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Differential Sensitivity to Prevention Programming: A Dopaminergic Polymorphism-Enhanced Prevention Effect on Protective Parenting and Adolescent Substance Use

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Abstract

Objective—The purpose of this study was to investigate a genetic moderation effect of dopamine receptor-4 gene (*DRD4*) alleles that have 7 or more repeats on the efficacy of a preventive intervention to deter rural African American adolescents' substance use.

Methods—Adolescents ($N = 502$, M age = 16 years) were assigned randomly to the Strong African American Families–Teen (SAAF–T) program or to a control condition and were followed for 22 months. Adolescents provided data on substance use, and both adolescents and their primary caregivers provided data on intervention-targeted protective parenting practices.

Results—Male adolescents who carried at least one allele of *DRD4* with 7 or more repeats who were assigned to the control condition evinced more substance use across 22 months than did (a)

carriers of at least one allele of *DRD4* with 7 or more repeats who were assigned to SAAF-T or (b) adolescents assigned to either condition who carried two alleles of *DRD4* with 6 or fewer repeats. These findings were mediated by *DRD4* × SAAF-T interaction effects on increases in intervention-targeted protective parenting practices, a mediated moderation effect.

Conclusions—The results imply that prevention effects on health-relevant outcomes for genetically susceptible individuals, such as carriers of at least one allele of *DRD4* with 7 or more repeats, may be underestimated.

Keywords

African American; genetics; intervention; prevention; substance use

Epidemiological data indicate that African American adolescents in rural areas use substances at rates that equal or exceed those among adolescents in densely populated inner cities (Kogan, Berkel, Chen, Brody, & Murry, 2006; Milhausen et al., 2003). This situation led to the development of the Strong African American Families–Teen program (SAAF-T; Brody et al., 2012; Kogan et al., 2012), a preventive intervention designed to deter substance use among African American youths living in the rural South. SAAF-T specifically targeted a cluster of developmentally appropriate, protective parenting practices that included monitoring, reciprocal communication, positive problem solving, and clear substance use norms. A randomized prevention trial confirmed SAAF-T's efficacy in preventing substance use across the 22 months that separated the pretest and a long-term follow-up (Brody et al., 2012).

Randomized prevention trials provide a unique opportunity to test hypotheses about the interaction of genetic predispositions with contextual processes to create variations in phenotypes over time. Such transaction are termed Gene × Environment (G×E) interactions (Shanahan & Hofer, 2005). Typically, G×E interactions have been studied using epidemiological research designs in which interactions among genotypes and environmental risk factors are observed at one point in time or as they unfold over time. This approach has some limitations, the most notable of which involves difficulty in determining whether an observed environmental effect is causal or results from unmeasured variables. Through the implementation of randomized prevention trials, a causal relationship between an environmental manipulation and the alteration of a phenotype can be identified, and the likelihood that genetic status moderates the environmental effect of the prevention program can be determined. An additional advantage of this approach is that, because the environmental variable is randomized, prevention trials control for gene-environment correlations that can masquerade as G×E interactions (Rutter, 2005). Thus, the first purpose of this study was to test predictions regarding genetic moderation of SAAF-T efficacy by variations of the dopamine receptor-4 gene (*DRD4*) that have 7 or more repeats.

The *DRD4* gene was targeted in this inquiry for several reasons. First, the 7-repeat allele appears to be associated with reduced gene expression (Schoots & Van Tol, 2003) and altered functioning (Asghari et al., 1995; Asghari et al., 1994). Second, this gene is associated with behavioral self-control problems such as alcoholism (Laucht, Becker, Blomeyer, & Schmidt, 2007), pathological gambling (Pérez de Castro, Ibáñez, Torres, Sáiz-Ruiz, & Fernández-Piqueras, 1997), and impulsivity (Eisenberg et al., 2007). Third, African American youths who carry at least one allele of *DRD4* with 7 or more repeats are more likely than those who do not carry such an allele to increase substance use over time (Brody et al., in press; but see Hoffer et al., 2005, who did not find this effect among a predominantly Caucasian subsample of adolescents in the Add Health study). Fourth, evidence is accumulating to indicate that (a) carriers of at least one allele of *DRD4* with 7 or more repeats experience heightened susceptibility to the influences of both positive and

negative environmental circumstances (Belsky et al., 2009) and (b) the effect of *DRD4* may be particularly salient among African Americans (Shields et al., 1998). Although some controversy continues regarding the best way to characterize variability in this highly polymorphic region (for additional details see Wang et al., 2002; Grady et al., 2003; and Ding et al., 2002), most studies in the substance abuse literature characterize alleles as either “short” (*s*) or “long” (*l*), with the *s* category defined as having 6 or fewer repeats and the *l* category as having 7 or more repeats (McGeary, 2009). Accordingly, this convention is followed in the present study, in which individuals with no *l* alleles were contrasted with those carrying one or more *l* alleles.

A second purpose of this study was to determine whether the hypothesized SAAF-T $\times$ *DRD4* interaction is specific to male youths. Although prior research has not addressed this gender hypothesis, the epidemiology of substance use across adolescence suggests that male youths use substances more often than do female youths. In addition, male youths are more likely to lose inhibitory controls when experiencing life stresses (Rutter, 1990), leading to an increase in substance use (Brody, Chen, & Kogan, 2010). Thus, a three-way interaction was hypothesized among SAAF-T participation $\times$ *DRD4* status $\times$ gender. Specifically, male adolescents carrying at least one *l* allele of *DRD4* who were assigned randomly to the control condition were expected to evince greater increases in substance use than would (a) those assigned to SAAF-T who carried at least one *l* allele of *DRD4* and (b) those assigned to either SAAF-T or the control condition who carried two *s* alleles.

