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DAT1 and Alcohol Use: Differential Responses to Life Stress during Adolescence

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Abstract

Stressful life events can impact both substance use initiation and the quantity of substances consumed by adolescents; however, the effect of stress on substance use may be contingent on other factors including social support, peers, and genotype. DAT1, a polymorphic dopamine transporter gene, is one such factor that may be responsible for differential susceptibility to cumulative life pressures. Data from the National Longitudinal Study of Adolescent Health was utilized to determine whether adolescents with the 10-repeat allele are more likely to respond to life stresses by engaging in alcohol use than those without the allele. Respondents' self-reports of key stressors were used to create a composite life stress scale. The interaction of this measure with the number of 10-repeat DAT1 alleles was evaluated in series of logistic regression models. A significant interaction emerged between stressful life experiences and DAT1 for alcohol use among females, but this pattern was not seen in males. Females with the 10-repeat allele appear to be more sensitive to life stress as compared to those without the allele. It appears that variation in the DAT1 gene may help explain why some women are more likely to consume alcohol when confronted with stress. It however does not appear to condition the reaction of men, in terms of alcohol use, to stress.

Keywords

alcohol; DAT1; stress; gene X environment interaction; adolescent alcohol use; gender differences

Introduction

Academic literature has long recognized that variation in substance use and dependence can partially be attributed to genetics (Prescott et al., 2006). A genetic effect appears to exist for almost all substances with problematic use of a substance typically being more highly linked to heredity than the general use of that substance (Young et al., 2006). Alcohol is no exception— meta-analyses estimate that genetic factors account for approximately 24% of the variation in alcohol use, 36% of the variation in problem drinking behaviors, and between 40% and 60% of the variation in alcohol dependence (Walters, 2002; Goldman et al., 2005). Some studies even report heritability estimates for alcohol dependence as high as

78% (Malouff et al., 2008). Further, genetics appears to be responsible for a significant portion of variation in both alcohol use and abuse for both genders (Kimura and Higuchi, 2011). Given the magnitude of these numbers and awareness that adolescent alcohol use is linked to outcomes such as poor academic performance (Cook and Moore, 1993; Wechsler et al., 2002), impaired cognition (Clark et al., 2008; Chassin et al., 2010), emotional instability (Hicks et al., 2012; Trim et al., 2007), traffic accidents, physical injury (Santamarina-Rubio et al., 2009), risky sexual behaviors (Wechsler et al., 1995; Hingson et al., 2002), violence, property offending, sexual victimization (Perkins, 2002), and contact with law enforcement (Slade et al., 2008), it becomes imperative to explore the genetic underpinnings of alcohol use among young adults.

Genome-wide association (GWA) studies often highlight that alcohol use and dependence are likely polygenic traits affected by genes in several distinct regions (Treutlein et al., 2009; Zuo et al., 2012; Edenberg et al., 2011; Bierut, 2010). However, findings from GWA studies are often not replicated in similar samples (Olfson and Bierut, 2012; Treutlein and Reitschel, 2011) and, overall, consistent findings are lacking. As such, it remains important to evaluate potential individual genes that may be influencing alcohol consumption. Several studies have attempted to find an association between alcohol use or abuse and variation in a particular gene. As a result, a variety of polymorphic genes have been labeled candidate genes and shown to have different degrees of connection with alcohol use. Dopamine receptor genes (Bau et al., 2001; Madrid et al., 2001), a serotonin transporter gene (Rose and Dick, 2005; Kaufmann et al., 2006), monoamine oxidase A (Ducci et al., 2007; Nillson et al., 2008), aldehyde dehydrogenase genes (Luczak et al., 2006; Hendershot et al., 2009), and/or alcohol dehydrogenase genes (Konishi et al., 2004) are typically the focus of works related to alcohol use. However, as alcohol intake is reinforced by the subsequent release of dopamine into the mesolimbic system (Gonzales et al., 2004), a sizeable contingent has argued that variation in alcohol use might better be understood through the DAT1 gene (Ueno et al., 1999; Guo et al., 2007; Lind et al., 2009; Du et al., 2011). This gene (SLC6A3) codes for the synthesis of a protein which assists with the reuptake of dopamine from the synaptic cleft. It has multiple alleles due to a 40-base sequence in the 3' untranslated region that is repeated a variable number of times. Most alleles within the population are either the 9-repeat form or the 10-repeat version that is thought to function more efficiently (Swanson et al., 2000), but the alleles can contain anywhere between 3 and 11 repeats of the sequence.

