk of alcohol use and abuse in an individual with a genetic disposition to use alcohol being exacerbated by environmental risk factors (e.g., Moffitt, Caspi, & Rutter, 2006; Rutter & Silberg, 2002). In the current paper we consider the unique and interactive effects of genes and three environmental risk factors (social norms, social controls, and stress) in the prediction of longitudinal trajectories of drinking and intoxication from early adolescence to adulthood.

Genes and Alcohol Use

Recent advances in molecular genetics suggest that variations in several genes that comprise the dopaminergic system are among the most promising indicators for understanding genetic influences on human behaviors (Clark & Grunstein, 2000; Le Foll et al., 2009). Studies have identified a number of polymorphisms in dopaminergic genes that are associated with substance use. Furthermore, recent gene-gene interaction (GxG) studies provide evidence suggesting that the effects of genes are often additive in nature, with phenotype being determined only by multiple allelic variations (Kendler & Greenspan, 2006). Medical studies have recently begun to examine the cumulative effect of multiple polymorphisms across several genes by combining individual polymorphisms to create aggregate genetic risk scores (AGRS) that examine the cumulative effect of multiple genes. AGRS studies of substance use have not yet been conducted, however, and many extant AGRS studies are limited in that they fail to account for environmental factors, despite evidence suggesting that doing so can further improve predictive power (see De Jager et al., 2009; Zheng et al., 2010). Thus, studies using AGRS methods with environmental measures are needed to study varying human behaviors, including substance use.

Environmental Influences on Substance Use

Prior theory and literature have delineated three leading environmental explanations for problematic alcohol use: social norms, social controls, and stress. Social norms are theorized to guide behavior through two mechanisms: subjective and descriptive norms. Subjective norms represent an individual's beliefs about what others will think of their behavior and influence youth through a desire to conform with important others' views (Ajzen & Fishbein, 1977). Descriptive norms are derived from the actual behavior of others; they guide individuals by providing information about "normal" behavior in social environments, and constrain behavior by indicating what behaviors are deviant or off-limits (Cialdini & Trost, 1999). Recent work suggests that social norms from parents, peers, and schoolmates uniquely predict membership in developmental trajectories of alcohol use during adolescence (Lynch, Coley, Sims, Lombardi, & Mahalik, 2013).

Social control theorists suggest that parental and community monitoring and control may represent another contextual force influencing adolescents' opportunities and wishes to engage in risk behaviors. For example, higher levels of parental monitoring have been linked with lower levels of alcohol use among male adolescents (Borawski, Ievers-Landis, Lovegreen, & Trapl, 2003) and parenting practices related to adolescent alcohol use are directly related to adolescent alcohol intake and later alcohol problems (van den Eijnden, van de Mheen, Vet, & Vermulst, 2011). Finally, psychological, physical, and contextual stressors may also increase risk for engaging in deviant by altering biological functioning, self-regulation, and individual goals and/or expectations. Evidence

suggests that adolescents who have experienced increased levels of stressful life events demonstrate elevated drug use (Bruns & Schiro Geist, 1984), alcohol consumption, and alcohol use disorders (Keyes, Hatzenbuehler, & Hasin, 2011).

GenexEnvironment Interactions

One of the most influential advances in genetic studies in recent years is the recognition that neither genes nor the environment act in isolation. Instead, interplay between the two, termed gene-environment interactions (GxEs), is likely more important for determining human behaviors than either genes or the environment alone (e.g., Moffitt, Caspi, & Rutter, 2006; Rutter & Silberg, 2002). A number of studies have examined GxEs in relation to substance use. Overall, these studies suggest that the effects of genetic risks for substance use are stronger for individuals who also experience environmental risk (e.g., life stress, childhood maltreatment, insecure parent-child attachment, exposure to substance-using peers) but lower or nonexistent for individuals who do not experience environmental risks (e.g., Harden et al., 2008; Vanyukov et al., 2007; van der Zwaluw & Engels, 2009). This recent attention to studying the joint effects of genetic and environmental input is an important step toward better understanding the etiology of substance use disorders. Thus far, however, methodological problems (e.g., small homogeneous samples, measures of single genes, narrow environmental measures) have limited our ability to detect GxE effects. A handful of studies that have used broader cumulative environmental measures suggest that doing so can greatly improve the likelihood of detecting GxEs, by providing more sensitive and reliable measures of environmental influence (Caspi et al., 2003; Moffit, Caspi, & Rutter, 2006), but very little attention has been paid to AGRS, an important omission in the literature.

Based on this literature, the current study sought to assess the unique and interactive effects of four proposed contributors to youth alcohol use and abuse: genetic risks assessed through an AGRS of dopaminergic genetic alleles; social norms from parents, peers and schoolmates; social control from parents and school; and life stress.