The third purpose of this study was to test a mediated moderation hypothesis in which parents assigned to SAAF-T whose children carry an *l* allele of *DRD4* would evince greater increases in intervention-targeted protective parenting processes (e.g., monitoring, reciprocal communication, positive problem solving, and a clear articulation of drug use norms) than would parents in the other *DRD4* $\times$ group assignment conditions. This interaction was further hypothesized to carry forward to account for the *DRD4* $\times$ SAAF-T interaction effect on substance use. The mediated moderation hypothesis would be supported if this model showed (a) a SAAF-T $\times$ *DRD4* interaction effect on increases in the frequency of substance use, (b) a SAAF-T $\times$ *DRD4* interaction effect on increases in protective parenting, (c) a link between increases in protective parenting and decreases in youths’ substance use, and (d) a nonsignificant SAAF-T $\times$ *DRD4* interaction effect on youth substance use when the SAAF-T $\times$ *DRD4* interaction effect on increases in protective parenting was included in the model.

Theoretical support for the mediated moderation hypothesis can be derived from a differential susceptibility hypothesis (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007). This hypothesis posits that genetic polymorphisms influence the extent to which individuals respond to environmental contexts, with some individuals primed by their genes to be more sensitive or adaptable than others. Recently, van IJzendoorn, Bakermans-Kranenburg, and Ebstein (2011) published a meta-analysis supporting this conjecture; the results showed that children and adolescents carrying at least one *l* allele of *DRD4* were more sensitive to both positive and negative environmental influences. Applied to this study, youths assigned randomly to the SAAF-T condition who carry at least one *l* allele of *DRD4* would be expected to be more responsive than other youths to intervention-induced changes in protective parenting practices. This sensitivity, in turn, would be expected to reinforce parents’ use of these practices, resulting in a decrease in youths’ substance use over time.

Method

Participants

In rural Georgia, 502 African American families were recruited; see Brody et al. (2012) and Kogan et al. (2012) for more details. In each family, an adolescent who was 16 years of age

at recruitment (56% female) and the adolescent's primary caregiver (in most cases, the youth's biological mother) took part in the study. More than 75% of the primary caregivers had completed high school or earned a general equivalency diploma; the median family income was \$1,482.50. Although the primary caregivers in the sample worked an average of 41.5 hours per week ($SD = 20.4$), 63.8% of the participants lived below federal poverty standards, and another 18% lived within 150% of the poverty threshold; they can be described as working poor.

Schools in six counties provided lists of 10th-grade students from which participants were selected randomly. During recruitment and prior to randomization, families were told that they would participate in a five-session program to build family skills that would promote adolescent well-being. A complete description of the recruitment process is provided in Brody et al. (2012) and Kogan et al. (2012). Of the 692 families screened, 638 (91%) were eligible to participate; of the eligible families, 502 (79%) agreed to take part in the study. Of the families recruited, 252 were assigned randomly to SAAF-T and 250 to the control. Of the families who provided data at pretest, 478 (95%) provided data 22 months later at long-term follow-up, 237 in the SAAF-T group and 241 in the control group. No demographic differences emerged between these families and the 24 families who left the study.

Procedure

All families took part in a pretest assessment, a posttest assessment that took place 5 months after the pretest, and a long-term follow-up assessment that took place 22 months after the pretest. The adolescents' mean ages were 16 years at pretest, 16 years 5 months at posttest, and 17 years 10 months at long-term follow-up. The five-session prevention programs began 1 month after pretest. African American university students and community members served as field researchers to collect data at each assessment. At each data collection point, the field researchers, who were blind to the families' group assignments, made a visit to each family's home. Interviews were administered via a self-paced computer program that the authors have used successfully with youths in epidemiological and prevention research.

Intervention Implementation

The SAAF-T program consisted of five consecutive meetings held at community facilities; it included separate caregiver and adolescent skill-building curricula and a family curriculum. Each meeting included separate 1-hour concurrent training sessions for caregivers and adolescents, followed by a 1-hour joint caregiver-adolescent session during which families practiced the skills they learned in the separate sessions. Thus, families received 10 hours of prevention programming. Concurrently with the implementation of SAAF-T, the control group participated in a family-centered intervention designed to promote healthful behaviors among adolescents by encouraging good nutrition, exercise, and informed consumer behavior. The school-based FUELTM program (Comprehensive Health Education Foundation; Seattle, Washington) was adapted into the five-session family skills format used in SAAF-T. The result was a program structurally similar to SAAF-T that was named FUEL for Families (FF). African American intervention leaders were trained to present SAAF-T and FF, both of which were manualized. Fidelity of intervention delivery was confirmed using established procedures (Fisher, Fisher, Bryan, & Misovich, 2002).

In SAAF-T, caregivers were taught consistent use of monitoring and control, reciprocal communication, establishment of clear norms and expectations about adolescent substance use, and cooperative caregiver-adolescent problem solving. Adolescents were taught the importance of having and following household rules, strategies to use when encountering racism, the importance of academic success, goal formation, and strategies for attaining

educational and occupational goals. An intent-to-treat approach was used in which all families were included in the data analysis regardless of the number of program sessions they attended. This preserved the random nature of the group assignments. Both SAAF-T and FF families attended an average of four of the five program sessions.

