Published in final edited form as:

J Fam Psychol. 2010 October ; 24(5): 513–521. doi:10.1037/a0020835.

Differential Susceptibility to Parenting among African American Youths: Testing the *DRD4* Hypothesis

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Abstract

To test the differential susceptibility to parenting hypothesis, a 4-wave, randomized prevention design was used to examine the impact of the Strong African American Families (SAAF) program on past-month substance use across 29 months as a function of *DRD4* genotype. Youths ($N = 337$; M age = 11.65 years) were assigned randomly to treatment condition. Those carrying a 7-repeat allele showed greater differential response to intervention vs. control than those with two 4-repeat alleles. Control youths but not treatment youths with a 7-repeat allele reported increases in past-month substance use across the 29-month study period, but this pattern did not emerge for those with the 4-repeat allele. Supporting the differential susceptibility to parenting hypothesis, the results suggest a greater preventive effect for youths carrying a 7-repeat allele, a role for *DRD4* in the escalation of substance use during adolescence, and potential for an enhanced understanding of early-onset substance use.

Keywords

DRD4; parenting; substance use; susceptibility

Belsky & Pluess (2009) suggest that children with so-called “risk alleles,” i.e., genetic variations thought to be associated with adverse outcomes, may be more sensitive to the impact of parenting behavior than are children who do not have these alleles. Preliminary evidence with young children has lent considerable support to the hypothesis that variability at *DRD4*, a well-studied 48-base pair (bp) repeat in the coding region of the dopamine D4 receptor, may

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indeed contribute to differential susceptibility to parenting (Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008; Bakermans-Kranenburg & van IJzendoorn, 2007; Belsky, Bakermans-Kranenburg & van IJzendoorn, 2007). Variation at *DRD4* also has been studied as a risk factor for certain problems in childhood, including ADHD (Gizer, Ficks, & Waldman, 2009) and risk for substance use (e.g., Conner, Helleman, Ritchie, & Noble, 2010). Based on the hypotheses that *DRD4* would confer differential susceptibility to parenting influences in adolescence and that substance use would escalate during adolescence, we predicted genetic moderation of a parenting-based prevention program on substance use outcomes would emerge.

We used the Strong African American Families (SAAF) program as the parenting intervention. SAAF is designed to prevent a cluster of risk behaviors, including alcohol use, marijuana use, and binge drinking (Brody et al., 2004); these behaviors are known to lead to problematic outcomes in adolescence and adulthood (Brook & Newcomb, 1995; Choi, Gilpin, Farkas, & Pierce, 2001). SAAF has been shown to prevent early initiation of substance use (Brody, Murry, Gerrard, et al., 2006) and recently has been shown to interact with a genetic polymorphism in *5HTT*, a 22-bp repeat element in the promoter region of that gene, in the prediction of risk behavior initiation (Brody, Beach, Philibert, Chen, & Murry, 2009; Brody, Beach, Philibert, Chen, Lei, et al., 2009). Several papers have documented the SAAF program's mechanism of action and predictors of response (Beach et al., 2008; Brody, Murry, Gerrard et al., 2006; Brody, Murry, Kogan et al., 2006; Brody et al., 2005; Brody, Murry, Chen, Kogan, & Brown, 2006; Gerrard et al., 2006; Murry et al., 2005). None of these papers, however, addressed the potential role of *DRD4* in moderating response to the intervention. In contrast to research on moderation of SAAF treatment effects by *5HTT*, which focused on initiation of risky behavior, in this article we focus on escalation of substance use across adolescence.

A Brief Primer on Genotyping

The genetic code is composed of nucleotide base pairs (bps) that are organized into genes. Genes represent segments of the genome that contribute to particular phenotypes or functions. Alternative forms of genes, termed "alleles," can be identified by examining specific locations within the gene. One type of genetic variation, produced by repeated sets of base pairs, is referred to as a Variable Number Tandem Repeat (VNTR). Both *DRD4* and *5HTT* contain well-characterized VNTRs. VNTRs may alter the product of the gene (as with *DRD4*) if they occur in the coding region (i.e. the Exon), or they may influence the amount of product produced (as with *5HTT*) if they occur in a promoter region. Within the coding region every three base pairs codes for a particular amino acid.

DRD4—The 48-bp VNTR in *DRD4* that we examined is a polymorphism in exon 3 that codes for a 16 amino acid insert in the dopamine D4 receptor. The VNTR contains 2 to 11 repeats, with the 4-repeat and 7-repeat alleles being most common. The 7-repeat allele functions in a way that yields a protein structure that produces less reactive D4 receptors in both *in vitro* and *in vivo* tests of responsiveness, resulting in weaker transmission of intracellular signals for those with the 7-repeat allele versus the 4-repeat allele (e.g., Levitan et al., 2006). It has been difficult to characterize fully the functional significance of the less common repeat alleles. Accordingly, in the current report we focus on contrasts between individuals with at least one 7-repeat allele versus those with two 4-repeat alleles.

