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Interaction between the DRD4 VNTR Polymorphism and Proximal and Distal Environments in Alcohol Dependence during Emerging and Young Adulthood

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Abstract

The manifestation of alcohol dependence at different developmental stages may be associated with different genetic and environmental factors. Taking a developmental approach, the current study characterized interaction between the dopamine receptor 4 variable number tandem repeat (DRD4 VNTR) polymorphism and developmentally specific environmental factors (childhood adversity, college/Greek involvement, and delayed adult role transition) on alcohol dependence during emerging and young adulthood. Prospective data were obtained from a cohort of 234 Caucasian individuals (56% female) followed up at ages 18 through 34. A longitudinal hierarchical factor model was estimated to model a trait-like persistent alcohol dependence factor throughout emerging and young adulthood and two residual state-like alcohol dependence factors limited to emerging adulthood and young adulthood, respectively. To account for those alcohol dependence factors, three two-way interaction effects between the DRD4 VNTR polymorphism and the three developmentally specific environment factors were modeled. Carriers of the DRD4 long allele showed greater susceptibility to environmental effects; they showed more persistent alcohol dependence symptoms as childhood adversity increased and more alcohol dependence symptoms limited to emerging adulthood as college/Greek involvement increased. Alcohol dependence among non-carriers of the long allele, however, did not differ as a function of those environments. Although replication is necessary, these findings highlight the importance of repeated phenotypic assessments across development and modeling both distal and proximal environments and their interaction with genetic susceptibility at specific developmental stages.

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Keywords

DRD4 VNTR; alcohol; gene-environment interaction; development

In general, problematic alcohol use changes over the course of the life span. To capture the time-varying nature of alcohol use behaviors, they need to be characterized longitudinally within their developmental contexts (Plomin, 1986; Zucker, 2006). Emerging adulthood (from late teens to mid-twenties; Arnett, 2000) and young adulthood (late twenties to thirties) are critical developmental stages with respect to the development and subsequent persistence or remission of alcohol dependence. For example, 50% and 75% of life-time alcohol dependence diagnoses were present by the ages of 23 and 31, respectively (Kessler et al., 2005). Rates of heavy drinking peaks in the late teens and early twenties and steadily decreases afterward (Johnston, O'Malley & Bachman, 2001a, 2001b). However, 20% to 30% of adults departed from this normative trend maintaining their alcohol dependence or developing new alcohol dependence in their late twenties or thirties (Fillmore, 1988; Jackson, Sher, Gotham & Wood, 2001). Thus, emerging and young adulthood is an optimal period to characterize persistent and developmentally-limited aspects of alcohol dependence.

Susceptibility to alcohol dependence is determined by both genetic and environmental influences, and the nature of those influences also changes as a function of developmental stages. In adolescence through young adulthood, genetic influence on alcohol use and abuse increases, whereas environmental influence decreases (Dick, Rose & Kaprio, 2006; Kendler, Schmitt, Aggen, & Prescott, 2008). In addition, different genes (e.g., Guo, Wilhelmsen & Hamilton, 2007; Hopfer et al., 2005) and environments (Masten, Faden, Zucker & Spear, 2008) may affect alcohol dependence at different developmental stages (as described below). Therefore, a developmentally sensitive study design is needed to delineate how specific genes interact with high-risk environments to affect persistent and developmentally-limited aspects of alcohol dependence during emerging and young adulthood.

Persistent and Time-Limited Environmental Effects

Alcohol use and associated problems are influenced by both early experience and concurrent social environments and these different types of environmental influences may vary widely in the persistence of their effects. Effects of some environments are more likely to be time-limited (e.g., spring break), whereas others are more enduring (e.g., religious upbringing). Childhood adversity – physical, sexual, and emotional abuse and neglect – has been associated with a higher rate of alcohol dependence later in life (Koss et al., 2003; Simpson & Miller, 2002; Molnar, Buka & Kessler, 2001). Thus, the effect of childhood adversity appears persistent even after the adversity is no longer present. In contrast, the effects of some college environments appear to be time-limited. College students tend to show a higher rate of heavy drinking during college years than do their non-college age peers (Johnston, O'Malley & Bachman, 2003; Slutske et al., 2004) but not after college (B. Muthén & L. Muthén, 2000; White, Labouvie & Papadaratsakis, 2005). Among college environments, detrimental effects of fraternity/sorority affiliation on heavy drinking also have been shown to be limited to the period of affiliation (Bartholow, Sher & Krull, 2003; Park, Sher & Krull, 2008). Adult role transitions, including full-time employment, marriage, and parenthood, have been associated with decreases in alcohol dependence after the mid-twenties (Bachman et al., 2002; Jessor, Donovan & Costa, 1991). In contrast, those who delayed the adoption of those adult roles were less likely to “mature out” of alcohol problems (Bachman, Wadsworth, O'Malley, Schulenberg, & Johnston, 1997; Gotham, Sher, & Wood, 1997) in comparison to their peers who assumed such roles. Although each of the role transitions represents different aspects of adult life, role incompatibility has been