Measures

Control variable: Socioeconomic and community risk—A family financial downturn scale developed for the Iowa Youth and Families Project was used at pretest. The measure has demonstrated good psychometric properties in past studies (Conger & Elder, 1994). Caregivers were asked whether their families had experienced during the past 6 months any of 11 financial downturns such as postponing major household purchases, reducing life or medical insurance, and filing for bankruptcy. The number of items endorsed constituted the financial downturn score, which ranged from 0 to 11; Cronbach's alpha was .83. Community risk was assessed at pretest with a 20-item scale adapted from the Project on Human Development in Chicago Neighborhoods (see Sampson, Raudenbush, & Earls, 1997); it has demonstrated good psychometric properties in past studies with African American youths (Simons et al., 2002). Caregivers assessed problems in their neighborhoods such as lack of employment and educational opportunities, dilapidation (e.g., vacant or deserted buildings, trash), and neighborhood deviance (e.g., gang activity). The response set ranged from 0 (*not a problem*) to 3 (*a big problem*). Responses to the items were summed to form a neighborhood risk scale ranging from 0 to 60; Cronbach's alpha was .91. The socioeconomic and community risk measures were standardized and summed to form the socioeconomic and community risk control variable.

Intervention status and youth gender—Intervention status and gender were dummy coded. SAAF-T participants were coded 1, and control program participants were coded 0; male participants were coded 1, and female participants were coded 0.

Intervention-targeted parenting—Four parenting scales to which both caregivers and adolescents responded at pretest and 5-month posttest were used to create the intervention-targeted parenting construct. *Parental monitoring* was assessed with a four-item scale for caregivers and a five-item scale for youths. On a response set ranging from 1 (*never*) to 4 (*always*), caregivers reported the regularity with which they knew about youths' daily activities, and youths reported their perceptions of the regularity with which their caregivers knew their daily schedules. Cronbach's alphas for the scales across pretest and posttest were above .65. Scores from both reporters were standardized and summed to create the parental monitoring scale. *Reciprocal communication* was assessed with a four-item scale. Caregivers and youths reported how often they discussed choice of friends, school, alcohol and substances, and sex. The response set ranged from 0 (*never*) to 4 (*always or nearly every time*). Cronbach's alphas for the scales across pretest and posttest were above .77. Scores from both reporters were standardized and summed to create the reciprocal communication scale. *Positive problem solving* was assessed with a four-item scale. Caregivers and youths reported how often the caregivers helped the youths to solve problems by showing interest, listening to youths' ideas, and considering youths' viewpoints. The response set ranged from 1 (*never*) to 5 (*always*). Cronbach's alphas for the scales across pretest and posttest were above .76. Scores from both reporters were standardized and summed to create the positive problem solving scale. *Caregivers' substance use norms and expectations* were assessed with a six-item scale. Caregivers and youths reported caregivers' norms regarding the use of alcohol and other substances, association with substance-using peers, and consequences for not following caregivers' substance-related rules. The response set ranged from 1 (*strongly disagree*) to 5 (*strongly agree*). Cronbach's alphas for the scales across pretest and posttest were above .90. Scores

from both reporters were standardized and summed to create the substance use norms and expectations scale. These scales were developed and tested in previous intervention studies (Brody et al., 2004), in which they evinced good predictive validity. Responses to these scales forecast substance use in longitudinal epidemiological analyses (Brody, Chen, & Kogan, 2010; Brody, Chen, et al., 2006; Brody & Ge, 2001) and analyses of randomized prevention trials (Brody, Chen, Kogan, Smith, & Brown, 2010; Brody, Murry, et al., 2006; Brody et al., 2004).

Substance use—Four items were used to assess substance use (Johnston, O'Malley, & Bachman, 2000). At pretest and 22-month follow-up, youths reported on a scale ranging from 0 (*not at all*) to 6 (*about two packs a day*) how often during the past month they had smoked cigarettes. Youths also reported on a scale ranging from 0 (*none*) to 6 (*30 or more times*) how often during the past 3 months they (a) had a drink of alcohol, (b) had three or more drinks of alcohol at one time, or (c) had used marijuana. Responses to the four items were summed to form the substance use index.

Genotyping—Adolescents' DNA was obtained using Oragene™ DNA kits (DNA Genotek; Kanata, Ontario, Canada). Adolescents rinsed their mouths with tap water and then deposited 4 ml of saliva in the Oragene sample vial. The vial was sealed, inverted, and shipped via courier to a central laboratory in Iowa City, where samples were prepared according to the manufacturer's specifications. Genotype at *DRD4* was determined for each adolescent as Lichter et al. (1993) described. This approach involved using the primers F- CGCGACTACGTGGTCT ACTCG and R-AGGACCCTCATGGCCTTG, standard *Taq* polymerase and buffer, standard dNTPs with the addition of 100 μM 7-deaza GTP, and 10% DMSO. The resulting PCR products were electrophoresed on a 6% nondenaturing polyacrylamide gel and the products visualized using silver staining. Genotype was then called by two individuals blind to the study hypotheses and other information about the participants. None of the alleles deviated from Hardy-Weinberg equilibrium ($p = .062$, ns). For tests of the G×E hypotheses, *DRD4* status was dummy coded; participants carrying at least one *l* allele were assigned a code of 1 (48.28% of the sample), and participants carrying two *s* alleles were assigned a code of 0 (51.72% of the sample). Of the participants in the total sample who carried an *l* allele, 8.52% carried two copies of 7-repeat alleles, 89.1% carried one allele with 7 or more repeats and one with 6 or fewer repeats, and 2.37% carried two alleles with 8 or more repeats. Of the participants in the total sample who carried an *s* allele, 74.78% carried two copies of the 4-repeat allele. As is conventional in the literature (van IJzendoorn et al., 2011), carriers of one or two copies of an *l* allele were combined because the number of participants carrying two copies was too small to analyze.