Methods

Data for the present study were drawn from the in-home survey sample of Add Health, a longitudinal survey of a nationally representative school-based sample of adolescents in the U.S. Add Health began in 1994 assessing a school sample of 7th through 12th graders (N = 90,118) through a random school selection procedure. From the baseline school sample, a stratified sample of participants was selected for in-home surveys and interviewed over 4 waves in 1995, 1996, 2001/2, and 2007/8, with response rates of 79%, 88%, 77%, and 80% respectively. Of these participants, genetic data was collected via cheek swabs of 13,427 youth at Wave 4. Parent and school administrator report also data were collected at wave 1. Our analytic sample included all youth participating in the in-home and genetic components of the study with valid survey weights and school IDs, resulting in a final analytic sample of 13,427.

Measures

Drinking and Intoxication. At each wave, youth reported the number of days they drank alcohol and became intoxicated. Responses were scored on a 7-point Likert scale ("never" to "every day or almost every day") which were recoded into a count variable of days per month that youth drank alcohol and were intoxicated.

Genetic Risk Variables. Three dopamine polymorphisms were tested individually and in a genetic risk score. These included DRD4 48 bp VNTR, DAT1 40 bp VNTR, and MAOA 30 bp VNTR. Long alleles (7+ repeats) of DRD4 were coded as risk, while all others were coded as non-risk. For DAT1, 10 repeats were coded as risk while 9 repeats were coded as non-risk. Finally, for MAOA, short alleles (2R and 3R) were coded as risk while all else was coded as non-risk. Risk alleles within each gene were summed to create individual measures of genetic risk ranging from 0 to 2 for all genes except MAOA for males. A *genetic risk score* (GRS) ranging from 0 to 6 for females and 0 to 5 for males was created by summing the total number of risk alleles across all three genes.

Social Norms. At wave 1, participants reported the number of their three closest peers who drink alcohol at least once per month, a measure of *peer drinking*. One parent in each family reported their and their residential

partner's frequency of alcohol use in the past year with values ranging from 1 ("never") to 6 ("nearly every day"); a measure of the highest drinking score reported was created to delineate *parent drinking*. *Schoolmate drinking* was assessed by averaging the number of days students within the same school reported drinking per month.

Stressful Life Events. Youth reported their experience of a variety of stressful life events within the previous calendar year at wave 1. These stressful life events were then aggregated into internal and external stressful life events categories. *Internal stressful life events* included events over which the youth had some control, such as being expelled from school or being convicted of a crime. *External stressful life events* included experienced outside of youth control, such as the death of a parent or moving to a new home.

Social Control. Youth, parent, and school administrator reports at wave 1 tapped into aspects of social control that adolescents experienced. *Parental knowledge* was assessed using parental report of knowledge of adolescent's closest friends and activities. *Parental monitoring* stemmed from youth reports of direct parental monitoring at various points throughout a typical day. Finally, a measure *school punishment* reflected administrator reports of the severity of school punishment policies regarding student consumption of alcohol on campus.

Covariates. A variety of youth, family, and school characteristics were included in analyses due to their associations with social norms and drinking behaviors in prior literature.

Analytic Technique

A series of multilevel negative bionomial growth models examined the role of genetic risks, social norms, social controls, and life stress on trajectories of (1) adolescent drinking and (2) adolescent intoxication. Each model was estimated separately by gender to account for varying ranges of genetic risk.

Results

Environmental effects

Table 1 presents model results for males and females respectively. Social norms and stressful life events demonstrated significant associations with drinking and intoxication behaviors across genders. Parental and friend drinking were associated with higher drinking behaviors among both females and males, and friend drinking was additionally associated with higher levels of intoxication for both genders. Schoolmate drinking, however, was only associated with drinking behaviors among males. The environmental measures of social control, in contrast, were largely nonsignificant. Further, both measures of stressful life events were strong predictors of both drinking and intoxication among males and females.

Main and interactive effects of Genes

Among males, analyses suggested no significant effects of the genetic risk score on initial levels or growth in drinking and intoxication frequency from adolescence through early adulthood. Further, no evidence of GxE interactions emerged within the male sample. Similarly, analyses among female participants indicated no significant effects of genetic risk on initial levels or growth in drinking behaviors. However, greater genetic risk was associated with marginally greater increases in the frequency of intoxication overtime. No significant gene by environment interactions emerged among females for either drinking or intoxication behaviors.

Conclusions

Results highlighted the importance of environmental factors including social norms and stressful life events in the prediction of adolescent and young adult drinking and intoxication. However, dopaminergic genes previously linked with alcohol and other substance use showed limited associations with drinking and intoxication from adolescence through early adulthood. Only for females and only for intoxication were significant genetic effects found. That is, greater genetic risk scores were linked with steeper and more rapid growth in the frequency of intoxication for females. These findings add to a building body of literature suggesting that females may react differently to genetic risks than their male counterparts. However, in concurrence with recent research failing to consistently replicate genetic effects, no evidence of gene by environmental interactions emerged.

