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Differential Susceptibility: The Genetic Moderation of Peer Pressure on Alcohol Use

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Abstract

Although peer pressure can influence adolescents' alcohol use, individual susceptibility to these pressures varies across individuals. The dopamine receptor D4 gene (*DRD4*) is a potential candidate gene that may influence adolescents' susceptibility to their peer environment due to the role dopamine plays in reward sensation during social interaction. We hypothesized that *DRD4* genotype status would moderate the impact of 7th-grade antisocial peer pressure on 12th-grade lifetime alcohol use (n = 414; 58.7 % female; 92.8 % White). The results revealed significant main effects for antisocial peer pressure, but no main effects for *DRD4* genotype on lifetime alcohol use. Adolescent *DRD4* genotype moderated the association between peer pressure and lifetime alcohol use. For individuals who carried at least one copy of the *DRD4* 7-repeat allele (7+), antisocial peer pressure was associated with increased lifetime alcohol use. These findings indicate that genetic sensitivity to peer pressure confers increased alcohol use in late adolescence.

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Author contributions AMG performed the analysis and wrote the manuscript. HHC, GLS, DJV, MEF participated in variable construction, data interpretation, and manuscript editing. HHC, DJV, and MEF managed the overall project. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

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Keywords

Differential susceptibility; DRD4; Alcohol; Antisocial peer pressure

Introduction

Among U.S. 12th graders, 66 % report having ever used alcohol (Johnston et al. 2014). This prevalence is a cause for concern as alcohol use has been associated with the failure to complete high school (Hill et al. 2000) and alcohol dependence in adulthood (Hingson et al. 2006). The greater the level of alcohol use during adolescence, the greater the long-term risk. For example, adolescents who report first getting drunk by 18 have 5.3 times greater odds of developing alcohol dependence in college (Hingson et al. 2003). Furthermore, a wide variety of environmental influences during childhood and early adolescence, such as peer relationships, have been shown to be risk factors for later alcohol use (Prinstein et al. 2001; for review, see Hawkins et al. 1992). In this article we investigate a major influence on adolescent alcohol use, peer pressure, and how specific genes moderate the associations between exposure to peer pressure in 7th grade and drinking in 12th grade.

Peers are a major influence on alcohol use among adolescents. Peer influences, whether prosocial or antisocial, may be especially important during middle adolescence when time spent with parents decreases (Larson et al. 1996). Increased exposure to peers who encourage antisocial, risky, and/or unhealthy behaviors can influence adolescents' attitudes regarding the acceptability of such behaviors, and therefore facilitate participation in behaviors such as alcohol use.

Although negative peer pressure can influence adolescents' alcohol use, susceptibility to these influences can differ across adolescents (Dielman et al. 1987; Hartup 2005). Susceptibility to peer influence appears to vary based on individual characteristics such as sensation-seeking, self-esteem, self-perceived risks associated with substance use, and social norms on abstaining from substance use (Hawkins et al. 1992). Differences in these characteristics can affect the perceived costs and benefits of conforming to negative peer influence. For example, adolescents with low self-esteem may highly value the acceptance to be gained from drinking with their peers, and discount the potential costs of alcohol use.

Genetics may also influence susceptibility to peer pressure. Recent research examining gene by environment (G × E) interactions has found that genetic variants can confer different degrees of sensitivity to environmental factors such as peers (i.e., Mrug and Windle 2014), parents, and preventive interventions (i.e., Brody et al. 2009; Cleveland et al. 2015; Schlomer et al. 2015). Most pertinent to the current inquiry is the dopamine receptor D4 gene (*DRD4*), a Variable Number of Tandem Repeats (VNTR) known to moderate the impact of experimentally manipulated peer influences on alcohol use (Creswell et al. 2012; Larsen et al. 2010).

Some prior G × E findings align with Differential Susceptibility Theory (DST), which provides that genetic variation may function as a sensitivity factor, disposing individuals to be more susceptible to both positive and negative influences in the environment (Belsky and

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Pluess 2009, 2013; Ellis et al. 2011). Related to DST is the diathesis stress model, which posits genetic variation can influence sensitivity to negative experiences (Ingram and Luxton 2005; Monroe and Simons 1991); unlike DST, however, diathesis-stress theory does not address sensitivity to positive environmental influences.

Based on longstanding research demonstrating the impact of peer pressure on adolescent alcohol use, and recent research demonstrating the moderation of environmental influences by specific genetic variants, and in particular *DRD4*, the present study investigates whether the *DRD4* gene moderates the influence of antisocial peer pressure on adolescent alcohol use. Before providing specific hypotheses, pertinent literature will be reviewed regarding how peers are thought to influence adolescent alcohol use, theories that support genetically-influenced sensitivity, and the biological role *DRD4* plays in peer relationships.

Peers and Adolescent Alcohol Use

Antisocial peer relationships are associated with increased problem behaviors such as alcohol use (Fisher et al. 2007). Differential Association Theory provides that adolescents are impacted by the degree to which their social contexts include peers who are in favor of, or opposed to, antisocial behaviors such as alcohol use (Sutherland 1942). Accordingly, peer contexts provide opportunities to adopt different sets of normative values and attitudes. Adolescents who associate with antisocial peers, as opposed to prosocial peers, are theorized to learn values, attitudes, and motives of antisocial behavior.