Plan of Analysis

Negative binomial models (Cameron & Trivedi, 1998) were used to examine the effects of *DRD4* status, intervention status, and the *DRD4* status × intervention status interaction on participants' substance use. Negative binomial models were used because the substance use measure consists of count data, which does not approximate a normal distribution. Although Poisson models can address this issue, negative binomial models were preferred because of the observed inequality between the mean ($M = 1.31$) and variance ($Var = 5.72$) of the substance use data at follow-up. This inequality is termed *overdispersion* and violates an assumption that must be met for Poisson models to be used (Cameron & Trivedi, 1998). Negative binomial models allow for overdispersion in the dependent measures, rendering them appropriate for the analyses. All the models were analyzed using STATA 12.0 with robust standard errors for the estimates (StataCorp, 2011). The negative binomial analyses comprised two models: (a) a main-effects model involving *DRD4* status, intervention status (SAAF-T or control), and gender, and (b) tests of two- and three-way interactions involving

the predictors in the main effects model. In these models, SAAF-T, *DRD4*, and their interaction predicted the logarithm of the mean count [$\log(\mu)$] in substance use. Thus, the estimated coefficients are in the $\log(\mu)$ metric, meaning one unit change in a predictor corresponds to one unit change in $\log(\mu)$. Exponentiation of the coefficients (e^β) provides the incident rate ratios (IRRs), which represent the increase or decrease in the frequency of substance use with each one-unit change in a predictor in the model. For interpretation purposes, percentage of change in IRR with each one-unit change in a predictor is calculated by first subtracting the IRR from 1 and then multiplying it by 100 [$100*(1 - e^\beta)$]. In the current study, the percentage of change was used as the index of effect size.

Next, structural equation modeling (SEM) was used to test the mediated moderation hypothesis that a SAAF-T $\times$ *DRD4* interaction effect on increases in protective parenting would mediate, or account for, the SAAF-T $\times$ *DRD4* interaction effect on substance use. To do this, a SEM model was executed to test the hypothesis that male youths in the SAAF-T condition who carried at least one *l* allele of *DRD4* would experience greater increases in protective parenting from pretest to posttest than would those in the control condition with this genotype or those in either the SAAF-T or control condition who carried two *s* alleles. Upon confirmation of this hypothesis, a second SEM model was executed to test the mediated moderation hypothesis. The mediated moderation hypothesis would be supported if this model showed (a) a SAAF-T $\times$ *DRD4* interaction effect on increases in the frequency of substance use, (b) a SAAF-T $\times$ *DRD4* interaction effect on increases in protective parenting, (c) a link between increases in protective parenting and decreases in youths' substance use, and (d) a nonsignificant SAAF-T $\times$ *DRD4* interaction effect on youth substance use when the SAAF-T $\times$ *DRD4* interaction effect on increases in protective parenting was included in the model. A negative binomial model was used in this second step because it allows for overdispersion in the substance use outcome measure. Figures 2 and 3 present the results from the SEM analysis that tests the SAAF-T $\times$ *DRD4* interaction for intervention-targeted protective parenting and the mediated moderation hypothesis, respectively. The Wald test (Wald, 1947) was used to test the hypothesized indirect effect, and all models were analyzed with Mplus 6.11 (Muthén & Muthén, 1998–2010).

Results

Preliminary Analyses

Minimal attrition occurred across the 22 months of the study; 95.2% of the sample completed the follow-up data collection. The attrition rates were similar for the SAAF-T and control groups. *DRD4* data were unavailable for 41 of the 502 participants; 2 youths declined to provide DNA samples, and the genotyping laboratory was unable to make a valid genotype determination for the other 39 youths. Comparisons on all study variables between adolescents with ($n = 461$) and without ($n = 41$) *DRD4* data revealed one difference. Families in which adolescents were genotyped reported more financial downturns at pretest than did those in which adolescents were not genotyped ($M = 3.63$ vs. 2.27 , $t = 2.99$, $p < .003$). This variable was controlled in all of the following data analyses.

Intervention $\times$ *DRD4* Effects on Increases in Youths' Substance Use

Table 1 presents predictors of residualized increases in substance use across the 22 months separating the pretest and long-term follow-up assessments. Model 1 in Table 1 showed a significant *DRD4* effect on youths' substance use. Youths who carried at least one *l* allele of *DRD4* showed a 53% increase [$100*(1 - e^{-.425})$] in frequency of substance use compared with youths carrying two *s* alleles. In the presence of *DRD4* status, neither intervention effects nor gender effects were detected. Model 2 in Table 1 presents tests of hypothesized interaction effects. The hypothesized three-way interaction among *DRD4* status, intervention

status, and youth gender was significant ($\beta = -1.398, p = .023$), indicating that a significant difference emerged in the *DRD4* status $\times$ intervention effect on increases in substance use for youths of one gender only. This finding was explored further via separate tests of the *DRD4* status $\times$ intervention status interaction for male and female youths. The results are presented in Table 2. Model 1 in Table 2 for male youths and female youths presents the main effect model. *DRD4* status predicted an increase in substance use for male, but not female, youths. For male youths, carrying at least one *l* allele of *DRD4* was associated with a 90% increase [$100 \times (1 - e^{-.642})$] in frequency of substance use compared with youths carrying two *s* alleles. Model 2 for male and female youths estimated the interaction effects for *DRD4* status and intervention status. As hypothesized, this interaction was significant only for male youths; Figure 1 illustrates the interaction effect. Male youths carrying at least one *l* allele of *DRD4* who were assigned randomly to the control program evinced larger increases in substance use than did their counterparts who were assigned randomly to the SAAF-T program or young men assigned to either condition who carried two *s* alleles. The next section deals with the results of tests of the mediated moderation hypothesis with male youths.