DAT1 may have an association with alcohol that is, at least partially, not contingent on the environment. Animal models suggest there is a relationship between DAT1 and alcohol consumption (Yoshimoto et al., 2000) and laboratory experiments have linked the 10-repeat allele to higher levels of risk-taking behavior (Mata et al., 2012). Outside of laboratory settings, DAT1 has been repeatedly linked to alcoholism and withdrawal symptoms (Sander et al., 1997; Schmidt et al., 1998; Ueno et al., 1999; Hopfer et al., 2005; Kohnke et al., 2005; Guo et al., 2007; Lind et al., 2009; Strat et al., 2009; Du et al., 2011), but a number of similar studies have failed to identify any significant connection between DAT1 and alcohol use outcomes (Franke et al., 1999; Bau et al., 2001; Werneke, 2002; Choi et al., 2006). Many of the studies noting a connection between alcohol and the DAT1 gene have found that the 9-repeat allele is more common among alcoholics and problem drinkers. However, the current literature may be best summarized by describing results as discrepant with some

studies indicating that the 9-repeat allele confers risk, others noting that the 10-repeat allele is most problematic, and still others finding no connection between DAT1 genotype and behavior (Strat et al., 2009; Kimura and Higuchi, 2011; Mata et al., 2012).

While potential exists for genes to be related to substance use and antisocial outcomes independent of environmental factors, it appears that the greatest understanding of behavior is realized through consideration of gene-environment interplay (Rutter, 2002). Gene-environment interplay, a term that subsumes both gene-environment correlations (rGE) and interactions between genes and the environment ($G \times E$), is clearly relevant to behavioral and substance use studies. The diathesis-stress $G \times E$ model argues that individuals are differentially vulnerable to negative environments due to genetic variability. Those that possess genetic “risk” factors are more at risk for engaging in substance use, becoming violent, and experiencing emotional instability in negative environments when compared to those who do not possess such risk. Thus, genetic risk is considered to increase susceptibility to the environment and increase the negative influence of problematic situations rather than having a more direct association with the outcome. Since Caspi et al.'s (2002) seminal study linking susceptibility to maltreatment to the MAOA gene, research has typically identified gene-environment interactions ($G \times E$) as being more important than genetic risk alone (Moffitt et al., 2006).

It is likely that DAT1's effects on alcohol use and abuse are contingent on environmental factors much in the same way that the gene's influence on other outcomes has been shown to be moderated by environmental conditions (e.g., Kahn et al., 2003; Laucht et al., 2007; Beaver et al., 2008a). Several studies have noted a significant DAT1 gene-environment interaction ($G \times E$) for alcohol use including Bau and colleagues' (2001) work which indicated the 10-repeat allele increased the likelihood of alcoholism when paired with high levels of novelty seeking. Schmid and colleagues' (2009) work suggests that the DAT1 genotype may exacerbate the effect of early alcohol onset on adult substance use problems. Another recent study suggested that DAT1 may play a key role in the intergenerational transmission of alcoholism. Vaske et al. (2009) demonstrated that the DAT1 10-repeat allele interacted with parental alcohol use to increase the occurrence of serious alcohol problems in adolescence, but only observed this relationship for men (Vaske et al., 2009). Consistent with Limosin et al (2004), Vaske et al. (2009) did find an independent association between the 9-repeat allele and alcohol problems in the female portion of the sample. DAT1 genotype may also alter the effect of alcohol use on other outcomes (Brookes et al., 2006; Schacht et al 2013) or that of other genes on alcohol use (Ray et al., 2010). Presently, no study has assessed whether DAT1 moderates the relationship between overall life stress and alcohol use during adolescence.

Life stress during adolescence has been identified as a critical risk factor for substance use (Hawkins et al., 1992; Agnew and White, 1992; Preston, 2006; Carson et al., 2009; Stogner and Gibson, 2011), yet there are inconsistencies with this relationship. While many adolescents deal with interpersonal and environmental stresses through use of alcohol and other drugs, many resist that temptation and choose to cope in more positive ways. Apparent inconsistencies in vulnerability are quite possibly linked to biological and trait-based differences that may exacerbate or lessen the propensity for self-destructive behavior to

result from stress (Sher, 2010; Aldridge-Gerry et al., 2011). Genetic vulnerability does seem to condition the effect of stressors on substance use (Ducci et al., 2008; Vaske et al., 2009), but the role of DAT1 is far from fully understood. Additionally, most studies focus on individual stressors rather than overall life stress; Stogner and Gibson (2013) did explore the potential moderation of life stress' relationship with substance use by the MAOA gene, but no such work has been done with DAT1. Though the diathesis-stress model is typically applied to individual stressors and not a cumulative stress measure, there is reason to suspect that utilizing a composite measure has utility. Non-biosocial studies have demonstrated a connection between cumulative adversity and substance use (Turner and Lloyd, 2003) and a composite measure may better represent the impact of life stress (Schilling, Aseltine, and Gore, 2008). Put another way, individual stressors may be managed if they occur in isolation, but both a greater amount of overall stress and stresses originating from multiple contexts are more likely to be overwhelming (Morales and Guerra, 2006). Studying specific stressors does offer insight, but cumulative adversity studies, such as this one, helps clarify the ways in which the sum of life's stress affects behavior.