Another framework relevant for peer socialization is social learning theory, which suggests peer influence can occur through active and passive peer pressure (Bauman and Ennett 1996; Cialdini and Trost 1998). Active peer pressure occurs when peers explicitly offer adolescents an opportunity to participate in antisocial behavior or direct verbal criticism at adolescents for refusing to participate. Passive pressure occurs when peers' behaviors, such as modeling antisocial behaviors, affect adolescents' perceptions of peers' antisocial behaviors so that adolescents feel the need to participant in order to fit in. Both active and passive peer pressure are a means of motivating youth to conform to their peers in order to gain social rewards such as acceptance.

Previous research has shown that active peer pressure is a strong predictor of adolescent alcohol initiation and drunkenness (Donovan and Molina 2008; Dielman et al. 1992). Furthermore, susceptibility to peer pressure, both active and passive, is associated with negative outcomes during adolescence, peaking around age 14 and falling off during late adolescence and early adulthood (Steinberg and Monahan 2007). The peak time for susceptibility to peer influence—around age 14—is particularly problematic because this is also when youth begin to spend less time with their parents and more time with their peers (Larson et al. 1996), establishing greater autonomy from parents and an opportunity for increased dependency on peers (Steinberg and Silverberg 1986). The combination of increased susceptibility to peer pressure and increased peer exposure during this time of social transition generally leads to an increase in conformity to group norms.

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Variation in Susceptibility to Peer Pressure

Although it is apparent that peers play a critical role in the development of adolescent behaviors, adolescents vary in their vulnerability to peer pressure (Hartup 2005). Some of the variability in vulnerability to peers has been ascribed to individual-level factors, such as an adolescent's autonomy and peer refusal skills (Brown et al. 2008). Studies of adolescent alcohol use have shown these individual factors to moderate the impact of passive peer pressure on adolescent drinking (Allen et al. 2012). As individual characteristics are often substantially influenced by genetics (Turkheimer and Gottesman 1991), it is reasonable to expect that genetic variation may be associated with susceptibility to antisocial peer pressure. Evidence of the possible role of genes in moderating peer pressure is found in a growing body of research on G × E interactions.

Much of human behavioral G × E research is grounded in Differential Susceptibility Theory (DST), which indicates that individuals differ in their sensitivity to a wide range of environmental experiences, and that part of this between-individual variability may be due to genetic differences (Belsky et al. 2007; Belsky and Pluess 2009, 2013; Ellis et al. 2011). The core concept of DST is that over evolutionary time, environmental uncertainty has favored parents passing down genes that allow their children to survive in a variety of environmental contexts (see Belsky 1997; Boyce and Ellis 2005; Ellis et al. 2009). As a result, some offspring may be relatively more sensitive to environmental influences compared to their less sensitive siblings (Belsky and Pluess 2009; Boyce and Ellis 2005; Ellis et al. 2009). Diversification in levels of environmental sensitivity guards against offspring failure as follows: In adverse environments, offspring with low environmental sensitivity are less affected by negative experiences encountered in their environment. However, in favorable environments, offspring with low environmental sensitivity are less positively affected while those with high environmental sensitivity tend to flourish. In contrast, offspring with high environmental sensitivity are more affected by adverse environments, but more positively affected by supportive environments. As a result, producing both less and more sensitive offspring guards against reproductive failure in adverse environments but provides for benefits in reproductive fitness in favorable environments.

The diathesis-stress model, which precedes DST, posits that predisposed individual vulnerability affects how environmental adversity influences normative development (Ingram and Luxton 2005; Monroe and Simons 1991). Specifically, individual differences result in some adolescents being more vulnerable to adversity, while other individuals who lack such vulnerabilities are resilient. In positive environments, "vulnerable" individuals' outcomes should not differ from those of "non-vulnerable" individuals. In this framework, genes can be viewed as "risk genes" or vulnerability factors (Caspi and Moffitt 2006; Caspi et al. 2003). One assumption of the diathesis-stress model is that individuals are vulnerable specifically to environmental adversity. Since the diathesis-stress model focuses on adverse experiences rather than negative and positive experiences, prior research has tended to focus on adverse environmental contexts rather than the full range of environmental experiences (Belsky and Pluess 2009; Ellis et al. 2011). One implication of these two theories is that they predict different G × E interaction shapes. DST predicts a crossover interaction while

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diathesis-stress predicts a fan-shaped interaction (Roisman et al. 2012). These different interaction shapes have further implications for whether analyses provide a main effect for genes; the fan-shaped interaction linked to diathesis-stress is more likely than DST's cross-over interaction to support a significant main effect for genes.

Dopamine and Peer Relationships

Candidate genes used to examine Differential Susceptibility Theory include the *DRD2* and *DAT1* genes (Belsky et al. 2009), but one gene commonly studied that is relevant to the present study is the *Dopamine Receptor D4* (*DRD4*) gene. The *DRD4* gene contains a polymorphic site called a Variable Number of Repeats (VNTR) in the third exon (Van Tol et al. 1992). This locus has ten alleles that vary from two to eleven repeats, with the 4- and 7-repeat alleles being the most common. The *DRD4* genotype is most frequently classified by the presence or absence of the 7-repeat allele because the sensitive genotype (7-repeat allele) is associated with less concentration-dependent inhibition of forskolin-stimulated cyclic AMP (cAMP) levels (Asghari et al. 1995), altered gene expression (Schoots and Van Tol 2003), and decreased ligand binding (Asghari et al. 1994). In addition, the work of Jovanovic et al. (1999) indicates that the 10-repeat allele functions similarly to the 2-repeat allele (longest vs. shortest alleles), suggesting that there is no simple relationship between allele length and protein function (Jovanovic et al. 1999). Thus, in the present study, the *DRD4* gene is analyzed by comparing the presence or absence of the 7-repeat allele to maintain consistency with other DST studies that include *DRD4* (Bakermans-Kranenburg and van IJzendoorn 2011). In this article the conventional notation for individuals being present (+) orabsent (−) for the presence of one or two 7-repeat alleles, which is 7+ versus 7−, respectively, is used. More details regarding the classification of individuals with different numbers of repeats is provided in the "Methods" section.