Intervention-targeted Parenting Mediates the *DRD4* $\times$ Intervention Effect

Figure 2 presents the hypothesized *DRD4* status $\times$ intervention status interaction effect on changes in intervention-targeted parenting from pretest to posttest. A SEM was estimated by regressing intervention-targeted parenting measured at posttest on *DRD4* status, intervention status, and *DRD4* status $\times$ intervention status with pretest levels of intervention-targeted parenting and socioeconomic and community risk controlled. The model fit the data fairly well ($\chi^2/df = 1.76$, CFI = .94, RMSEA = .06). The results indicated a significant *DRD4* status $\times$ intervention status interaction effect ($\beta = .22, p < .05$) on the intervention-targeted parenting construct. SAAF-T families with a youth who carried at least one *l* allele of *DRD4* evinced greater increases in intervention-targeted parenting between pretest and posttest than did either families of SAAF-T youth carrying two *s* alleles or control families. A similar SEM was fit with substance use as the outcome variable. Consistent with analyses reported previously, the results indicated a significant *DRD4* status $\times$ intervention status interaction effect ($\beta = -.72, p < .01$).

Figure 3 presents the test of the mediated moderation hypothesis. Consistent with this hypothesis, the results depicted in Figure 3 show that the SAAF-T $\times$ *DRD4* status interaction effect on changes in substance use became nonsignificant, changing from $\beta = -.72, p < .01$ when the interaction effect on intervention-targeted protective parenting was *not* included in the SEM to $\beta = -.39, p > .05$ when the interaction effect on intervention-targeted parenting was included in the SEM. As expected, increases in intervention-targeted parenting forecast decreases in substance use, $\beta = -.56, p < .01$. A Wald test confirmed the significance of this indirect effect (Wald $\chi^2_{(1)} = 4.44, p < .035$).

Power

To ensure adequate power to detect a significant *DRD4* status $\times$ intervention status interaction effect given the current sample size, power analyses were conducted based on the results presented in Tables 1 and 2 and Figure 2. The results indicated .86 power to detect a significant two-way interaction effect in the negative binomial model presented in Table 2. Furthermore, on the basis of a method that Luan, Wong, Day, and Wareham (2001) used, the power to detect a significant interaction effect for the model presented in Figure 2 was .93.

Discussion

On the basis of resilience and differential susceptibility theories (Belsky et al., 2007; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Cicchetti & Blender, 2006), a G×E hypothesis about the genetic moderation of prevention effects on increases in adolescent substance use was tested. The results indicated that male adolescents who carried at least one *l* allele of *DRD4* who were assigned to the attention control evinced more substance use over time than did (a) those who were assigned to SAAF-T or (b) adolescents assigned to either condition who carried two *s* alleles. These G×E effects were mediated by G×E effects on protective parenting processes. The results extend previous findings that carrying an *l* allele of *DRD4* increases sensitivity to intervention or prevention programs among toddlers (Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008), kindergarten children (Kegel, Bus, & van IJzendoorn, 2011), and 11-year-old children (Beach, Brody, Lei, & Philibert, 2010).

The results support Belsky and colleagues' (2007) differential susceptibility hypothesis in which variants of specific genes, including *DRD4*, are proposed to render individuals more susceptible to the surrounding environment whether it is characterized by high positivity or high risk. The finding that, after exposure to the protective processes that SAAF-T offered, carriers of at least one *l* allele as well as adolescents carrying two nonsusceptibility *s* alleles of *DRD4* evinced less substance use over time than did similar youths in the control condition supports differential susceptibility predictions. If supported on a broader basis, these results imply that general estimates of intervention effects on health-relevant outcomes both under- and overestimate efficacy. The estimates underestimate efficacy for genetically susceptible individuals and overestimate it for those without genetic susceptibilities. Clearly, more genetically informed prevention/intervention research is required to confirm this conclusion.

Tests also were made for gender differences in the G×E hypothesis advanced. Although gender has been identified as an important source of variability in substance use and abuse among members of all racial and ethnic minority groups (Johnston et al., 2004), few empirical studies have explored gendered G×E effects. As expected, the hypothesized G×E effects emerged for male, but not female, adolescents. Two explanations can be offered for this finding. First, the rates of substance use for male adolescents were several times those of female adolescents throughout the study. Greater prevalence of substance use renders interactions easier to detect. A much larger sample than the one included in the present study may include female youths who engage in higher rates of substance use and permit an adequately powered test of the G×E hypothesis addressed in this study. Second, gender differences in substance use rates may reflect a tendency for male adolescents to turn to substance use as a coping tactic. It is also consistent with other studies in which male adolescents were found to be more likely than female youths to respond to life stress by losing inhibitory controls (Brody, Chen, et al., 2006; Hetherington, 1989; Rutter, 1990).