suggested as a common mechanism underlying their impacts on alcohol dependence in young adulthood. Because of high structure and demands, adoption of those adult roles is incompatible with problematic alcohol use, which in turn leads a change in alcohol use behavior over time (Yamaguchi & Kandel, 1985a, 1985b). Taken together, different environmental factors would appear to affect alcohol dependence as a function of developmental stages. However, a majority of gene and environment interaction studies have modeled environmental effects on alcohol use behavior without regard to developmental timing. Moreover, there has not been a general recognition that although some environmental exposures are likely to have enduring dispositional effects (i.e., distal factors), others are likely to have more time-varying effects (i.e., proximal factors). Thus, to adequately model environmental effects it is critical to adopt a developmental framework that jointly considers: (1) the timing and intensity of various environmental exposures, and (2) durable and developmentally specific manifestations of the phenotype.

The DRD4 VNTR Polymorphism and alcohol dependence

Given the importance of the dopamine system in the neurobiological basis of reward, dependence and craving (Wise, 2004), the dopamine D4 receptor (DRD4) gene on chromosome 11p15.5 has been studied as a promising candidate gene for alcohol dependence. The most frequently studied polymorphism of the DRD4 gene is a 48-base-pair variable number tandem repeats (VNTR) in the third exon (Van Tol et al., 1992). The number of repeats has been shown to range from 2 to 10, but 4-repeat allele, is the most prevalent in a population of European ancestry, followed by 7- and 2-repeat alleles (Chang, Kidd, Livak, Pakstis & Kidd, 1996). Compared with short alleles (6 or fewer repeats), long alleles (7 or more repeats) may reduce DRD4 gene expression (Schoots & Van Tol, 2003) as well as encoding receptors with reduced reactivity to endogenous dopamine (Asghari et al., 1994; Asghari et al., 1995). However, the underlying mechanisms by which the functional differences in the long versus short alleles increase risk for alcohol-related phenotypes remain largely unknown.

Association and linkage studies of the DRD4 gene found its role in diverse phenotypes, with consistent findings of its role in attention-deficit hyperactivity disorders (see Kebir, Tabbane, Sengupta & Joobar, 2009) and major depressive disorder (see López León et al., 2005). Association studies of the DRD4 polymorphism with alcohol and substance dependence (see Dick & Found, 2003; McGeary, 2009) and novelty seeking (see Munafò, Yalcin, Willis-Owen & Flint, 2008; Tochigi et al., 2006) have largely yielded null findings. However, findings on the association of its long allele with urges in response to alcohol and substance cues appear robust (see McGeary, 2009). Three linkage studies also found an association of alcohol dependence with a region on chromosome 11 close to the DRD4 gene (Ehlers et al., 2004; Long et al., 1998; Reich et al., 1998).

Emerging evidence suggests that effects of the DRD4 VNTR polymorphism change over time. For example, in one study, the DRD4 VNTR polymorphism was associated with alcohol quantity at age 26 but not at age 16 (Hopfer et al., 2005). Five polymorphisms that affect monoamine function, including the DRD4 polymorphism, were associated with alcohol frequency at ages 19 to 26 but not at ages 13 to 18 (Guo et al., 2007). These findings emphasize the need for a prospective study design to model genetic effects that differ as a function of development.

Time-Varying Gene-environment Interaction

Manifestation of genetic susceptibility also may differ depending on environmental exposure: that is, gene $\times$ environment interaction ($G \times E$; Plomin, DeFries & Loehlin, 1977). Emerging evidence suggests that individuals with genetic susceptibility for alcohol

dependence are more affected by certain developmental experiences. Findings of behavioral genetic studies seem to suggest that genetic influences on alcohol use are greater in individuals exposed to alcohol conducive environments: college-bound siblings (vs. non-college bound siblings; Timberlake et al., 2007), singles (vs. married individuals; Heath, Jardine & Martin, 1989), women from a non-religious upbringing (vs. religious upbringing; Koopmans, Slutske, van Baal & Boomsma, 1999), adolescents in urban areas (vs. rural areas; Rose, Dick, Viken & Kaprio, 2001; Dick, Rose, Viken, Kaprio & Koskenvuo, 2001) and adolescents whose best friends had greater alcohol use (Harden, Hill, Turkheimer & Emery, 2008). Adverse experiences in childhood has been shown to increase alcohol problems only in the presence of a susceptible genotype (Ducci et al., 2008; Nilsson et al., 2007; Nilsson, Wargelius, Sjöberg, Leppert, & Orelan, 2008), although extant studies focused on a polymorphism in the promoter region of the monoamine oxidase A gene. Taken together, individuals with genetic susceptibility appear to be more affected by adverse and/or alcohol-conducive developmental environments than are individuals without genetic susceptibility. However, there is a lack of studies on interactions between a specific polymorphism (as opposed to a latent genetic effect) and developmentally specific environmental factor (see van der Zwaluw & Engels, 2009).