Dopamine activation is evident in several midbrain structures (i.e., ventral tegmental area and substantia nigra) that project to the ventral striatum and prefrontal cortex. In these brain structures, differences in dopamine activation are linked to the processing of reward salience and magnitude (Bromberg-Martin et al. 2010). Changes in dopamine activation are linked with reinforcing the value and salience of stimuli (Schultz 1998), enabling behavioral change in response to environment (Tobler et al. 2005), and anticipating rewards (Kelley et al. 2005). For example, dopamine activation is related to the stimulatory and rewarding effects of alcohol consumption (Littleton and Little 1994; Samson and Harris 1992).

Of particular importance to the current study is experimental research demonstrating how the *DRD4* 7+ genotype can influence transactions between social experiences and alcohol use. For example, Creswell et al. (2012) found that the sensitive *DRD4* 7+ genotype increases individuals' sense of reward from alcohol consumption when in a group context, leading to greater perceived social bonding when drinking. Related research has found that the *DRD4* 7+ genotype increases susceptibility to alcohol-related social cues, such as being in the presence of a same-age individual who drinks heavily (Larsen et al. 2010). Thus, individuals with the *DRD4* 7+ genotype are more likely to consume alcohol in an attempt to conform to their social contexts (Larsen et al. 2010). It follows, therefore, that adolescents

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who possess the 7+ genotype may be particularly susceptible to the influence of peer pressure on alcohol use.

A number of studies have examined sensitivity to peer-influences using the *DRD4* genotype; however, the operationalization of peer-influences has varied and these studies have rarely examined alcohol use during adolescence (Buil et al. 2015; Kretschmer et al. 2013; Mrug and Windle 2014). One study examined the genetic moderation of peer influence—operationalized as positive (social well-being) and negative (peer victimization) peer contexts—on delinquency (Kretschmer et al. 2013). Kretschmer et al. (2013) utilized both positive and negative peer contexts, thereby directly assessing DST. Contrary to previous studies (Creswell et al. 2012; Larsen et al. 2010), non-carriers of the *DRD4* 7-repeat allele, rather than those carrying the 7-repeat allele, were more sensitive to the effects of both peer victimization and social well-being on delinquency later in adolescence.

Two longitudinal studies are especially relevant for the present research. One longitudinal study of alcohol use from late adolescence to adulthood investigated the effects of peer alcohol use on individual use and found that carriers of the sensitive *DRD4* genotype were more susceptible to peer alcohol use during adulthood compared to during adolescence (Mrug and Windle 2014). Contrary to Mrug and Windle (2014)'s findings, however, a longitudinal study examining the bi-directional relationship between friends' drinking and adolescents' alcohol consumption failed to find a moderating effect for *DRD4* (van der Zwaluw et al. 2012). van der Zwaluw et al. (2012)'s null results may be due to a reliance on youth reports of friends' alcohol consumption, which prior research has found to be prone to projective biases (Bauman and Ennett 1996). The specific ways in which genes and peer influences work together to influence alcohol use may differ depending on the developmental stage of the individuals being assessed, given that adolescents have lower alcohol consumption rates than college-age youths (i.e., Creswell et al. 2012; Larsen et al. 2010). The null result of van der Zwaluw et al. (2012) notwithstanding, existing research suggests that exposure to antisocial peer influences may differ by *DRD4* genotype.

Current Study

Based on the perspective that genetic differences may be as important in influencing environmental sensitivity as they are to directly influencing behaviors, the current study examined how the relationship between antisocial peer pressure and alcohol use may be moderated by the *DRD4* gene. Based on research demonstrating the importance of peer pressure during early adolescence and recent G × E findings, we hypothesized 7th-grade antisocial peer pressure to be positively associated with 12th-grade lifetime alcohol use. We also expected the relationship between antisocial peer pressure and alcohol use would be moderated by the *DRD4* genotype; specifically, we expected antisocial peer pressure to be positively and relatively more strongly associated with alcohol use for adolescents who carry the *DRD4* 7+ allele compared to those who do not (i.e., *DRD4* 7−). Whether the shape of the interaction would be consistent with DST or diathesis-stress was unclear. On the one hand, *DRD4* variation has been linked to several DST findings. On the other hand, the peer pressure variable used in this study only assessed the level of a negative environment rather than a range of experiences from high positive to high negative wherein the midpoint would

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be neutral. By only assessing the degree of negative experiences, this variable seems more suitable for exploring diathesis-stress. Since it is unclear whether the interaction will take a shape consistent with DST or diathesis-stress, we did not have a hypothesis regarding a main effect for *DRD4*.

Methods

Data from the PROSPER Project (PROmoting School-community-university Partnerships to Enhance Resilience) was used to investigate the research questions. PROSPER is an evidence-based intervention program aimed at reducing future substance use by targeting middle school-aged youth and their families. The PROSPER Project consists of 28 communities in Iowa and Pennsylvania randomized into 14 control and 14 intervention units (for more information see Spoth et al. 2007, 2013). PROSPER investigates the effectiveness of interventions on a variety of substance use outcomes, such as alcohol, tobacco, and marijuana use. In-school assessments included pre-tests during the fall semester of the 6th grade, post-tests during the spring semester of the 6th grade, and annual follow-ups assessments until the completion of high school.