The present study was also designed to address questions about the mechanisms through which G×E prevention effects operate. Recently, Brody and colleagues (in press) extended the G×E and the differential susceptibility perspectives to include a focus on mediators or intermediate phenotypes. That study focused on a cohort of rural African American emerging adults who were 17 years old at the first assessment and 20 years old at a third assessment. A *DRD4* × life stress interaction forecast substance use, with carriers of at least one *l* allele evincing increases in use. *DRD4* × life stress interaction effects on two intermediate phenotypes—increases in vulnerability cognitions for substance use and increases in affiliations with substance-using peers—accounted for this finding. Carriers of at least one *l* allele of *DRD4* who experienced high levels of life stress evinced increases in

both intermediate phenotypes. Carriers of two *s* alleles of *DRD4* who experienced high levels of life stress did not evince increases in substance use or in either intermediate phenotype. Similarly, the present study demonstrated that G×E effects on the intermediate phenotype of protective parenting processes accounted for G×E effects on a prevention outcome. Together, these two studies have begun to identify the mechanisms through which G×E effects operate and provide information that informs the etiology of substance use and abuse.

Generalizability of the present research is limited because SAAF–T was designed to meet a need in rural Southern communities for efficacious prevention programming for African American adolescents. The findings' applicability with ethnically and socioeconomically diverse participants residing in urban and rural locations must be established empirically. Even though the distribution of *DRD4* exon III VNTR alleles has been shown not to vary between persons of African and European descent (Chang, Kidd, Livak, Pakstis, & Kidd, 1996; Chen, Burton, Greenberger, & Dmitrieva, 1999), in attempting future replications, researchers should note whether their study populations differ in the distribution of these alleles. Such studies are important to an understanding of the etiology of substance use and abuse. These issues aside, the present study demonstrates the utility of using randomized prevention trials to test G×E hypotheses and furthers understanding of substance use etiology.

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References

- Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HHM. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry*. 1995; 65:1157–1165.10.1046/j.1471-4159.1995.65031157.x [PubMed: 7643093]
- Asghari V, Schoots O, Vankats S, Ohara K, Jovanovic V, Guan HC, Van Tol HHM. Dopamine D4 receptor repeat—Analysis of different native and mutant forms of the human and rat genes. *Molecular Pharmacology*. 1994; 46:364–373. Retrieved from <http://molpharm.aspetjournals.org/content/46/2/364.abstract>. [PubMed: 8078498]
- Bakermans-Kranenburg MJ, van IJzendoorn MH, Pijlman FTA, Mesman J, Juffer F. Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (*DRD4* VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Developmental Psychology*. 2008; 44:293–300.10.1037/0012-1649.44.1.293 [PubMed: 18194028]
- Beach SRH, Brody GH, Lei M-K, Philibert RA. Differential susceptibility to parenting among African American youths: Testing the *DRD4* hypothesis. *Journal of Family Psychology*. 2010; 24:513–521.10.1037/a0020835 [PubMed: 20954761]
- Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. For better *and* for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science*. 2007; 16:300–304.10.1111/j.1467-8721.2007.00525.x
- Belsky J, Jonassaint CR, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? *Molecular Psychiatry*. 2009; 14:746–754.10.1038/mp.2009.44 [PubMed: 19455150]
- Brody GH, Chen Y-f, Kogan SM. A cascade model connecting life stress to risk behavior among rural African American emerging adults. *Development and Psychopathology*. 2010; 22:667–678.10.1017/S0954579410000350 [PubMed: 20576186]

- Brody GH, Chen Y-f, Kogan SM, Smith K, Brown AC. Buffering effects of a family-based intervention for African American emerging adults. *Journal of Marriage and Family*. 2010; 72:1426–1435.10.1111/j.1741-3737.2010.00774.x [PubMed: 20976130]
- Brody GH, Chen Y-f, Kogan SM, Yu T, Molgaard VK, DiClemente RJ, Wingood GM. Family-centered program to prevent substance use, conduct problems, and depressive symptoms in Black adolescents. *Pediatrics*. 2012; 129:108–115.10.1542/peds.2011-0623 [PubMed: 22157131]
- Brody GH, Chen Y-f, Murry VM, Ge X, Simons RL, Gibbons FX, Cutrona CE. Perceived discrimination and the adjustment of African American youths: A five-year longitudinal analysis with contextual moderation effects. *Child Development*. 2006; 77:1170–1189.10.1111/j.1467-8624.2006.00927.x [PubMed: 16999791]
- Brody GH, Chen Y-f, Yu T, Beach SRH, Kogan SM, Simons RL, Philibert RA. Life stress, the dopamine receptor gene, and emerging adult drug use trajectories: A longitudinal, multilevel, mediated moderation analysis. *Development and Psychopathology*. (in press).
- Brody GH, Ge X. Linking parenting processes and self-regulation to psychological functioning and alcohol use during early adolescence. *Journal of Family Psychology*. 2001; 15:82–94.10.1037/0893-3200.15.1.82 [PubMed: 11322087]
- Brody GH, Murry VM, Gerrard M, Gibbons FX, McNair LD, Brown AC, Chen Y-f. The Strong African American Families Program: Prevention of youths' high-risk behavior and a test of a model of change. *Journal of Family Psychology*. 2006; 20:1–11.10.1037/0893-3200.20.1.1 [PubMed: 16569084]
- Brody GH, Murry VM, Gerrard M, Gibbons FX, Molgaard V, McNair LD, Neubaum-Carlan E. The Strong African American Families program: Translating research into prevention programming. *Child Development*. 2004; 75:900–917.10.1111/j.1467-8624.2004.00713.x [PubMed: 15144493]
- Cameron, AC.; Trivedi, PK. Regression analysis of count data. New York, NY: Cambridge University Press; 1998.
- Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*. 2010; 167:509–527.10.1176/appi.ajp.2010.09101452 [PubMed: 20231323]
- Chang FM, Kidd JR, Livak KJ, Pakstis AJ, Kidd KK. The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Human Genetics*. 1996; 98:91–101. [PubMed: 8682515]
- Chen C, Burton M, Greenberger E, Dmitrieva J. Population migration and the variation of dopamine D4 receptor (*DRD4*) allele frequencies around the globe. *Evolution and Human Behavior*. 1999; 20:309–324.10.1016/S1090-5138(99)00015-X
- Cicchetti D, Blender JA. A multiple-levels-of-analysis perspective on resilience: Implications for the developing brain, neural plasticity, and preventive interventions. *Annals of the New York Academy of Sciences*. 2006; 1094:248–258.10.1196/annals.1376.029 [PubMed: 17347356]
- Conger, RD.; Elder, GH, Jr. Families in troubled times: Adaptation to change in rural America. New York, NY: Aldine de Gruyter; 1994.
- Ding Y-C, Chi H-C, Grady DL, Morishima A, Kidd JR, Kidd KK, Moyzis RK. Evidence of positive selection acting at the human dopamine receptor D4 locus. *Proceedings of the National Academy of Sciences*. 2002; 99:309–314.10.1073/pnas.012464099
- Eisenberg DTA, MacKillop J, Modi M, Beauchemin J, Dang D, Lisan SA, Wilson DS. Examining impulsivity as an endophenotype using a behavioral approach: A *DRD2 TaqI A* and *DRD4* 48-bp VNTR association study. *Behavioral and Brain Functions*. 2007; 3 Article 2. 10.1186/1744-9081-3-2
- Fisher JD, Fisher WA, Bryan AD, Misovich SJ. Information-motivation-behavioral skills model-based HIV risk behavior change intervention for inner-city high school youth. *Health Psychology*. 2002; 21:177–186.10.1037/0278-6133.21.2.177 [PubMed: 11950108]
- Grady DL, Chi HC, Ding YC, Smith M, Wang E, Schuck S, Moyzis RK. High prevalence of rare dopamine receptor D4 alleles in children diagnosed with attention-deficit hyperactivity disorder. *Molecular Psychiatry*. 2003; 8:536–545.10.1038/sj.mp.4001350 [PubMed: 12808433]