The present study attempts to determine whether DAT1 genotype affects the impact of life stress on adolescent alcohol use in a nationally representative sample of American youth. Unlike the majority of DAT1 studies, the focus is on adolescents since early initiation and use strongly impacts long-term substance use problems as well as future educational and occupational opportunities (Hawkins et al., 1992; Kenkel et al., 1994; O'Donnell et al., 1995; Dee and Evans, 2004). Further, analyses are separated by gender as research generally suggests that different factors influence substance use decisions for males and females (Kendler and Prescott, 2006) and that the DAT1 gene's relationship with alcohol use may be contingent on gender (Vaske et al., 2009).

Methods

Data

The present study utilizes data from the National Longitudinal Study of Adolescent Health, or Add Health, which is a nationally representative, longitudinal study of American youth that were enrolled in grades seven through twelve during the 1994-1995 school year (Harris et al., 2008). Eighty high schools and fifty-two middle schools were selected for inclusion via a multi-stage stratified sampling design that yielded a group of 132 schools representative of schools within the United States in terms of region of country, urbanicity, size, type, and ethnic composition (Harris et al., 2008). During Wave I, over 90,000 students completed a brief in-school questionnaire— 20,745 of whom participated in the detailed in-home survey. Wave I in-home participants that were still in school one year later were interviewed in their homes once again as part of Wave II. A third wave was collected six years later and a fourth wave collected additional data. The present analysis utilizes self-reported stress, risk factors, protective factors, and demographic information collected as part of Wave I to predict alcohol use at Wave II in a subsample of 2,574 participants that were later genotyped in Wave III.

Measures

Alcohol Use—A single Wave II variable that asked respondents whether they “had a drink of beer, wine, or liquor—not just a sip or a taste of someone else's drink—more than 2 or 3 times in your life?” was utilized to assess alcohol use. “Yes” responses were considered alcohol users and coded 1; those responding “no” were considered abstainers and coded 0. This use/non-use item was utilized instead of frequency or quantity of use because youth often have difficulty reporting amount or frequency accurately (O'Malley et al., 1983) and additional factors (e.g., body mass) may influence quantity that are unrelated to whether an individual uses. Among the genetic subsample, 64.4% were alcohol users at Wave II. More specifically, 66.4% of the males and 62.5% of the females had initiated alcohol use.

Cumulative Life Stress—Eight distinct sources of stress at or prior to Wave I were operationalized and combined into a single score representing overall life stress. To form the cumulative life stress measure, each of the eight stresses was coded so higher scores represented more stress and then standardized. These standardized scores were then averaged to create the final measure. The included stresses are as follows: 1) Four Likert items assessing trouble getting along with teachers, trouble paying attention, trouble getting homework done, and trouble with other students were summed to create a scale representing school-based problems. Higher scores indicate more school problems ($\alpha = .694$; Johnson and Morris, 2008). 2) An indicator of perceived parental rejection (adapted from Wright, Beaver, Delisi, and Vaughn [2008]) was created by averaging reverse coded Likert items that asked the respondent to assess their overall relationship quality and whether they felt that their parents were warm and loving, encouraged independent thought, and taught ethics ($\alpha = .836$ maternal; $\alpha = .887$ paternal). The more stressful parental relationship score was utilized for respondents living in two parent households. 3) A measure of perceived discrimination at school was created by summing two items that asked respondents whether teachers and students were prejudiced (Stogner and Gibson, 2013). 4) Similarly, a summated two-item perceptual measure of neighborhood problems was created using items that assessed the respondents happiness with their neighborhood and desire to move (Stogner and Gibson, 2013). 5) A violent victimization dichotomous measure was created using five items that asked the respondents if they had been jumped, shot, stabbed, threatened with a weapon, or sexually assaulted (sexual assault question was posed only to women). Those reporting any of these forms of victimization were coded 1 and all others coded 0 (Kaufman, 2009). 6) Kim (2009) and Schulz-Heik et al.'s (2009) measure of physical abuse or neglect as a child was also included. Respondents reporting that they were inappropriately left alone, did not have their basic needs met, were physically abused, or were inappropriately touched before sixth grade were scored a 1; all others were scored 0. 7) A dichotomous poverty item was created with all those adolescents in a household that received government aid or that was below 200% of the poverty line for a household of that size scored 1. 8) Finally, a measure of frustration from lack of autonomy was created by averaging seven items that asked how much freedom they had with decisions regarding to their clothing, television, friends, bedtime, and free time. All 37 component questions are depicted in their entirety in Appendix A. Scores on the overall scale ranged from -1.2 to 1.8.