In addition to the annual in-school data collection, a subsample of participants' families was recruited to participate in detailed in-home data collections. Of the randomly selected 2267 families who were invited, 977 (43.1 %) agreed to participate in the in-home data collections. In-home assessments were conducted twice in the 6th grade and annually thereafter until the 9th grade. The in-home assessments included written questionnaires completed independently by the participant and one (typically the mother) or both parents/guardians. DNA was collected from 594 youth who took part in the 9th grade (Wave 5) in-home data collection. Included in these assessments were detailed measures of peer relationships.

Sample and Participants

The data analyzed in this study were drawn from PROSPER's in-home youth who also provided DNA (n = 594). Predictor variables were composed of items assessed during the 7th-grade in-home assessment (M_{age} = 13.42), while the outcome variable was composed of items assessed during the 12th-grade in-school survey (M_{age} = 18.16). The final sample size (n = 414) for the current analyses consisted of students who: (1) Completed the 7th-grade in-home assessment, (2) Provided a DNA sample, and (3) Completed the 12th-grade assessment. Missing data were primarily due to attrition; participants were not followed if they left the school district over the course of middle or high school and therefore could not be included in our sample. The analytic sample was predominantly self-identified Caucasians (92.8 %), with a limited number of self-identified Hispanics/Latinos (4.1 %), African-Americans (0.7 %), Asians (0.5 %), and other individuals (1.9 %). All procedures performed in these studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Measures

DRD4 Genotyping—DNA was collected using buccal swabs and extracted using a modified phenol–chloroform technique (Freeman et al. 2003). The 3730XL DNA Analyzer and Genotyper software v4.0 (Applied Biosystems, Foster City, CA) were used to analyze amplification products of the extracted DNA. The 48-base pair VNTR in the third exon of the D4 gene (Anchordoquy et al. 2003; Sander et al. 1997) was genotyped by the Penn State Genomics Core using primer sequences developed by Lichter et al. (1993). Of the total sample (n = 594), 98.5 % were successfully genotyped for the *DRD4* polymorphism ranging from 2 to 11 repeats (n = 584). An error rate of 7.5 % was determined by regenotyping 10 % of the sample. The error rate is due to the difficulty in genotyping *DRD4* heterozygous individuals. Errors are common when amplifying the 7-repeat allele in the presence of shorter alleles (typically the 4-repeat allele), and results were tested for Hardy–Weinberg equilibrium to determine if there was significant dropout of the 7-repeat allele in heterozygotes. *DRD4* status was coded as youth who were carriers of the 7-allele (1) (7+; n = 154, 37.2 %), and those who were not (0) (7−; n = 260, 62.8 %). Only 16 individuals possessed alleles longer than 7-repeats, and conducting the analysis including these individuals as 7+ or 7− did not affect results. Before analysis, we tested for differences in sex, intervention condition, and ethnicity by *DRD4* status (see Table 1).

Control for Population Stratification (PC1)—An inherent analytic challenge presented by G × E research is addressing the potential effects of population stratification. Population stratification refers to differences in allele distribution across different ancestral populations. Differences in allele distribution can create spurious, rather than causal, associations between alleles and phenotypes (Freedman et al. 2004). If the population structure within a sample is not accounted for, research findings can be false positives (Cardon and Palmer 2003).

To assess and control for population stratification, this study used principal coordinates analysis (PCoA; Halder et al. 2008). In PCoA, allele-sharing distances are used to extract principal coordinates (PCs) that describe the genetic ancestry of the sample. PCs were used in two ways in the present study: (1) To assess the extent to which population stratification contributes to variation in analysis variables, and (2) To determine whether the study's results were robust against population stratification controls.

Of the total in-home sample of 594, genetic data from an Affymetrix Array (Exome 319) were available for 511 (93.5 %) participants. Principal Coordinates Analysis (PCoA) was conducted on all participants with Affymetrix data. Allelic distances were used to identify dimensions of population ancestry stratification (for details see Cleveland et al. 2015). Single Nucleotide Polymorphisms (SNPs) were selected from the Affymetrix Array using PLINK (v1.07; Purcell et al. 2007). To estimate genetic ancestry, SNPs with a minor allele frequency greater than 0.05 (41,126 SNPs) were used to generate allele-sharing vectors between all participants. Using the statistical package R, PCoA was performed on the allelic distance matrix to generate multiple PCs representing the major axes of genetic variation in the sample. The first PC (PC1) accounted for approximately 10 % of total allele-sharing distance, while the second PC (PC2) accounted for approximately 6 %.

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PC1 provided an index of non-European ancestry that complemented information from self-reported ethnicity. The highest PC1 scores belonged to individuals who self-reported Hispanic and African-American ethnicity. Comparing PC1 means across self-reported non-Hispanic Whites (M = −0.008, SD = 0.008, n = 493) and those reporting a different ethnicity (i.e., Hispanic and African-American; M = 0.067, SD = 0.035, n = 53) revealed a significant difference between self-reported Whites and minorities (t(544) = 39.79, $p < 0.001$). The Cohen's *d* for this difference was 3.0. Thus, PC1 was a strong linear indicator of European ancestry. In contrast, PC2 distinguished African-Americans and Hispanics and was not used as a control due to the low number, and low proportion, of non-Europeans in the analyzed sample.