5HTT—The serotonin transporter (*5HTT*) is a key regulator of serotonergic neurotransmission, localized to 17p13 and consisting of 14 exons and a single promoter. The 5HTTLPR (*5HTT* linked polymorphic region) is a well-explored genetic marker contributing to childhood temperament. Variation in the promoter region of the gene results in two main variants, a short and a long allele; presence of the short allele results in lower serotonin transporter availability.

The short variant has 12 copies, and the long variant 14 copies, of a 22-bp repeat element. The short allele appears to exert a similar effect on temperament for both males and females (Munafo, Clark, & Flint, 2004). In the current report, we focus on contrasts between individuals with at least one short allele and those with no short alleles.

Why Should *DRD4* Predict Escalation of Substance Use?

Individual differences in craving for substances may be important in predicting escalation of substance use, and considerable evidence indicates that one of the major neural substrates of craving is variation in the mesolimbic dopaminergic neurotransmission pathway (Berridge & Robinson, 1998; Wise, 1987). As noted previously, variation at *DRD4* has been found to result in weaker transmission of intracellular signals for those with the 7-repeat allele relative to those with the 4-repeat allele, and the resulting hypodopaminergic functioning is associated with indicators of substance use in adolescents. For example, youths carrying at least one 7-repeat allele have been found to have higher lifetime rates of alcohol use (Conner et al., 2010; Laucht, Becker, Blomeyer, & Schmidt, 2007; Ray et al., 2008; Skowronek, Laucht, Hohm, Becker, & Schmidt, 2006; Vaughn, Beaver, DeLisi, Howard, & Perron, 2009) than do similar youths without a 7-repeat allele.

Why Examine the Interaction of SAAF and *DRD4* in the Current Study?

Prior research suggests the potential importance of the *DRD4* 7-repeat allele in conferring susceptibility to parental influence early in childhood, and our own previous work has addressed the issues of genetic moderation with regard to initiation of risk behavior, including substance use. No studies, however, have been designed to determine whether the susceptibility to parental influence that *DRD4* confers continues into adolescence and whether parenting continues to interact with the presence of the *DRD4* 7-repeat allele to predict escalation of substance use in late childhood and early adolescence. If variation in *DRD4* is associated with both the attractiveness of certain risk activities and greater susceptibility to the impact of intervention-targeted parenting, a *DRD4* × SAAF interaction should emerge. Given prior work with *5HTT*, we are interested in determining whether the impact of *DRD4* is independent of the impact of *5HTT*.

Hypotheses

The foregoing considerations lead to three specific hypotheses. First, we predicted that the intervention would yield similar outcomes for intervention-targeted parenting behavior regardless of youth genotype at *DRD4* and that the SAAF program would work to alter intervention-targeted parenting behavior regardless of youth genotype. Second, we predicted that youths with one or two copies of the 7-repeat allele of *DRD4* who were assigned randomly to the control condition would show greater increases in substance use over time than would youths with the same genotype who were assigned randomly to SAAF; this would not be true for youths with two copies of the 4-repeat allele. We further hypothesized that the differences would be due to differences in youth genotypes, not parental genotypes. In addition, we examined the exploratory hypothesis that parents with the *DRD4* 7-repeat allele might show less change in intervention-targeted parenting as a function of SAAF participation. Although this is not directly relevant to the differential susceptibility hypothesis, it is relevant to the broader issue of optimal construction of preventive intervention programs. The availability of parent genotypes provided an opportunity to explore this hypothesis. Given prior work indicating that youth *5HTT* predicts differential initiation of risk behavior (Brody, Beach, Philibert, Chen, & Murry, 2009), we entered this genetic polymorphism into our analyses of youth susceptibility to the parenting intervention as a control variable.

Method

Data were collected as part of the evaluation of the SAAF family-based preventive intervention study. The data reported in this paper were collected from families randomly assigned to the prevention or control condition. Risk behaviors were assessed when the youths were 11 (pretest), 12 (posttest), 13 (follow-up) and 14 (long-term follow-up) years old. Data on intervention-targeted parenting practices were obtained at the posttest assessment; genetic data were obtained 2 years after the long-term follow-up assessment. All youths with at least one 7-repeat allele or two 4-repeat alleles who also had data for *5HTT* ($N = 337$) were included in the analyses. We provide here a brief description of subject recruitment and enrollment, intervention implementation and fidelity, and data collection procedures; these procedures are described extensively in earlier reports on SAAF's efficacy (Brody et al., 2004; Brody, Murry, Gerrard et al., 2006; Brody, Murry, Kogan et al., 2006).