Overview of the Current Study

Using prospective data from 234 individuals followed up at ages 18 through 34, the current study examined interaction effects between the DRD4 VNTR polymorphism and three developmental environments (i.e., childhood adversity, college/Greek involvement and delayed adult role transition) on alcohol dependence during emerging and young adulthood. A developmental perspective was taken via modeling persistent and developmentally-limited alcohol dependence and modeling persistent and time-limited effects of a genotype and developmental environments. Specifically, first, a longitudinal hierarchical factor model was estimated to decompose variability in alcohol dependence into one trait-like persistent alcohol dependence factor throughout emerging and young adulthood and two state-like alcohol dependence factors limited to emerging adulthood and to young adulthood, respectively. Second, interactions between the DRD4 VNTR polymorphism and three environmental risks were modeled to account for those persistent and developmentally-limited alcohol dependence factors. Developmental timing and persistence of environmental risks were modeled as an enduring effect of childhood adversity and time-limited effects of college/Greek involvement and delayed adult role transition. It was hypothesized that individuals with the DRD4 long allele would show more alcohol dependence symptoms when they were exposed to adverse and/or alcohol-conducive environments.

Method

Participants

Data were derived from a prospective study, in which 489 incoming first year students at a large Midwestern university were followed up and assessed on alcohol use and its correlates over 16 years at the mean ages of 18, 19, 20, 21, 25, 29, and 34 (for detailed participant recruitment and screening procedures, see Sher, Walitzer, Wood & Brent, 1991). Initially, 3,156 first-time incoming first year students (80% of entire incoming freshmen) were screened for family history of alcohol use disorders using adapted versions (Crews & Sher, 1992) of the Short Michigan Alcoholism Screening Test (Selzer, Vinokur & van Rooijen, 1975) and the Family History-Research Diagnostic Criteria interview (Endicott, Andreasen & Spitzer, 1978). Based on the screening, 489 participants (53% female, 94% Caucasian) were retained for the prospective study, consisting of roughly equal numbers of high-risk participants (whose biological fathers met diagnostic criteria for alcoholism; $n = 250$, 53% female) and low-risk participants (none of whose biological first-degree relatives met

criteria for alcoholism and substance abuse or antisocial personality disorder and none of whose biological second-degree relatives met criteria for alcoholism or substance abuse; $n = 237$, 52% female). By the time of the last assessment at the mean age of 34, 383 participants (78% of baseline sample) participated in the study. The baseline sample who had not actively withdrawn from the study was contacted and invited to take part in the new genetic component of this study at the mean age of 35. A tube for blood sampling and instructions for phlebotomists were sent to those interested in participating ($n = 435$; 89% of the baseline sample). Written consent was obtained from each participant. All measures and procedures were reviewed and approved by a human subjects institutional review board.

For the current study, the data from 234 participants were used, excluding 255 (52%) participants from the baseline sample based on the following three exclusion criteria. First, 30 non-Caucasian participants were excluded to control for potential confounds from population stratification. To determine participants' race, self-reported ancestry was used. Self-report assessment has been shown as a reasonable measurement to control for the potential threat of population stratification (Hutchison, Stallings, McGeary & Bryan, 2004). Second, because of potentially different genetic and environmental influences on abstinence from those influences on alcohol dependence (Rhee et al., 2003), an additional five participants who reported no alcohol consumption throughout the seven assessments of the study were excluded. Third, an additional 220 participants who did not provide blood samples for genotyping were excluded. The resulting final sample consisted of 234 individuals who were 18.49 years old on average ($SD = 0.60$) at the baseline assessment, including 56% women and 50% with a positive family history of alcoholism.

Attrition analyses were conducted to compare the final sample ($n = 234$) to Caucasian non-abstainers who were excluded from the current analyses due to their missing data on the DRD4 VNTR polymorphism ($n = 220$). The effect size of each study variable on attrition was measured by h and d , standardized measures of the magnitude of the difference between two proportions and two means, respectively (Cohen, 1988). The effects of study variables on attrition were trivial to small; being positive in family history of alcoholism ($h = .06$), greater childhood adversity ($d = .09$), being older ($d = .14$), less college/Greek involvement ($d = -.15$), being male ($h = .17$), greater alcohol dependence symptoms (ranging from $d = .04$ at age 34 to $d = .24$ at age 21 across seven measurements) and greater delay in adult role transition ($d = .33$) were associated with a higher probability of attrition. The combined effect of those variables on attrition also was minimal, as indicated by 4% of Nagelkerke R^2 in multiple logistic regression (Nagelkerke, 1991).