In addition to using PC1 as a continuous control for non-European ancestry, a cut-off value of 1 SD below the PC1 mean of self-reported non-Europeans was used to classify individuals with significant non-European ancestry. Among the analytic sample of 414 participants, this cut-off (0.031) classified 352 participants as European descendants and 33 participants as having non-European ancestry based on a cut-off of 1SD below the mean. The PC1-informed classification strongly agreed with adolescent self-report. Using the PC1 criteria, two individuals who self-reported as African-American, seventeen who self-reported as Hispanic, two who self-reported as Asian, and six of eight who self-reported as "Other" matched their self-reported classification as non-European. The PC1-derived cut-off classified six self-reported Caucasians as having significant non-European ancestry.

Intervention Status—Among the 414 participants in the analytic sample, 243 (58.7 %) attended and participated in the school intervention. Intervention status was coded as either "control" (0) or "intervention" (1) (see Table 1). All analyses controlled for intervention status.

Antisocial Peer Pressure—Antisocial peer pressure was assessed with a seven-item self-reported measure during 7th-grade in-home interviews (M_{age} = 13.42). Items asked about the frequency of friends' attempts to persuade the interviewed youth to engage in antisocial behavior normative during the 7th grade (i.e., lying, cheating, and petty theft); for example, "Do your friends try to…get you to skip school without an excuse". Items were coded from "Never" (1) to "Often" (4) and showed positive internal consistency (Cronbach's α = 0.93, *M* = 1.16, SD = 0.32).

Alcohol Use Cumulative Index (AUCI)—Cumulative alcohol use by the 12th grade (M_{age} = 18.16) was measured with a cumulative index based on six alcohol use items. The index used items that assessed lifetime, past year, and past month alcohol use. If individuals had missing data, assessments from the previous year were used. Example items included: "During the past year, how many times have you been drunk from drinking wine, wine coolers, or other liquor?" and "During the past month, how many times have you had beer, wine, wine coolers, or other liquor?" All six items were dichotomized, "Yes" (1) or "No" (0), and summed to yield a measure with values ranging from 0 to 6 (Cronbach's α = 0.78, *M* = 3.33, SD = 2.27).

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Data Analysis

To address the potential non-independent structure of the data (i.e., adolescents nested within school districts), we fit a multilevel model in SAS PROC MIXED and used the REPEATED statement to model non-independence and restricted maximum likelihood estimation (REML) for parameter estimates. The amount of between-school variance in AUCI was low (intra-class correlation = 0.011), which suggests little clustering within schools.

To help ensure that results were not influenced by population stratification, the models were run in three analytic steps. First, models were fit to all cases using self-report of ethnicity as a control. Second, models were fit using the genetically informed ethnicity control (PC1). Third, models were fit on a subsample composed of European descent-only participants, constructed by removing PC1-identified non-Europeans.

Results

Preliminary Analysis

Five sets of preliminary analyses were conducted. First, we tested for differential attrition between adolescents with and without missing data on the outcomes assessed during the 12th grade on all study predictors (PC1, Antisocial Peer Pressure, and *DRD4* status) and key sociodemographic characteristics (gender, receiving free and reduced cost school lunch, and living with both biological parents). Two instances of statistically significant differential attrition were found between the missing and non-missing data groups: participants who attrited had higher levels of free and reduced cost school lunch (Cohen's $d = .67$) and lived with only one biological parent (Cohen's $d = .53$).

Second, we analyzed the distribution of *DRD4* genotypes for Hardy–Weinberg Equilibrium, which determines whether sample allele and genotype frequencies are related to one another as predicted from Mendelian patterns of inheritance. These analyses indicated that *DRD4* allele distribution was in equilibrium [$\chi^2(1) = 0.03$, *ns*], diminishing concern for mistakes in calling genotypes. Third, we tested for sample differences in demographic variables (i.e., age, intervention status, ethnicity, and PC1 ethnicity control) using *t* test and Chi square comparisons across genotype. These analyses showed that the demographic variables did not differ based on *DRD4* 7+ versus 7− status (see Table 1). Fourth, we computed correlations between PC1 and the predictor and outcome variables. As mentioned above, if population stratification significantly covaries with predictors and outcome variables, there is a possibility that the candidate-gene and phenotype associations are spurious and due to genetic ancestry. Analyses revealed that primary study variables were not related to European ancestry, and therefore population stratification was unlikely to be a confound. Finally, we tested for three-way interactions with intervention status ($b = 0.44$, *ns*) and gender ($b = 0.73$, *ns*); however, neither were significant and both were included as covariates.

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Primary Analysis

A two-step analysis was run on both outcomes of interest: Model 1 included the main effects of Antisocial Peer Pressure and *DRD4* status; Model 2 added the two-way interaction between Antisocial Peer Pressure and *DRD4* (Table 2). Model 1 results revealed a main effect for Antisocial Peer Pressure on AUCI ($b = .59$, $p < .01$). The direction of these main effects indicated that higher peer pressure was linked to higher levels of cumulative alcohol use reported in 12th grade. The *DRD4* 7 + genotype was not associated with AUCI ($b = 0.08$, ns). Model 2 results revealed a significant two-way interaction between Antisocial Peer Pressure and *DRD4* on AUCI ($b = 1.00$, $p < .01$). We used a *pseudo* R-squared to calculate the percent of variance explained for each model (Singer and Willett 2003), Model 1 explained 4 % and Model 2 explained 7 % of alcohol use. The results indicated that the association between levels of early adolescent peer pressure and cumulative alcohol use was dependent on *DRD4* status.