DAT1 10-Repeat Alleles—As the 10-repeat allele has been considered a risk for deviant behavior (Guo et al., 2007; Beaver et al., 2008b; Burt and Mikolajewski, 2008), respondents with two 10-repeat alleles were scored 2 for the DAT1 genetic risk measure, those heterozygous for the gene (one 10-repeat allele, one 9-repeat allele) were coded 1, and those with only 9-repeat alleles were coded 0. Within the sample, 61.1% were homozygous for the 10-repeat allele, 34.0% were heterozygous with one 10-repeat allele, and 4.9% were without a 10-repeat allele. These percentages resemble those found in other samples (Young et al., 2002). The 10 repeat alleles were found to be slightly more common in the nonwhite portion of the sample (69.32% homozygous) as compared to the white portion of the sample (57.09%).

The potential relationship between this genetic measure and cumulative life stress was evaluated prior to completing any further analyses. The presence of a significant gene-environment correlation (r_{GE}) has the potential to confound results and yield GxE findings that are entirely spurious. Regardless of whether an active, passive, or evocative r_{GE} is suspected, it is appropriate to rule out significant r_{GE} s (or modify analyses as appropriate; Distel et al., 2011). The cumulative life stress measure was not significantly associated with genotype ($p=.523$), nor was the genetic measure significantly associated with any of the component stressors. As such analyses proceeded as planned.¹

Risk factors—Indicators of 4 risk factors for adolescent alcohol use were created and incorporated into regression models as separate controls. This included a measure of peer deviance operationalized using the respondents' perceptions of their three closest friends' tobacco, alcohol, and marijuana use. This perceptual peer delinquency measure showed acceptable reliability ($\alpha=.756$) and is often used as a measure of peer deviance (Beaver et al., 2009a; Wright et al., 2008). A low self-control was measure was created by averaging four attitudinal items that assessed whether the respondent made decisions in a systematic way, whether they seek facts before making a decision, whether they consider multiple solutions to problems. This scale also showed acceptable reliability ($\alpha=.742$) and has been used in past research (Daigle et al., 2007; Stogner, Gibson, and Miller, 2014). Additionally, two forms of negative emotionality were included: a ten-item depression measure previously used by Johnson and Morris (2008; $\alpha=.809$) and a dichotomous angry temperament item collected as part of the parent's interview. Measures were coded so that higher scores represented more deviant peers, lower self-control, more depression symptoms, and angry temperament, respectively.

Protective factors—In an effort to account for factors that may help deter adolescent alcohol use, three potential protective factors, measured at Wave I, were incorporated into the analysis. Each of these measures incorporates a number of indicator items; however, we

¹A potential r_{GE} was assessed for each component stressor primarily to ensure the presented results are not inappropriately confounded. In some cases, a passive r_{GE} is theoretically viable (parental problems) whereas other component stressors may be more easily conceptually linked to an active r_{GE} (victimization) and others to an evocative r_{GE} (negative school experiences). In other cases, there may not have been clear reason to suspect a potential r_{GE} . Regardless, each potential r_{GE} was evaluated to ensure statistical accuracy- not because of underlying theoretical expectations. As a result, no portion of this preliminary check should not be interpreted as victim blaming, but instead as related to methodological comprehensiveness. None of these associations were significant at the .05 level.

follow the lead of most Add Health studies and consider the larger constructs rather than individual indicators. First, a social support measure was created as the average of seven items that each assessed the degree that others cared for them and were involved in their life ($\alpha = .784$; Johnson and Morris, 2008; Kaufman, 2009; Stogner and Gibson, 2010). A seven-item self-esteem measure was calculated using items that assessed the respondents' perceptions of themselves ($\alpha = .849$; Stogner and Gibson, 2013). Finally, three Wave I items that asked the respondent about the value they place on religion, their attendance at religious services, and their participation in religious youth groups were averaged to create a religiosity measure ($\alpha = .800$; Rostosky et al., 2003). Scales showed acceptable reliability and were coded so that higher scores indicate higher levels of social support, self-esteem, and religiosity respectively.

Demographic controls—Gender [female=0, male=1], age, race dichotomized as white [coded 0] and nonwhite [coded 1], and family income (measured in thousands of dollars) were included as control variables. The genetic subsample is 52.0% female and 65.2% Caucasian with an average age of 15.8 years-old. Descriptive statistics for cumulative life stress and each of the risk factors, protective factors, and demographic controls are presented in Table 1.

Analytic Strategy

A pair of logistic regression models was estimated with STATA 11 predicting alcohol initiation prior to Wave II with the entire genetic subsample. The first of these models includes cumulative stress, the four risk factors, the three protective factors, and the demographic controls. The second incorporated both the DAT1 10-repeat allele measure and a multiplicative interaction term representing the potential GxE interaction. This term is the mean-centered life stress measure multiplied by the number of DAT1 10-repeat alleles. Following this evaluation of the sample as a whole, the analysis was then repeated separately for males and females. Bivariate analysis had revealed that males ($M = .012$) on average reported more life stress than females ($M = -.041$, $t = 2.73$, $p = .0062$). Similarly, significantly more males (66.43%) had initiated alcohol use than females (62.48%, $\chi^2 = 4.050$, $p = .044$). Predictors of alcohol use have also been shown to vary by gender which suggests that a different process may be in play for men and women when it comes to alcohol initiation (Wilsnack et al., 1987; Nolen-Hoeksema, 2004; Holmila and Raitasalo, 2005). More specifically, research has suggested that stress is more predictive of alcohol use among men (Cooper et al., 1992), that social camaraderie's relationship with drinking may vary by gender (LaBrie, Hummer, and Pederson, 2007), and that the decision to drink for women is more strongly influenced by psychological well-being, health, and perceived social class (Green, Freeborn, and Polen, 2001). Taken in whole, this information suggests that there is utility in examining predictors of drinking separately for males and females.