Measures

Alcohol dependence symptom counts—At all seven assessment points, 13 items were administered to measure alcohol dependence symptoms during the past year. Those items were part of the Young Adult Alcohol Problems Screening Test (YAAPST; Hurlbut & Sher, 1992), a self-report measure of diverse alcohol-related problems. In order to assess the dependence phenotype for these analyses, we used the YAAPST items assessing criteria for alcohol dependence of the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; American Psychiatric Association, 1994), such as “Felt that you needed larger amounts of alcohol than you used to use in order to get any effect,” “Had the shakes after stopping or cutting down on drinking,” “Felt like you needed a drink just after you'd gotten up,” “After you have had several drinks, unable to stop drinking if you want,” “Not gone to work or missed classes at school because of drinking, a hangover, or an illness caused by drinking,” “Neglected your obligations, your family, your work, or schoolwork for two or more days in a row because of your drinking,” and “Tried to cut down or quit drinking.” A sum of 13

dichotomously scored items (0 = did not experience in the past year; 1 = did experience in the past year) was used for data analyses.

Childhood adversity—To measure experiences of abandonment, neglect, verbal, physical, emotional, and sexual abuse prior to the age of 18, 15 items were administered retrospectively at the mean age of 25 as part of a structured interview of Childhood Life Events (Sher, Gershuny, Peterson & Raskin, 1997). Trained, Masters-level clinical interviewers used strategies to improve accuracy of retrospective self-reports, such as providing recognition cues and responding sensitively to respondents' emotional status (Brewin, Andrews & Gotlib, 1993). A sum score of the dichotomously scored 15 items (0 = did not experience; 1 = did experience prior to age 18) was used for data analyses. Internal consistency, as indicated by coefficient alpha of .80, suggested that adverse childhood events clustered within individuals.

College/Greek involvement—At the mean ages of 18, 19, 20, and 21, two items were administered to measure the degree of college and Greek organization involvement. College student status was determined dichotomously as full-time (1) versus part-time or non-college student status (0). Fraternity/sorority affiliation status was also dichotomously coded as members (1) versus nonmembers (0). A mean score of these two items over the four assessments, multiplied by 8, was used for data analyses.

Delayed adult role transition—At the mean ages of 25, 29, and 34, delay in adult role transition was assessed in terms of employment, marital and parenthood status. Employment status was determined dichotomously as full-time (0) versus part-time or unemployed (1). Being a full-time homemaker was coded as employed full-time. Marital status was dichotomized into currently married (0) versus not currently married (i.e., widowed, separated, divorced, engaged, or never married; 1). Parental status was also coded dichotomously as raising any child (including any biological, adopted, foster, or step child; 0) or not raising any child (1). A mean score of these three items over the three assessments, multiplied by 9, was used for data analyses.

Dopamine D4 receptor (DRD4) gene polymorphism—Genotyping the DRD4 polymorphism of 48-base pair Variable Number of Tandem Repeat (VNTR) in exon 3 was performed as described by LaHoste et al. (1996). The observed numbers of repeats per allele were 2 ($n = 55$), 3 ($n = 23$), 4 ($n = 285$), 5 ($n = 3$), 6 ($n = 4$), 7 ($n = 93$), 8 ($n = 4$), and 10 ($n = 1$) repeats. Those numbers of repeats were dichotomized into short (i.e., 2- to 6-repeats) and long (i.e., 7 to 10-repeats) alleles. For data analyses, participants were dichotomized into carriers of one or two long alleles (1; $n = 85$) versus non-carriers of a long allele (0; $n = 149$).¹

Analyses

Mplus version 5.21 (L. Muthén & B. Muthén, 1998 - 2009), a structural equation modeling package, was used. Whereas participants missing on the DRD4 VNTR were excluded, participants missing on other study variables were included in the analyses. Ninety one

¹We conducted an ancillary analysis with carriers of common alleles (i.e., 2-, 4-, and 7-repeat alleles), after dropping carriers of rare alleles ($n = 26$; 11% of the sample). This sample consisted of 83 carriers of one or two 7-repeat alleles and 125 non-carriers. Similar to the model presented in text, there was a significant interaction between college/Greek involvement and the DRD4 VNTR on emerging adulthood alcohol dependence symptoms ($\beta = .58$, $b = .21$, $ps = .02$), and a non-significant interaction between delayed adult role transition and the DRD4 VNTR on young adulthood alcohol dependence symptoms ($\beta = -.02$, $b = -.002$, $ps = .97$). Unlike in the model presented in text, however, there was a non-significant interaction between childhood adversity and the DRD4 VNTR on alcohol dependence symptoms throughout emerging & young adulthood ($\beta = .09$, $p = .44$; $b = .02$, $p = .45$); this difference in the analyses with versus without carriers of rare alleles may be due to lack of power.

percentage ($n = 213$) of the final sample had complete data. To accommodate missing data, we used full-information maximum likelihood (FIML) estimation, which determines the parameters that maximize the probability of the sample data. FIML generates excellent estimates and reasonable standard errors through estimating a likelihood function for each individual based on all the available data (Graham, Cumsille, & Elek-Fisk, 2003).