To investigate the meaning of the two-way interaction between Antisocial Peer Pressure and *DRD4* on AUCI, conditional main effects were examined (see Frazier et al. 2004). First, *DRD4* status was reverse coded (i.e., 1 = 7− vs. 0 = 7+) and Antisocial Peer Pressure was re-centered (i.e., ±1SD). The associations between Antisocial Peer Pressure and AUCI are shown separately for *DRD4* 7+ versus 7− youth in Fig. 1. Among 7− youth, there was no significant difference in slope based on low, mean, and high levels of Antisocial Peer Pressure ($b = 0.35$, *ns*). However, for youth with the 7+ genotype, Antisocial Peer Pressure was positively associated with AUCI ($b = 1.00$, $p < .01$), with a linearly increasing effect on AUCI across low, mean, and high levels of Antisocial Peer Pressure. The cut-offs used to block the sample into low, mean, and high levels of Antisocial Peer Pressure were based on a one standard deviation difference. A regions of significance (RoS) analysis was conducted using the Johnson–Neyman technique (Preacher et al. 2006; Roisman et al. 2012). RoS analysis showed that the lower and upper bounds of the Antisocial Peer Pressure effect on AUCI were significant for all values that fell outside of −0.27 and −0.14 SD, respectively (see Fig. 1). This result indicates that the two regression lines were significantly different for all possible points when the score for Antisocial Peer Pressure was lower than −0.27 or higher than −0.14. The shaded areas displayed in Fig. 1 indicate the area wherein differences in alcohol use were significant across peer pressure.

Follow-up Analyses

In addition to the RoS, we sought to better describe the difference between *DRD4* 7+ versus 7− youth who experience high and low peer pressure. One way to do this is to estimate the cross-over point of an interaction term according to Widaman et al. (2012) method. The advantage of including the cross-over point as a model parameter is that a confidence interval (CI) for the cross-over point can also be obtained. Evaluating the cross-over and its CI allows one to determine if the analysis reveals an ordinal interaction, consistent with the diathesis-stress model, or disordinal interaction, consistent with DST. An ordinal interaction occurs when the cross-over point is at the boundary or outside the range of the predictor. A disordinal interaction occurs, which is when the cross-over point falls within the middle-range of the predictor.

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To test if the difference between groups described above is ordinal or disordinal, we followed the SAS procedure described in Widaman et al. (2012) and estimated a re-parameterized regression interaction model that included the cross-over as a model parameter. Results for the intercept showed the cross-over point estimated at −0.25 (95 % CI [−0.67, 0.18]), consistent with the Fig. 1 depiction. The cross-over point falls in the boundary of the predictor (antisocial peer pressure) and the confidence interval is within the predictor range, suggesting a disordinal interaction and is consistent with DST.

Discussion

Although peers play a critical role in the development of adolescent alcohol use (Kuntsche et al. 2005), there is limited understanding regarding what factors make some adolescents more vulnerable than others to environmental contexts, such as peer pressure (Hartup 2005). One individual factor that may be associated with susceptibility to antisocial peer pressure towards alcohol use is genetic variation; previous research has shown differential effects due to the *DRD4* genotype (Buil et al. 2015; Kretschmer et al. 2013; Mrug and Windle 2014). The present study showed that inter-individual genetic differences moderated the influence of early adolescence peer pressure on late adolescence alcohol use. Specifically, the *DRD4* genotype moderated the association between 7th-grade antisocial peer pressure and 12th-grade alcohol use.

Consistent with previous research which showed that peer pressure strongly predicts adolescent alcohol use (Dielman et al. 1992), we found that antisocial peer pressure is associated with greater adolescent alcohol use. Differential Susceptibility Theory (DST) posits that genetic sensitivity to environmental experiences results in increased benefits due to favorable social contexts but more detriment due to adverse social contexts (Belsky et al. 2007; Belsky and Pluess 2009, 2013; Bakermans-Kranenburg and van Ijzendoorn 2011). Within the context of this study, the effect of genetic differences was dependent on the presence of antisocial peer pressure. Consistent with the DST framework, we found no main effects for *DRD4* on 12th-grade alcohol use. The lack of genetic main effects demonstrates that specific genetic variation leads to an increased sensitivity to environmental experiences rather than contributing more directly to differences in behaviors regardless of experiences (Reiss et al. 2013).

The dopaminergic system is known to influence attention and reward mechanisms in social contexts (Robbins and Everitt 1999). *DRD4* has been implicated in sensitivity to peer contexts, such as victimization, social well-being, and the degree to which youth are liked by their peers (Buil et al. 2015; Kretschmer et al. 2013). These findings led us to examine the effect of *DRD4* on the association between peer pressure and alcohol use. We found genetic moderation of the effect of antisocial peer pressure on 12th-grade alcohol use.

Prior research provides several clues to the mechanisms through which the 7-repeat allele of *DRD4* may increase susceptibility to peer pressure regarding alcohol use in adolescence. Specifically, *DRD4* 7+ individuals have an increased sensitivity to dopamine responses triggered by priming doses of alcohol (Hutchinson et al. 2002) and an increased perceived ability to bond with their peers while consuming alcohol (Larsen et al. 2010). Moreover, the

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DRD4 7+ genotype also increases the sense of reward from alcohol consumption when in a group context (Creswell et al. 2012). The presence of the 7-repeat allele may influence adolescents' sensitivity to peer pressure by affecting the sense of reward they feel from joining their peers in antisocial behaviors and the social connection adolescents feel with their peers. Our study builds on these prior peer context × *DRD4* findings by demonstrating that the peer environments to which *DRD4* can confer sensitivity can extend beyond those that directly urge alcohol use.