Results

In Model 1, displayed within Table 2, adolescent alcohol use is regressed onto cumulative life stress, the protective factors, the risk factors, and demographic controls to determine whether life stress is connected to adolescent alcohol use prior to accounting for DAT1

genotype. Cumulative life stress was linked to significantly increased odds of alcohol use ($b=.380$, $OR=1.462$). Of the risk and protective factors, only deviant peers ($b=1.290$, $OR=3.633$), religiosity ($b=-.275$, $OR=.759$), and social support ($b=-.369$, $OR=.691$) were significantly linked to alcohol use controlling for the other variables. Age was significantly linked to alcohol use ($b=.210$, $OR=1.234$), but gender, race, and income were not. Both the DAT1 10-repeat allele measure and the interaction term were added to Model 2. Neither reached significance.

The sample was then split by gender to determine whether cumulative life stress or DAT1 had effects on alcohol use that were contingent on gender. Model 3 repeats the analysis only using males within the sample. As was the case for the entire sample, life stress ($b=.619$, $OR=1.857$), deviant peers ($b=1.291$, $OR=3.638$), religiosity ($b=-.277$, $OR=.758$), and age ($b=.168$, $OR=1.183$) were significantly related with alcohol use. Unlike the full sample, however, social support ($b=-.354$, $OR=.701$) was not. For males, self-esteem ($b=-.471$, $OR=.624$) also emerges as a significant predictor. The number of 10-repeat alleles and GxE interaction term were added in Model 4, but neither reached significance.

Results for the female subsample are presented in Models 5 and 6. Prior to the inclusion of DAT1 genotype and the interaction term, only substance using peers ($b=1.310$, $OR=3.708$), religiosity ($b=-.279$, $OR=.756$), and age ($b=.261$, $OR=1.298$) were significantly related to alcohol use. For females generally, cumulative life stress is not significantly related to alcohol use ($b=.151$, $OR=1.162$). Once the DAT1 measure and interaction terms were added, however, a clearer picture of adolescent female alcohol use emerges. Both DAT1 genotype ($b=-.350$, $OR=.705$) and the interaction term ($b=.904$, $OR=2.470$) had significant coefficients. It appears that, for females, cumulative life stress has a relationship with alcohol use that is conditioned by the DAT1 genotype. Those with 10-repeat alleles appear to be more sensitive to life stress compared to those without the allele. That is, at higher levels of stress, females with the 10-repeat allele are more likely to engage in alcohol use.

An evaluation of conditional predicted probabilities (all other variables were held at their respective means) depicted that females homozygous for the 10-repeat allele are approximately 2.93 times more likely to initiate alcohol use at the highest level of stress as compared to females without the allele and 1.43 times as likely as those with one 10-repeat allele. This analysis also revealed that females with the 10-repeat allele were actually less likely to engage in alcohol use than other females in low stress environments. No significant differences existed between heterozygotes and those without any 10-repeat alleles predicted probabilities of alcohol use when life stress was below the mean, but the predicted probability for 10-repeat allele homozygotes were actually 42.1% lower than those without a 10-repeat allele at the low stress extreme. This suggests that rather than acting as a “risk” allele for deviant behavior and substance use, the 10-repeat allele may act to increase susceptibility to the environment whereby the allele is associated with more negative outcomes in poor situations and better outcomes in positive environments.²

Discussion

A number of interesting findings emerge from the present analysis. First, unlike adult alcoholism (e.g., Ueno et al., 2009), the DAT1 genotype does not seem to be associated with alcohol use among male adolescents. Similarly, while Hopfer et al. (2005) indicated the gene is linked to the quantity of alcohol consumed by teenage drinkers, it was not linked to whether adolescents drank for the whole sample. Consistent with previous research (Vaske et al., 2009; Limosin et al., 2004), females were less likely to report alcohol use when possessing a 10-repeat allele but the relationship was not seen for males. This association appears to be minor in magnitude relative to a significant GxE whereby the 10-repeat allele appears to increase susceptibility to the environment. Females with the 10-repeat allele, particularly those with two copies, are far more likely to initiate alcohol use in high-stress environments. On the other hand, these same individuals are much less likely to report having used alcohol in low stress environments.