- Hetherington EM. Coping with family transitions: Winners, losers, and survivors. *Child Development*. 1989; 60:1–14.10.1111/1467-8624.ep7250664 [PubMed: 2649320]
- Hopfer CJ, Timberlake D, Haberstick BC, Lessem JM, Ehringer MA, Smolen A, Hewitt JK. Genetic influences on quantity of alcohol consumed by adolescents and young adults. *Drug and Alcohol Dependence*. 2005; 78:187–193.10.1016/j.drugalcdep.2004.11.003 [PubMed: 15845322]
- Johnston, LD.; O'Malley, PM.; Bachman, JG. NIH Publication No 00-4802. Bethesda, MD: National Institute on Drug Abuse; 2000. Monitoring the Future national survey results on drug use, 1975–1999. Volume I: Secondary school students.
- Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. NIH Publication No 04-5506. Bethesda, MD: National Institute on Drug Abuse; 2004. Monitoring the Future national results on adolescent drug use: Overview of key findings, 2003.
- Kegel CAT, Bus AG, van IJzendoorn MH. Differential susceptibility in early literacy instruction through computer games: The role of the dopamine D4 receptor gene (*DRD4*). *Mind, Brain and Education*. 2011; 5:71–78.10.1111/j.1751-228X.2011.01112.x
- Kogan SM, Berkel C, Chen Y-f, Brody GH, Murry VM. Metro status and African-American adolescents' risk for substance use. *Journal of Adolescent Health*. 2006; 38:454–457.10.1016/j.jadohealth.2005.05.024 [PubMed: 16549312]
- Kogan SM, Brody GH, Molgaard VK, Grange CM, Oliver DAH, Anderson TN, Sperr MC. The Strong African American Families–Teen trial: Rationale, design, engagement processes, and family-specific effects. *Prevention Science*. 2012; 13:206–217.10.1007/s11121-011-0257-y [PubMed: 22124939]
- Laucht M, Becker K, Blomeyer D, Schmidt MH. Novelty seeking involved in mediating the association between the dopamine D4 receptor gene exon III polymorphism and heavy drinking in male adolescents: Results from a high-risk community sample. *Biological Psychiatry*. 2007; 61:87–92.10.1016/j.biopsych.2006.05.025 [PubMed: 16945348]
- Lichter JB, Barr CL, Kennedy JL, Van Tol HHM, Kidd KK, Livak KJ. A hypervariable segment in the human dopamine receptor D4 (*DRD4*) gene. *Human Molecular Genetics*. 1993; 2:767–773.10.1093/hmg/2.6.767 [PubMed: 8353495]
- Luan JA, Wong MY, Day NE, Wareham NJ. Sample size determination for studies of gene-environment interaction. *International Journal of Epidemiology*. 2001; 30:1035–1040.10.1093/ije/30.5.1035 [PubMed: 11689518]
- McGeary J. The *DRD4* exon 3 VNTR polymorphism and addiction-related phenotypes: A review. *Pharmacology, Biochemistry and Behavior*. 2009; 93:222–229.10.1016/j.pbb.2009.03.010
- Milhausen RR, Crosby R, Yarber WL, DiClemente RJ, Wingood GM, Ding K. Rural and nonrural African American high school students and STD/HIV sexual-risk behaviors. *American Journal of Health Behavior*. 2003; 27:373–379.10.5555/ajhb.2003.27.4.373 [PubMed: 12882431]
- Muthén, LK.; Muthén, BO. *Mplus user's guide*. 6. Los Angeles, CA: Authors; 1998–2010.
- Pérez de Castro I, Ibáñez A, Torres P, Sáiz-Ruiz J, Fernández-Piqueras J. Genetic association study between pathological gambling and a functional DNA polymorphism at the D4 receptor gene. *Pharmacogenetics*. 1997; 7:345–348. [PubMed: 9352568]
- Rutter ML. Commentary: Some focus and process considerations regarding effects of parental depression on children. *Developmental Psychology*. 1990; 26:60–67.10.1037/h0092669
- Rutter ML. Environmentally mediated risks for psychopathology: Research strategies and findings. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2005; 44:3–18.10.1097/01.chi.0000145374.45992.c9 [PubMed: 15608539]
- Sampson RJ, Raudenbush SW, Earls F. Neighborhoods and violent crime: A multilevel study of collective efficacy. *Science*. 1997 Aug 15;277:918–924.10.1126/science.277.5328.918 [PubMed: 9252316]
- Schoots O, Van Tol HHM. The human dopamine D4 receptor repeat sequences modulate expression. *Pharmacogenomics Journal*. 2003; 3:343–348.10.1038/sj.tpj.6500208 [PubMed: 14581929]
- Shanahan MJ, Hofer SM. Social context in gene-environment interactions: Retrospect and prospect. *Journals of Gerontology: Series B. Psychological Sciences and Social Sciences*. 2005; 60B(Suppl 1):65–76. Retrieved from <http://search.proquest.com/docview/210118302?accountid=14537>.