Returning to theory, DST provides that individuals vary in their susceptibility to environmental contexts both "for better" and "for worse" (Belsky et al. 2007). Previous evidence has been found supporting the "for worse" peer context while evidence of the "for better" context is currently limited (Buil et al. 2015; Kretschmer et al. 2013). Although the DST framework guided these research questions, other theories, such as the diathesis-stress theory, are also relevant for considering G × E phenomena. Most relevant to our study, recent research on peer victimization and social well-being on delinquency has been able to consider a range of peer relationships, but found the opposite pattern of sensitivity, with carriers of the 7-repeat *DRD4* allele being less sensitive to the effects of the peer environment (Kretschmer et al. 2013).

Evidence of DST would be suggested by an association between antisocial peer pressure and the alcohol use outcomes for those who possess the *DRD4* 7+ genotype that forms a crossover intersection near the middle of the distribution of antisocial peer pressure (i.e., mean levels of antisocial peer pressure; Ellis et al. 2011). Within the context of our findings, no association was found between antisocial peer pressure and alcohol use outcomes among *DRD4* 7− individuals. Those who possess the *DRD4* 7+ genotype, however, differ in alcohol use depending on specific levels of antisocial peer pressure, with high peer pressure associated with higher alcohol use. Our results demonstrate a cross-over intersection, supporting differential susceptibility. However, this support for DST is limited by our study design, specifically the environments assessed by our peer variable, as low levels of antisocial peer influence are not necessarily equivalent to an enriching peer context. Although unmeasured herein, it is certainly possible that individuals who report zero and very low levels of antisocial peer pressure have relationships that are supportive and prosocial, including but not limited to peer pressure to abstain from alcohol use. If so, this would also be consistent with DST. Future research will have to consider the role of *DRD4* and other genes in moderating the impact of different dimensions of positive peer environments as well as sensitivity to peer environments that support abstaining from alcohol use.

In contrast to Differential Susceptibility Theory, the diathesis-stress model provides that in the absence of an environmental stressor, such as antisocial peer pressure, there should be no differences between vulnerable and resilient individuals. In the context of this study, the high level of antisocial peer pressure would be the environmental stressor that would act as the "trigger" for *DRD4* 7+ youth that results in increased alcohol use. Evidence of diathesis-stress would be suggested by a fan shaped interaction whereby *DRD4* 7− individuals who experience peer pressure would not have increased alcohol use. Those who possess the

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DRD4 7+ genotype and experience peer pressure, however, would have increased alcohol use. This was not depicted in our graphs.

The results of this study should be interpreted in the context of several limitations. The PROSPER sample relied on school-based data collection, which can risk under-sampling high-risk populations, such as school dropouts and those with poor school attendance, who may be at the greatest risk for alcohol use (Berk 1983). Peer pressure was measured using youth self-report, which is subject to social desirability bias. Using network data or parent-reports on peer relationships in the future may increase the quality of peer relationship measures. Attrition analysis revealed that respondents excluded from the current analyses due to missing 12th-grade data had reported relatively higher levels of free and reduced school lunch and a higher likelihood of being from a single-parent household. Thus, those who had dropped out of the study by the 12th grade were likely to have an increased risk for alcohol use. Therefore, findings from the current study are less applicable to those at the highest end of the risk spectrum. However, differences in antisocial peer pressure by missingness were not detected. This ensures that results based on the range of peer pressure experienced are not due to attrition.

The present sample was predominantly of European descent and located within rural and semi-rural towns. Although rural European-American populations are at considerable risk for alcohol consumption, the sample's demographics limit the cross-population generalizability of the findings. Further, while Differential Susceptibility Theory emphasizes that genetic variations affect individuals' sensitivity to both favorable and adverse environmental contexts, this article does not include both enriching and adverse peer relationships and potential positive outcomes. Within G × E literature, there are concerns regarding the lack of direct replication (Caspi et al. 2002, 2003; see Munafò et al. 2009; Risch et al. 2009); however, this issue has been shown to be due to differences in study design such as sample and quality of construct measurement (Uher and McGuffin 2007). While the present study had a modest sample size, the pattern of results was generally consistent with previous studies using similar constructs. These findings should be interpreted with caution until future replication is possible.

Conclusion

This study extends the field of adolescent substance use research by furthering the understanding of individual difference's effect on adolescent susceptibility to peer pressure —specifically, how genetic differences can explain why some adolescents may, or may not, be influenced by antisocial peer pressure. We used the longitudinal structure of the PROSPER data set to examine the effect of peer pressure during early adolescence, a critical developmental period (Steinberg and Monahan 2007), on late adolescence alcohol use. Specifically, 7th-grade antisocial peer pressure was associated with increased 12th-grade lifetime alcohol use, but there was no effect of the *DRD4* genotype. We found that the *DRD4* genotype moderated the effect of 7th-grade antisocial peer pressure on 12th-grade alcohol use; antisocial peer pressure was associated with increased lifetime alcohol use for individuals who carried at least one copy of the *DRD4* 7-repeat allele (7+). The empirical findings have been elaborated within the framework of Differential Susceptibility Theory

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and the diathesis-stress model to determine how researchers should interpret genetic moderation of peer pressure on subsequent alcohol use. Our findings have implications for alcohol use interventions for adolescents, such that adolescents who are more sensitive to their social environments may benefit more from learning peer communication and refusal skills.