The identification of this GxE should help to clarify why some adolescent females are more resilient when faced with stress and similarly help to identify individuals that are at increased susceptibility to the deleterious effects of stress. Whereas some girls' genotype may insulate them from the effects of a hostile home or negative interpersonal relationships, others are more likely to cope by initiating substance use. This suggests that programs designed to help adolescent females cope with stress may have greater benefits related to abstinence from substances for some women than others; however, given that stress also effects educational outcomes (Dee and Evans, 2003; Townsend et al., 2007), mood (Bolger et al., 1989), and health (McEwen, 2008) more generally, it is likely that programs that assist in stress reduction and management would help young females regardless of genotype.

The finding that different factors are at play for male and female alcohol initiation is interesting, but not surprising. A number of studies suggest the causes of alcohol use are distinct, or at least are of distinct levels of importance, for young men and young women (Wilsnack et al., 1987; Nolen-Hoeksema, 2004; Holmila and Raitasalo, 2005; Green, Freeborn, and Polen, 2001). Similarly, the effects of stress on behavior are conditioned by gender. Whereas females appear to be more susceptible to internalizing problems (anxiety, depression, etc.) as a result of stress, males tend to engage in external reactions such as aggression or violence (Gore, Aseltine, and Colten, 1993; Leadbeater et al., 1999). Not only are these categories of problematic reactions associated with gender—the process by which they develop is also considered to be distinct (Achenbach and Edelbrock, 1984; Daughters et al., 2009). As such, the connection between stress and substance use is likely differentially

²The analyses presented in this section were repeated with individual stress measures as opposed to the composite scale. Logistic regression models were estimated which included DAT1 genotype, each of the eight stressors, the four risk factors, the three protective factors, the four demographic variables, and a GxE interaction term as predictors and alcohol use as the dependent variable. To avoid multicollinearity, the interaction of each stressor with DAT1 genotype was entered into a separate model. Appendix B depicts the coefficient and standard errors of each of these terms (other predictors are omitted to allow for a parsimonious display of results). Only one individual stressor emerges as significant at the $p < .05$ level (parental maltreatment among females). However, this information should not be interpreted as an indication that parental maltreatment was the driving force behind the results presented in the text. As discussed earlier, stressors may have an incremental effect whereby the sum of stress is more important than the source(s) of the stress. Parental maltreatment is certainly an important stressor, but an examination of the table also demonstrates that other terms are trending towards significance and likely contributed to the significant interaction between cumulative adversity and DAT1 (albeit that these contributions may have been too small to identify in isolation in a sample of this size).

be affected genotype. Further, it is possible substance use is more often a direct externalized response for males and an indirect manifestation of internalizing behavior for women (i.e., a result of depression or anxiety).

The present study has a number of strengths. It utilizes a reputable nationally representative dataset and, unlike most genetic studies, it also controls for a number of potential sociological confounders. A potentially important GxE is identified that remains significant controlling for several risk factors, protective factors, and demographics. The present study, however, is not without limitation. First, the results are specific to whether an individual engages in drinking and not to the frequency of drinking, quantity consumed, binge drinking, dependence, or alcohol related problems. Previous research would suggest that some factors influence each but also that each has a distinct set of predictors. DAT1 may condition stress's effect on initiation for women but not its effect on dependence or quantity of alcohol consumed. Future research should explore whether this GxE also alters other alcohol related outcomes. Second, only eight types of stress were incorporated into the cumulative life stress measure. While this represents an improvement over studies that focus on only one or two noxious environmental factors, it certainly does not represent the full scope of stresses endured by adolescents. Future research should seek to utilize an even broader measure of life stress. Third, any individual GxE study must be viewed cautiously prior to replication with a distinct sample due to the threat of false positive results (Flint and Munafo, 2008). Finally, the frequent divergent results for DAT1 and drinking suggest that it may have culture-specific effects (e.g., Bhaskar et al., 2012); prior to replication it would be inappropriate to assume a similar relationship exists in other cultures.

Despite its limitations, the present study offers valuable insight into female adolescent alcohol use and reactions to life stress. With early alcohol use being linked to numerous problems even when quantities consumed are limited (Reimuller et al., 2011; Stolle et al., 2009), it appears beneficial to deter or delay the initial alcohol use of young people. Awareness that DAT1 conditions reactions to stress among females may assist in the design of interventions in that programs may successfully postpone alcohol use not only by concentrating on alcohol directly but also by exploring avenues of alleviating stress or teaching more appropriate coping skills. While the 10-repeat allele does appear to increase adolescent females' susceptibility to environmental pressures, genetic influence needs not to be viewed as deterministic; as the genetic effect on alcohol use is contingent on stress, it may be avoided in the absence of a negative environment.

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Appendix A: Items Composing Cumulative Life Stress Measure

Parental Rejection

All items scored 1=strongly agree, 2=agree, 3=neither agree nor disagree, 4=disagree, 5=strongly disagree.