Results

Descriptive Statistics

Means and standard deviations of all study variables (in the diagonal) and zero-order Pearson correlations among them (in the off-diagonal) are presented in Table 1. The mean levels of alcohol dependence symptom counts decreased from the age of 18 (1.96, $SD = 1.68$) to the age of 34 (0.55, $SD = 1.14$). Associations of gender ($r = -.01$ to .20) and the DRD4 VNTR ($r = -.06$ to .14) with genetic and environmental risk factors and alcohol dependence symptom counts were small. Associations with three environmental risk factors with alcohol dependence symptom counts were small to moderate ($r = -.16$ to .29). Associations among alcohol dependence symptom counts over the seven assessment points were large ($r = .27$ to .61).

Factor Models of Alcohol Dependence Symptoms

To model seven assessments of alcohol dependence at the mean ages of 18 through 34, three factor models were fit. First, a single-factor model was fit, where all seven observed alcohol dependence variables loaded on an alcohol dependence trait factor. The single-factor model showed a poor fit to the data, $\chi^2(14, n = 234) = 118.44, p < .001$, Comparative Fit Index (CFI) = .81, Tucker Lewis Index (TLI) = .71, Root Mean Square Error of Approximation (RMSEA) = .18 (95% confidence interval [CI] = .15, .21), Standardized Root Mean Square Residual (SRMR) = .09. Second, a correlated two-factor model was fit, where four alcohol dependence variables assessed at ages 18 to 21 loaded to a factor of alcohol dependence in emerging adulthood and the remaining three alcohol dependence variables assessed at ages 25 to 34 loaded to a factor of alcohol dependence in young adulthood. The two-factor model also showed a poor fit to the data, $\chi^2(13, n = 234) = 49.28, p < .001$, CFI = .93, TLI = .89, RMSEA = .11 (95% CI = .08, .14), SRMR = .06.2

Third, a hierarchical factor model was fit, which included one overarching factor and two residual factors. As shown in Figure 1, all seven observed alcohol dependence variables loaded to a factor of alcohol dependence trait throughout emerging and young adulthood. In addition, the residual variances of observed alcohol dependence variables, after accounting for the alcohol dependence trait, were fit to two developmentally-limited alcohol

²As an ancillary analysis, a conditional correlated two-factor model was fit. This model included two latent factors of alcohol dependence: one for ages 18 to 21 and another one for ages 25 to 34, respectively. To model a persistent environmental risk, main effects of childhood adversity and its interaction with the DRD4 VNTR on the both alcohol dependence factors were estimated. To model developmentally specific environmental risks, a main effect of college/Greek involvement and its interaction effect with the DRD4 VNTR on the factor of alcohol dependence at 18 to 21 were estimated. Similarly, a main effect of delayed adult role transition and its interaction effect with the DRD4 VNTR on the factor of alcohol dependence at 25 to 34 were estimated. Effects of gender on the both alcohol dependence factors were controlled. Although the unconditional two-factor model did not provide a good fit as described above, when adding the genetic and environmental covariates the model showed an acceptable fit to the data, $\chi^2(57, N = 234) = 110.36, p = .00$, CFI = .91, TLI = .88, RMSEA = .06 (95% CI = .05, .08), SRMR = .05. Results of this correlated two-factor model were very similar to the results of the hierarchical three-factor model. Specifically, for the alcohol dependence at ages 18 to 21, a significant interaction effect between the DRD4 VNTR and childhood trauma ($\beta = .23, b = 15, ps = .03$) and a significant interaction effect between the DRD4 VNTR and college/Greek involvement ($\beta = .42, b = .17, ps = .03$) were found. For the alcohol dependence at ages 25 to 34, there was a significant main effect of delayed adult role transition ($\beta = .35, b = .11, ps < .001$) was found. However, a non-significant interaction effect between the DRD4 VNTR and childhood trauma ($\beta = .11, b = .04, ps = .31$) and a non-significant interaction effect between the DRD4 VNTR and delayed adult role transition ($\beta = -.14, b = -.04, ps = .30$) were found on the alcohol dependence at ages 25 to 34. These results overall support the robustness of the predictive findings based on the hierarchical factor model as well as the efficiency and interpretative value of the hierarchical modeling approach.

dependence factors: a factor of alcohol dependence limited to emerging adulthood (loaded by the four alcohol dependence variables assessed at ages 18 to 21) and a factor of alcohol dependence limited to young adulthood (loaded by the remaining three alcohol dependence variables assessed at ages 25 to 34). Thus, correlations of the alcohol dependence trait factor with the two developmentally-limited alcohol dependence factors were set to be zero. The correlation between the two developmentally-limited alcohol dependence factors was also set to be zero, based on our theoretical assumption that the state-like alcohol dependence in emerging adulthood and the state-like alcohol dependence in young adulthood were not associated with each other over and above their association with the alcohol dependence trait.