Table 1

Summary of Coefficients and Standard Errors for Model Predicting Days Drinking and Days Intoxicated *(N=13,427)*

	Days Drinking						Days Intoxicated					
	Intercept		Slope		Slope Squared		Intercept		Slope		Slope Squared	
	Coef(SE)	ERR	Coef(SE)	ERR	Coef(SE)	ERR	Coef(SE)	ERR	Coef(SE)	ERR	Coef(SE)	ERR
Table 1a: Males												
Genetics												
Genetic Risk Score	-0.04(0.04)	0.964	0.00(0.01)	1.002	0.00(0.00)	1.000	-0.04(0.07)	0.966	0.01(0.02)	1.010	0.00(0.00)	1.000
Social Norms												
Parent Drink	0.07(0.03)*	1.069	0.00(0.01)	1.000	0.00(0.00)	1.000	0.07(0.04)+	1.069	-0.01(0.01)	0.993	0.00(0.00)	1.000
Friend Drink	0.73(0.04)**	2.079	-0.12(0.01)**	0.887	0.01(0.00)**	1.006	0.78(0.05)**	2.179	-0.13(0.02)**	0.882	0.01(0.00)**	1.006
School Drink	0.31(0.13)*	0.945	-0.06(0.03)+	1.003	0.00(0.00)	1.000	0.33(0.18)+	1.397	-0.08(0.05)	0.928	0.00(0.00)	1.000
Social Control												
Parental Knowledge	0.45(0.21)*	1.562	-0.06(0.06)	0.942	0.00(0.00)	1.000	0.39(0.28)	1.481	-0.03(0.08)	0.975	0.00(0.01)	1.000
Parental Monitoring	-0.05(0.06)	0.956	0.00(0.02)	1.000	0.00(0.00)	1.000	-0.06(0.07)	0.941	0.02(0.02)	1.022	0.00(0.00)	1.000
School Punish	0.02(0.15)	0.972	-0.03(0.04)	1.002	0.00(0.00)	1.000	0.06(0.17)	1.062	-0.05(0.05)	0.950	0.00(0.00)	1.000
Stressful Life Events												
Internal SLE	0.36(0.05)**	1.428	-0.07(0.01)**	0.929	0.00(0.00)**	1.000	0.49(0.08)**	1.629	-0.09(0.03)**	0.910	0.01(0.00)**	1.005
External SLE	0.23(0.03)**	1.257	-0.05(0.01)**	0.948	0.00(0.00)**	1.000	0.26(0.06)**	1.297	-0.06(0.02)**	0.938	0.00(0.00)**	1.000
Table 1b: Females												
Genetics												
Genetic Risk Score	0.01(0.04)	1.009	-0.01(0.01)	0.992	0.00(0.00)	1.000	-0.09(0.07)	0.910	0.03(0.02)+	1.035	0.00(0.00)+	0.998
Social Norms												
Parent Drink	0.10(0.03)**	1.107	-0.01(0.01)	0.992	0.00(0.00)	1.000	0.08(0.04)+	1.081	-0.01(0.02)	0.995	0.00(0.00)	1.001
Friend Drink	0.80(0.04)**	2.223	-0.13(0.01)**	0.875	0.01(0.00)**	1.006	0.87(0.06)**	2.389	-0.15(0.02)**	0.862	0.01(0.00)**	1.008
School Drink	0.16(0.14)	1.169	-0.02(0.04)	0.985	0.00(0.00)	1.000	0.15(0.15)	1.000	-0.03(0.04)	1.000	0.00(0.00)	1.000
Social Control												
Parental Knowledge	0.23(0.20)	1.257	0.00(0.08)	1.002	0.00(0.01)	1.000	0.13(0.33)	1.138	-0.02(0.12)	0.978	0.00(0.01)	1.002
Parental Monitoring	-0.10(0.05)+	0.904	0.02(0.02)	1.021	0.00(0.00)	1.000	-0.11(0.09)	0.896	0.02(0.03)	1.017	0.00(0.00)	0.999
School Punish	0.15(0.14)	1.156	-0.04(0.05)	0.966	0.00(0.00)	1.000	0.11(0.17)	1.000	-0.04(0.06)	1.000	0.00(0.00)	1.000
Stressful Life Events												
Internal SLE	0.36(0.06)**	1.426	-0.09(0.02)**	0.919	0.01(0.00)**	1.005	0.55(0.07)**	1.725	-0.12(0.03)**	0.890	0.01(0.00)**	1.007
External SLE	0.16(0.04)**	1.175	-0.04(0.01)**	0.963	000(0.00)**	1.000	0.18(0.04)**	1.198	-0.06(0.02)**	0.946	0.00(0.00)*	1.003

Note: +p<.10, *p<.05, **p<.01. Within each row, groups with shared subscript letters are different from each other at the p<.05 level. All models controlled for age, race, youth and parental levels of educational attainment, parent marital status, household composition, income, region, and urbanicity.