- Shields PC, Lerman C, Audrain J, Bowman ED, Main D, Boyd NR, Caporaso NE. Dopamine D4 receptors and the risk of cigarette smoking in African-Americans and Caucasians. *Cancer Epidemiology, Biomarkers and Prevention*. 1998; 7:453–458. Retrieved from <http://cebp.aacrjournals.org/content/7/6/453.full.pdf+html>.
- Simons RL, Lin K-H, Gordon LC, Brody GH, Murry VM, Conger RD. Community differences in the association between parenting practices and child conduct problems. *Journal of Marriage and Family*. 2002; 64:331–345.10.1111/j.1741-3737.2002.00331.x
- StataCorp. Stata statistical software: Release 12. College Station, TX: Author; 2011.
- van IJzendoorn MH, Bakermans-Kranenburg MJ, Ebstein RP. Methylation matters in child development: Toward developmental behavioral epigenetics. *Child Development Perspectives*. 2011; 5:305–310.10.1111/j.1750-8606.2011.00202.x
- Wald, A. Sequential analysis. Oxford, UK: Wiley; 1947.
- Wang X, Zhong P, Yan Z. Dopamine D₄ receptors modulate GABAergic signaling in pyramidal neurons of prefrontal cortex. *Journal of Neuroscience*. 2002; 22:9185–9193. Retrieved from <http://www.jneurosci.org/content/22/21/9185.abstract>. [PubMed: 12417643]

Figure 1.

Intervention status $\times$ *DRD4* status effect on male youths' predicted substance use. The vertical lines represent 95% confidence intervals.

Figure 2.

Intervention × *DRD4* effects on increases in intervention-targeted parenting for male youths. Socioeconomic and neighborhood risks were controlled. Standardized regression coefficients were used.

Figure 3. A mediated moderation model of the intervention $\times$ DRD4 effect on increases in intervention-targeted parenting and predicted frequency of substance use for male youths. Socioeconomic and neighborhood risks were controlled. Standardized regression coefficients were used.

Table 1

Negative Binomial Models for Intervention $\times$ DRD4 $\times$ Target Sex Effects on Increases in Youth Substance Use

	Model 1		Model 2	
	Estimate	SE	Estimate	SE
Constant	-1.038***	.287	-1.124***	.310
Substance use, pretest	1.268***	.155	1.367***	.149
DRD4 status	0.425**	.160	-0.042	.266
Intervention status			-0.105	.260
Youth gender			0.006	.348
Intervention status $\times$ DRD4 status			0.089	.407
Youth gender $\times$ DRD4 status			1.288**	.458
Intervention status $\times$ youth gender			0.608	.444
Intervention status $\times$ DRD4 status $\times$ youth gender			-1.398*	.613
Socioeconomic risk	-0.014	.028	-0.022	.028
Community risk	0.016*	.008	0.019**	.007

Note: The estimates presented in the table are in $\log(\mu)$ metric. The standard errors (SE) presented in the table are the robust standard errors.

*
 $p < .05$.

**
 $p < .01$.

 $p < .001$.

Negative Binomial Models for Intervention $\times$ DRD4 Effects on Increases in Youth Substance Use

Table 2

	Male youths				Female youths			
	Model 1		Model 2		Model 1		Model 2	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Constant	-0.688***	.411	-1.197**	.460	-1.453***	.384	-1.337**	.392
Substance use, pretest	1.108***	.232	1.23***	.233	1.582***	.194	1.573***	.193
DRD4 status	0.642**	.231	1.312***	.373	0.024	.203	-0.049	.269
Intervention status			0.523	.363			-0.188	.269
Intervention status $\times$ DRD4 status			-1.396**	.460			0.149	.411
Socioeconomic risk	-0.089*	.040	-0.098*	.043	0.058	.038	0.060	.038
Community risk	0.021*	.011	0.027**	.009	0.012	.009	0.011	.009

Note: The estimates presented in the table are in log(μ) metric. The standard errors (SE) presented in the table are the robust standard errors.

*
 $p < .05$.
**
 $p < .01$.

 $p < .001$.