This unconditional hierarchical factor model showed a good fit to the data, $\chi^2(7, N = 234) = 12.17, p = .10, CFI = .99, TLI = .97, RMSEA = .06$ (95% CI = .00, .11), SRMR = .02. Standardized factor loadings are shown in Figure 1. The factor loading of the alcohol dependence variable measured at age 21 on the residual alcohol dependence factor limited to emerging adulthood was non-significant, β (standardized estimate) = $-.03, p = .80$. This result indicated that most variance of alcohol dependence at 21 were accounted for by alcohol dependence persistent during emerging and young adulthood, but not by alcohol dependence unique to emerging adulthood. The proportion of variance for each alcohol dependence manifest variable explained by the three alcohol dependence factors (the squared multiple correlation, R^2) ranged from 33% to 90%.

Gene and Environment Interactions ($G \times Es$)

To test the DRD4 VNTR's interaction with three developmental environment variables on the three alcohol dependence factors, a conditional hierarchical factor model was estimated. As shown in Figure 2, a main effect of the DRD4 VNTR and main effects of three environment variables were included as manifest variables. An interaction effect of the DRD4 VNTR with each environment variable was included as a manifest variable, which was calculated by multiplying the DRD4 VNTR variable by each centered environment variable. Effects of gender on the three alcohol dependence factors were controlled for (paths not shown). Resulting standardized estimates (unstandardized estimates in parentheses) are presented in Figure 2.

The model showed a good fit to the data, $\chi^2(51, N = 234) = 79.83, p = .006, CFI = .95, TLI = .93, RMSEA = .05$ (95% CI = .03, .07), SRMR = .04. The proportion of variance for each alcohol dependence factor explained by all exogenous variables (the squared multiple correlation, R^2) ranged from 12% to 17%. A significant interaction effect between the DRD4 VNTR and childhood adversity on the alcohol dependence trait factor was found, $\beta = .22, p = .02; b = .12, p = .03$. A significant interaction effect between the DRD4 VNTR and college/Greek involvement on alcohol dependence limited to emerging adulthood also was found, $\beta = .26, p = .02; b = .20, p = .03$. Finally there was no significant interaction effect between the DRD4 VNTR and delayed adult role transition on alcohol dependence limited to young adulthood, $\beta = -.10, p = .35; b = -.02, p = .38$.

To probe the significant $G \times E$ effects, a multiple group analysis as a function of the DRD4 VNTR polymorphism was conducted. Results showed that, among non-carriers of the long allele ($n = 149$), childhood adversity did not show a significant effect on the alcohol dependence trait, b (unstandardized estimate) = $.01$ ($\beta = .03$), $p = .80$. In contrast, among carriers of the long allele ($n = 85$), childhood adversity significantly increased the alcohol dependence trait, $b = .12$ ($\beta = .33$), $p = .01$. This pattern is also illustrated in Figure 3, top panel. Among carriers of the long allele, those high in childhood adversity (the upper one third) showed a higher mean factor score of the alcohol dependence trait factor than did those middle in childhood adversity (the middle one third) as well as those low in childhood

adversity (the lower one third). However, among non-carriers of the long allele, mean factor scores of the alcohol dependence trait factor did not appear to differ as a function of childhood adversity. Multi-group analysis also showed that college/Greek involvement increased alcohol dependence limited to young adulthood in a greater degree among carriers of the long allele, $b = .28$ ($\beta = .50$), $p = .001$, than did among non-carriers, $b = .07$ ($\beta = .18$), $p = .13$. This pattern is also illustrated in Figure 3, bottom panel, where a mean factor score of the emerging adulthood alcohol dependence factor was higher among carriers of the long allele who were high in college/Greek involvement (the upper one third), compared to a mean factor score among carriers of the same genotype who were middle (the middle one third) or low (the lower one third) in college/Greek involvement.

Discussion

Although the interaction between nature and nurture in developmental trajectories has long been recognized (e.g., Bronfenrenner & Ceci, 1994), different gene $\times$ environment interactions in phenotypes at specific developmental stages has rarely been characterized. Though replication is necessary, the current findings represent a “proof of concept” of a developmental perspective in gene association studies and gene by environment interaction studies. To date, most candidate gene studies have failed to consider the changing nature of alcohol dependence as a function of adult development, with a few exceptions (e.g., Hopfer et al., 2005; Guo et al., 2007). Much extant research simply uses lifetime diagnoses, which are known to be unreliable even over periods as short as one year (Vandiver & Sher, 1991). Even if lifetime diagnosis was perfectly reliable, aggregation of different developmental timings of alcohol dependence obscures potential roles of age-specific genetic and environmental risks. Thus, the types of interactions found in the current study (especially those involving residual life-stage effects) would not likely have been found with static phenotype measures.

The current study represents a radical departure from the typical static approach to studying the phenotypes of psychological disorders. Specifically, this study adopts a developmentally sensitive approach to characterizing gene-environment interactions via (1) decomposing variance associated with trait-like persistent alcohol dependence from variance associated with time-limited alcohol dependence and (2) modeling different developmental timings of genetic and environmental risks. This developmentally sensitive study design is critical, given that emerging and young adulthood – the highest risk period for alcohol dependence – is characterized by dramatic changes in social environments and alcohol use behaviors.