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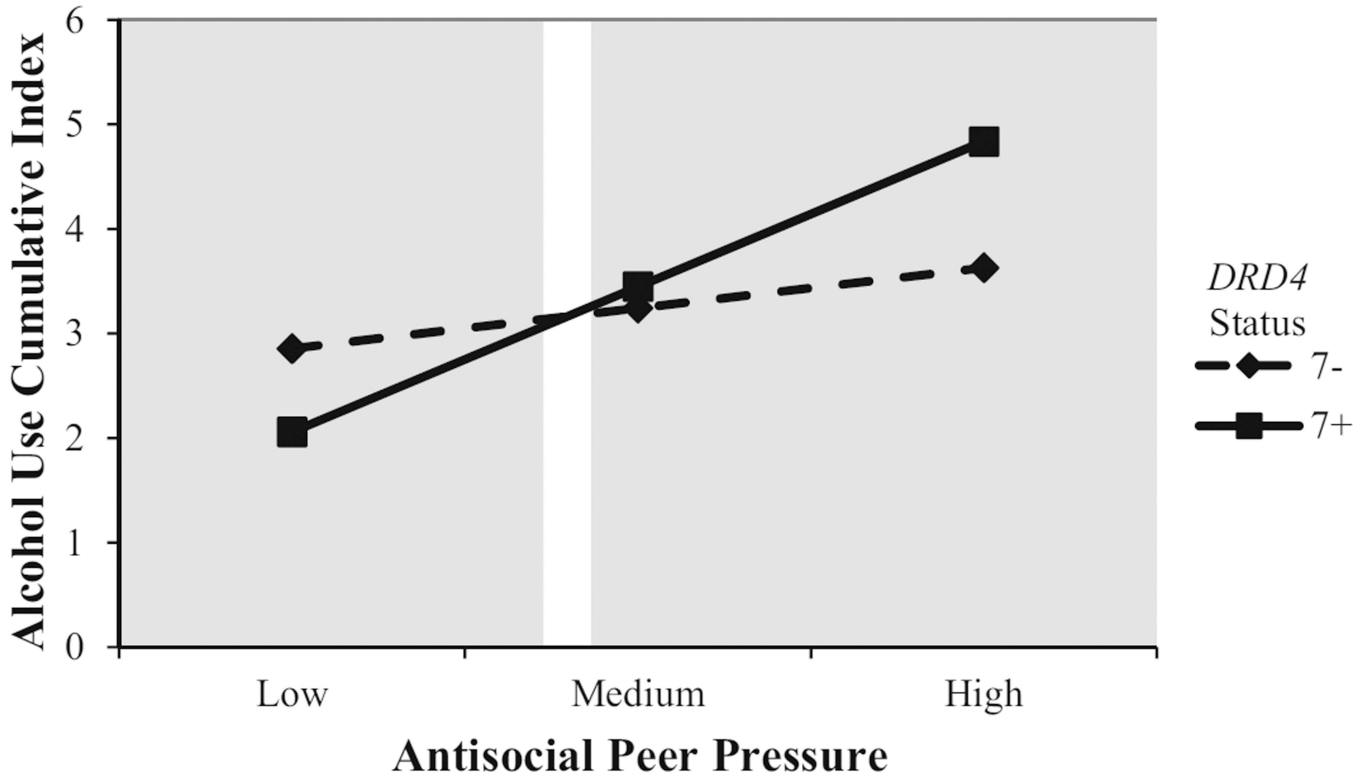

Fig. 1.

Differential effects of 7th-grade antisocial peer pressure on 12th-grade alcohol use cumulative index by *DRD4* genotype. *Note*: The shaded regions represent significant differences between *DRD4* 7− and 7+ status

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Table 1

Demographic comparisons by *DRD4* genotype and for analytic sample

	% (*n*)		
Variable	***DRD4 7−***	***DRD4 7+***	**Total (*n* = 414)**
Gender			
Female	66.4 (148)	33.6 (75)	53.9 (223)
Condition			
Intervention	63.8 (155)	36.2 (88)	58.7 (243)
European			
European	65.1 (229)	34.9 (123)	85.0 (352)
Race			
White	63.3 (243)	36.7 (141)	92.8 (384)
Hispanic/Latino	41.2 (7)	58.8 (10)	4.1 (17)
Black	33.3 (1)	66.7 (2)	0.7 (3)
Asian	100 (2)	0 (0)	0.5 (2)
Other	87.5 (7)	12.5 (1)	1.9 (8)

Variable	**Categories/unit**	**M (SD)**	**M (SD)**	**M (SD)**
Age	Years	13.43 (0.36)	13.40 (0.38)	13.42 (0.37)
Antisocial peer pressure	Unstandardized	1.17 (0.37)	1.15 (0.18)	1.16 (0.32)

PC1, control for population stratification; % European is based on PC1, and race is based on participant self-report. PC1 is reported here in standard deviation units

* $p < .05$;

** $p < .01$

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Table 2

Parameter estimates and standard errors for antisocial peer pressure models

	Parameter estimate (standard errors)	
	AUCI	
Variables	**Model 1**	**Model 2**
Main effects		
APP	0.50 (.12)**	0.39 (.12)**
DRD4	0.08 (.25)	0.20 (.25)
Two-way interaction		
APP*D4		1.00 (.36)**
Covariates		
PC1	−4.18 (5.15)	−3.76 (5.11)
Cond	−0.07 (.24)	−0.02 (.24)
Gender	−0.07 (.24)	−0.05 (.23)

PC1, control for population stratification; Cond, control for intervention condition; APP, 7th-grade antisocial peer pressure; D4, DRD4; AUCI, 12th-grade alcohol use cumulative index

* $p < .05$;

** $p < .01$