Maternal Rejection

1. Most of the time, your mother is warm and loving toward you.
2. Your mother encourages you to be independent.
3. When you do something wrong that is important, your mother talks about it with you and helps you understand why it is wrong.
4. You are satisfied with the way your mother and you communicate with each other.
5. Overall, you are satisfied with your relationship with your mother.

Paternal Rejection

1. Most of the time, your father is warm and loving toward you.
2. You are satisfied with the way your father and you communicate with each other.
3. Overall, you are satisfied with your relationship with your father.

Parental Abuse or Neglect

All items scored 1=one time, 2=two times, 3=three to five times, 4=six to ten times, 5=more than ten times, 6=this has never happened. (Recoded 1-5→1, 6→0)

1. By the time you started 6th grade, how often had your parents or other adult care-givers left you home alone when an adult should have been with you?
2. How often had your parents or other adult care-givers not taken care of your basic needs, such as keeping you clean or providing food or clothing?
3. How often had your parents or other adult care-givers slapped, hit, or kicked you?
4. How often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?

Negative School Experiences

All items scored 0=never, 1=just a few times, 2=about once a week, 3=almost every day, 4=everyday

Since school started this year, how often have you had trouble...

1. getting along with your teachers?
2. paying attention in school?

3. getting your homework done?
4. getting along with other students?

Discrimination

Both items scored 1=strongly agree, 2=agree, 3=neither agree nor disagree, 4=disagree, 5=strongly disagree.

1. Students at your school are prejudiced. (*recoded 1→5, 2→4, 3→3, 4→2, 5→1*)
2. The teachers at your school treat students fairly.

Violent Victimization

All items scored 0=never, 1=once, 2=more than once.

During the past 12 months, how often did each of the following things happen?

1. Someone pulled a knife or gun on you.
2. Someone shot you.
3. Someone cut or stabbed you.
4. You were jumped.
5. Were you ever physically forced to have sexual intercourse against your will? (*only asked of women*).

Neighborhood Strain

1. On the whole, how happy are you with living in your neighborhood?

1=not at all, 2=very little, 3=somewhat, 4=quite a bit, 5=very much (recoded 1→5, 2→4, 3→3, 4→2, 5→1)

1. If, for any reason, you had to move from here to some other neighborhood, how happy or unhappy would you be?

1=very unhappy, 2=a little unhappy, 3=wouldn't make any difference, 4=a little happy, 5=very happy

Failure to Achieve Autonomy

All items scored 0=no, 1=yes, 7=legitimate skip. Recoded (0→1, 1→0, 7→1) so that higher scores indicate less achieved autonomy. Legitimate skips recoded to low autonomy since they represent institutionalized youth who are likely to have little autonomy.

Do your parents let you make your own decisions about:

1. The people you hang around with?
2. What you wear?

3. How much television you watch?
4. What television programs you watch?
5. What time you go to bed on week nights?
6. What you eat?
7. The time you must be home on weekend nights?

Failure to Achieve Financial Success

First four items scored 0=no, 1=yes.

Last month, did you or any member of your household receive:

1. Aid to Families with Dependent Children (AFDC)?
2. Food stamps?
3. Unemployment or worker's compensations?
4. A housing subsidy or public housing?
5. About how much total income, before taxes did your family receive in 1994?
Include your own income, the income of everyone else in your household, and income from welfare benefits, dividends, and all other sources.

(families below 200% of the poverty line were coded 1. According to the US Census Bureau the poverty line in 1994 for a family of two was \$19,322, three: \$23,642, four: \$30,282, five \$35,800, six: \$40,470)

Appendix B

Assessing Potential Interactions between DAT1 and Individual Stressors

	Full sample	Males	Females
Neighborhood disadvantage	-.003 (.062)	-.035 (.092)	.060 (.089)
Parental abuse/ neglect	.404 (.217) [†]	-.142 (.250)	.852 (.310)*
Government financial aid	.129 (.220)	.292 (.326)	-.097 (.312)
Parental rejection	.068 (.144)	.018 (.324)	.230 (.183)
Lack of autonomy	.012 (.069)	-.030 (.107)	.024 (.094)
Negative school experiences	.165 (.163)	-.111 (.238)	.381 (.242)
Discrimination	.026 (.062)	-.077 (.092)	.143 (.087) [†]
Violent victimization	-.199 (.345)	-.376 (.410)	-1.089 (1.114)

* indicates $p < .05$;

[†] indicates $p < .10$. Each cell represents the unstandardized coefficient and standard error of a mean-centered multiplicative interaction term (representing the interaction of DAT1 genotype and the stressor listed at the head of that row) within a logistic regression model predicting alcohol initiation that included DAT1 genotype, each of the eight stressors, the four risk factors, the three protective factors, and the four demographic variables. Models were estimated independently to avoid introducing multicollinearity. Thus, each column represents eight separate logistic regression models. Other coefficients are omitted from the table as they are substantively redundant with information presented in the manuscript.