Our findings suggest that carriers of the DRD4 VNTR long allele are more sensitive to childhood adversity and college/Greek involvement in alcohol dependence, whereas non-carriers were not affected by them. Thus, the absence of the long allele appears to protect against detrimental effects of those environmental risks on alcohol dependence. These findings may partially explain inconsistent findings of the DRD4 VNTR gene's association with alcohol dependence (Dick & Fount, 2003; McGeary, 2009). That is, the DRD4 VNTR gene appears to be associated with alcohol dependence in emerging and young adulthood only in the presence of environmental risks such as childhood adversity and college/Greek involvement. We did not find an interaction between the DRD4 VNTR and delayed adult role transition. However, other genes in the dopaminergic and/or other neurotransmission systems may involve alcohol dependence in young adulthood, interacting with delayed adult role transition.

Pathways by which those environmental risks increase alcohol dependence among the DRD4 VNTR long-allele carriers are yet to be characterized. However, underlying mechanisms of gene-environment interactions are likely to differ as a function of persistence

of environmental risks. For example, in the case of childhood adversity, prolonged changes in the developing brain may mediate the increased susceptibility to alcohol dependence later in life. There is considerable evidence of enduring neurobiological changes due to childhood adversity, leading to increased sensitization to drugs/alcohol effects (Zimmermann, Blomeyer, Laucht & Mann, 2007). Of particular interest, stress-induced corticosteroid secretion has been shown to stimulate mesolimbic dopaminergic systems similar to the way that alcohol and drugs do (Berridge & Robinson, 1998; Piazza & Le Moal, 1997). However, specific roles of the DRD4 VNTR gene in the association between the neurobiological changes due to early stress and consequent alcohol dependence later in life need to be further clarified.

While time-limited environmental risks at later developmental stages are less likely to lead to persistent neurobiological changes that affect susceptibility to alcohol dependence, they may serve as facilitating milieus that permit individuals to actualize their inherited susceptibility. For example, college campuses are characterized by diverse alcohol-conducive factors, such as exaggerated perception of peers' drinking, easy access to alcohol, and low structure in life (Jackson, Sher & Park, 2004). Embedded in highly alcohol-conducive environments, individuals with genetic susceptibility are more likely to develop alcohol dependence than are those without such a predisposition. The DRD4 gene has been found to be strongly related to urges to drink alcohol (McGeary, 2009). For example, carriers of the DRD4 long allele showed greater neural response to alcohol cues (Ray et al., 2010) and they reported a higher level of craving after consuming a priming dose of alcohol (Hutchison, McGeary, Smolen, Bryan & Swift, 2002; McGeary et al., 2006) than non-carriers. Thus, exposure to alcohol cues rampant in college campuses may trigger carriers of the DRD4 VNTR long allele to experience greater and more frequent urges to drink and, in turn, alcohol consumption and alcohol dependence. This effect of the DRD4 VNTR long allele is likely to be limited to a time period when individuals with genetic susceptibility are exposed to alcohol-conducive environments. Specific factors in college environments that interact with the DRD4 gene to increase alcohol dependence in emerging adulthood need to be identified.

In sum, using a novel developmentally sensitive modeling approach, we found two types of gene-environment interactions involved with the DRD4 VNTR polymorphism: (1) an interaction with a distal environmental risk (i.e., childhood adversity) that affects susceptibility to persistent alcohol dependence, which is likely to be mediated by enduring neurobiological changes, and (2) an interaction with a proximal environmental risk (i.e., college/Greek involvement) that affects susceptibility to developmentally-limited alcohol dependence, which is likely to be mediated by alcohol-conducive factors. These different types of gene-environment interactions appear to be associated with different aspects of alcohol dependence characterized with distinct etiological pathways (such as different types of environmental risks) and clinical presentations (such as persistence or desistance of alcohol dependence). Thus, this study demonstrates the limitations of traditional static approaches and the value of adopting a developmental approach that models persistent and time-limited forms of pathology and distal and proximal environmental influences that interact with genetic susceptibility at specific developmental stages.

It is of note that the DRD4 VNTR showed trivial bivariate correlations with alcohol dependence symptom counts at each measurement, as shown in Table 1. As noted by Moffitt et al. (2005), the "main-effects approach" embodied in traditional gene finding including genome-wide association studies becomes inefficient if expression of the gene is conditional upon environmental exposure. Consequently, consideration of the environment in genetic studies should result in improved understanding about how gene effects on behavior are

actualized in environmental contexts. Thus, this kind of gene and environment interaction studies may contribute to explaining some inconsistencies in the DRD4 VNTR literature.

However, lack of replication of some gene and environment interaction findings (e.g., Risch et al., 2009) has caused growing skepticism about the role of gene and environment interaction. Given the inherent low power for detection of interaction effects (McClelland & Judd, 1993) and the vast range of potential gene-environment interactions, maintaining statistical control of Type 1 errors is a daunting task. Thus, replication and meta-analytic synthesis (Moffitt et al., 2005) is crucial for any significant findings including the current ones. In the replication effort and its interpretation, however, one should note that samples used in individual studies may vary in the scope and extent of exposure to certain environmental risks. If a large population-based study is not plausible, a sample enriched for specific environmental exposures of interest should be considered. Although thousands of subjects may be necessary to detect reliable gene-environment interactions, the current study suggests that a study with a relatively small sample size may be effective when the gene and environment variables are carefully chosen and the timing of exposure to relevant environments is considered in study design.

Several limitations and future directions of the current study are worthy of mention. First, we used a small sample from a selected population (Caucasian incoming college students, half of whom were positive in family history of alcoholism), and thus, our findings may not generalize to other populations. Clearly, our findings should be interpreted with consideration of sample characteristics and need to be replicated in independent samples. This study, however, provides a worked example and a “proof of concept” of how it is feasible to exploit an existing prospective study that is rich in assessment of environmental exposures and phenotypic assessment to study genetic and environmental effects. Further, oversampling individuals positive in family history of alcoholism may have made it easier to observe alcohol dependence and genetic and environmental risk factors, compared with other college-based samples. Second, similar to most other studies in this area, childhood adversity was assessed retrospectively. Although we employed strategies to improve accuracy of retrospective report, reporting biases can still affect our findings in unknown ways. Third, although it is beyond the scope of the current study, neurobiological and psychological mechanisms underlying the differential reactivity to childhood adversity and college environments as a function of the DRD4 VNTR need to be characterized in order to demonstrate the functional meaning of the current findings. Finally, much work needs to be done before gene-environment interaction findings can provide direct implications for intervention and prevention strategies. However, accumulation of replicated gene-environment interaction findings over time would lead to development of preventive strategies targeted for individuals with genetic susceptibility to reduce their exposure or reactivity to environmental risks.

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Figure 1.

A hierarchical factor model of alcohol dependence at the ages of 18 to 34. Standardized factor loadings are shown. The proportion of variance for each alcohol dependence manifest variable explained by the three alcohol dependence factors (R^2) is also shown. Correlation among the three alcohol dependence factors were set to be zero. * $p < .05$. ** $p < .01$. *** $p < .001$.

Figure 2.

Standardized estimates (unstandardized estimates in parentheses) of a conditional hierarchical factor model of alcohol dependence at the ages of 18 to 34 to test the DRD4 VNTR's interaction with three developmental environment variables. The proportion of variance for each alcohol dependence factor explained by all exogenous variables (R^2) is also shown. Effects of gender on the three alcohol dependence factors were controlled for (paths not shown). * $p < .05$. ** $p < .01$. *** $p < .001$.

Figure 3.

Factor scores of alcohol dependence factors obtained from the hierarchical factor models (shown in Figure 1) as a function of DRD4 VNTR genotype (0 vs. 1 or 2 long alleles) and risky environments (those in the upper, middle, vs. low one third in a risky environment). A mean factor score of each alcohol dependence factor was set to be zero. Standard deviations were 0.82 for the factor of alcohol dependence trait throughout emerging and young adulthood and 0.51 for the factor of alcohol dependence limited to emerging adulthood. Vertical bars represent the standard error below and above the mean factor scores.

Table 1
Means (and Standard Deviations) of Study Variables and Their Pearson Correlations

	1	2	3	4	5	6	7	8	9	10	11	12
1. Gender ^a	0.44 (0.50)											
2. DRD4 VNTR ^b	-.01	0.36 (0.48)										
3. Childhood adversity	-.06	.02	1.86 (2.37)									
4. College/Greek involvement	-.09	.09	-.16*	5.18 (1.99)								
5. Delayed adult role transition	.20**	.02	.06	.08	3.68 (2.20)							
6. Alcohol dependence at 18	.02	.05	.05	.12	.01	1.96 (1.68)						
7. Alcohol dependence at 19	.09	.09	.12	.22***	.03	.60***	1.81 (1.67)					
8. Alcohol dependence at 20	.12	.14	.07	.08	.15*	.48***	.62***	1.54 (1.55)				
9. Alcohol dependence at 21	.13	.01	.01	.12	.13*	.42***	.45***	.54***	1.33 (1.42)			
10. Alcohol dependence at 25	.09	.12	.14*	.02	.23***	.27***	.35***	.42***	.37***	0.83 (1.20)		
11. Alcohol dependence at 29	.05	.04	.20**	-.02	.26***	.19**	.26***	.37***	.38***	.46***	0.56 (1.01)	
12. Alcohol dependence at 34	.05	-.06	.17*	-.01	.29***	.27***	.28***	.28***	.38***	.35***	.61***	0.55 (1.14)

Note. *ns* range from .224 to .234 due to missing data. Numbers in the diagonal indicate means (and standard deviations in parentheses); numbers in the off-diagonal indicate Pearson correlation.

^a0 = female; 1 = male.

^b0 = non-carrier of a long allele; 1 = carrier of one or two long alleles.

*
 $p < .05$.

**
 $p < .01$.

 $p < .001$.