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Table 1

Descriptive statistics (N=2574)

	Mean	S.D.	Min	Max	Male Mean	Female Mean
Main variables						
Alcohol use	.644	.479	0	1	.664	.625
DAT110-repeat alleles	1.562	.587	0	2	1.550	1.576
Cumulative life stress	-.016	.436	-1.16	1.82	.012	-.041
Individual stressors (prior to standardization)						
Neighborhood disadvantage	4.529	1.863	2	10	4.511	4.544
Parental abuse/ neglect	.550	.498	0	1	.572	.532
Government financial aid	.399	.490	0	1	.413	.386
Parental rejection	2.055	.812	1	5	1.989	2.115
Lack of autonomy	2.003	1.694	0	7	2.006	2.000
Negative school experiences	1.017	.739	0	4	1.104	.937
Discrimination	5.664	1.775	2	10	5.624	5.702
Violent victimization	.209	.407	0	1	.267	.155
Risk Factors						
Deviant peers	.815	.872	0	3	.839	.792
Low self-control	2.201	.623	1	5	2.205	2.198
Depression	.661	.464	0	2.70	.623	.741
Angry Temperament	.318	.466	0	1	.313	.322
Protective Factors						
Religiosity	1.716	.995	0	3	1.628	1.796
Self-esteem	1.931	.602	1	5	1.811	2.042
Social support	4.042	.572	1.43	6	4.026	4.056
Demographic Controls						
Age	15.579	1.672	12	20	15.640	15.522
Gender (1=male)	.480	.500	0	1	-	-
Race (1=nonwhite)	.348	.477	0	1	.3449	.351
Income	47.320	53.758	0	999	44.962	49.534

Table 2
Logistic regression models predicting alcohol use using composite strain and individual risk alleles

	Full Sample						Males			Females		
	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	b(se)	O.R.	b(se)	O.R.	b(se)	O.R.	b(se)	O.R.	b(se)	O.R.	b(se)	O.R.
Cumulative Life Stress	.380* (.186)	1.462	-.116 (.473)	.890	.619* (.271)	1.857	1.202 [†] (.719)	3.328	.151 (.263)	1.162	-1.335* (.668)	.263
DAT1 Risk alleles	-	-	-.277* (.109)	.758	-	-	-.172 (.160)	.842	-	-	-.350* (.155)	.705
DAT1 X life stress interaction	-	-	.317 (.273)	1.372	-	-	-.344 (.425)	.709	-	-	.904* (.380)	2.470
Anger	.202 (.142)	1.224	.226 (.144)	1.254	.088 (.211)	1.091	.158 (.216)	1.171	.330 (.195)	1.391	.327 (.199)	1.386
Depression	-.132 (.174)	.876	-.165 (.178)	.848	-.024 (.269)	.976	-.059 (.275)	.942	-.259 (.233)	.771	-.285 (.239)	.752
Deviant peers	1.290* (.107)	3.633	1.318* (.110)	3.736	1.291* (.155)	3.638	1.322* (.160)	3.749	1.310* (.152)	3.708	1.350* (.157)	3.858
Low constraint	.022 (.106)	1.022	.039 (.108)	1.041	-.101 (.157)	1.106	.136 (.160)	1.145	.031 (.148)	.970	.017 (.152)	1.017
Religiosity	-.275* (.065)	.759	-.287* (.067)	.750	-.277* (.093)	.758	-.285* (.094)	.752	-.279* (.093)	.756	-.290* (.096)	.748
Self-esteem	-.184 (.136)	.981	-.013 (.140)	.987	-.471* (.203)	.624	-.492* (.208)	.611	.353 [†] (.190)	1.423	.366 [†] (.195)	1.442
Social support	-.369* (.145)	.691	-.349* (.148)	.706	-.354 [†] (.212)	.701	-.299 (.214)	.742	-.358 (.203) [†]	.698	-.401 [†] (.209)	.670
Age	.210* (.040)	1.234	.218* (.041)	1.243	.168* (.058)	1.183	.174* (.059)	1.190	.261* (.056)	1.298	.277* (.058)	1.320
Gender (1=male)	-.073 (.127)	.929	-.102 (.131)	.903	-	-	-	-	-	-	-	-
Race (1=nonwhite)	-.200 (.140)	.818	-.094 (.144)	.910	.018 (.208)	1.018	.125 (.217)	1.133	-.347 [†] (.194)	.707	-.261 (.202)	.770
Income	.000 (.001)	1.000	.000 (.001)	1.000	.001 (.003)	1.001	.002 (.002)	1.002	-.001 (.002)	.999	-.001 (.002)	.999
Constant	1.308		-1.128		-.324		-.459		-2.624		-2.309	
Pseudo R ²	.212		.218		.213		.218		.225		.240	

Results are presented in the form of b (se).

* indicates $p < .05$;

[†] indicates $p < .10$.