Participants

Participants in the SAAF trial included 667 African American families who resided in rural Georgia. From each family, a youth who was 11 years old when recruited and the youth's primary caregiver, typically the biological mother, provided data. Each family was paid \$100 after each of the assessments.

The sample eligible for the present study included the 350 families randomly assigned to receive the SAAF intervention and the 291 randomly assigned to the control condition who completed the posttest; families assigned to SAAF were oversampled. Because only the 4-repeat and 7-repeat alleles are well characterized in terms of biological effects, only participants ($N = 340$) with these alleles were included in the analyses. Three additional participants were excluded because their data for *5HTT* could not be characterized unambiguously.

Intervention Implementation and Fidelity

The SAAF prevention program consisted of seven consecutive meetings held at community facilities, with separate parent and youth skill-building curricula and a family curriculum. Each meeting included separate, concurrent training sessions for parents and youths followed by a joint parent-youth session during which the families practiced the skills they learned in their separate sessions. Concurrent and family sessions each lasted 1 hour; thus, parents and youths received 14 hours of prevention training. Additional details regarding the intervention can be found in Brody, Murry, Gerrard et al. (2006).

Procedure

To enhance rapport and cultural understanding, African American students and community members served as field researchers to collect pretest, posttest, and long-term follow-up data. During each wave of data collection, the field researchers, who were blind to the families' group assignments, made one home visit lasting 2 hours to each family. Well-established procedures for the study of the development of risk behaviors were used, including computer-based interviewing, matching of researchers and participants by ethnicity, and reassurance concerning confidentiality of the data (Murry & Brody, 2004). Each interview was conducted privately, with no other family members present or able to overhear the conversation. Youths provided data on their own past-month substance use and caregivers provided data on their own intervention-targeted parenting practices. Genetic data were obtained from youths and caregivers using procedures developed in partnership with rural African American community members (Brody et al., 2004).

Two years after the long-term follow-up (4.5 years after the pretest), we attempted to contact the study families to obtain youths' and parents' DNA from saliva samples. Of the original

sample assessed at posttest, 88% ($n = 566$) of the families were located and one or more members of the family agreed to provide a DNA sample. This resulted in successful genotyping at *DRD4* for 448 youths and 436 primary caregivers. Among youths, 171 carried at least one *DRD4* 7-repeat allele and 169 carried two 4-repeat alleles. Among caregivers, 175 carried at least one *DRD4* 7-repeat allele and 169 carried two 4-repeat alleles. Participants with other infrequent alleles (e.g. 2,2; 2,3; 2,4) were excluded ($n = 108$); most of these individuals carried the 4-repeat allele in combination with a rare variant. Three additional participants were excluded because they could not be adequately characterized with regard to *5HTT*.

Informed consent forms were completed at all data collection points. Caregivers consented to their own and the youths' participation in the study, and youths assented to their own participation.

Measures

The measures were selected for their relevance to the evaluation of the preventive intervention program. They were derived from previous research, which included focus group meetings and pilot testing followed by construct validation of the instruments (Brody et al., 2004). Parenting data were collected from caregivers and substance use data from youths.

Demographics—Youth age and gender, maternal age, maternal employment, and monthly income were recorded. Each caregiver reported the number of children and adults living in the home and her marital/significant relationship status. No association between demographic variables and *DRD4* genotype emerged (see Table 1). In addition, no significant correlations emerged between demographic variables and past-month substance use or baseline intervention-targeted parenting behavior; accordingly demographic variables were not included as covariates in the analyses.

Caregivers' reports of intervention-targeted parenting behavior—Intervention-targeted parenting was assessed at each wave through caregiver self-report using an instrument developed in previous research with rural African American families (Brody & Ge, 2001; Ge, Brody, Conger, Simons, & Murry, 2002). The scale is composed of 43 items tapping five key intervention-targeted domains: child management, nurturant-involved parenting, racial socialization, sexual communication, and clear expectations about substance use. Sample items include, "I keep from blowing up at my child when I punish him/her. I remind my child that very few children his/her age get involved with alcohol or drugs." Cronbach's alpha for the scale was .83.

Past-month substance use—Consistent with other work (Johnston, O'Malley, & Bachman, 2000), youths were asked about frequency of substance use in the past month. The items were, "During the past month, how many times have you: drunk beer, wine, wine coolers, whiskey, gin, or other liquor; had three or more drinks of alcohol at one time; smoked marijuana?" Responses to these three items were summed to form a past-month substance use index, a procedure that is consistent with prior research (Brody & Ge, 2001; Hays, Widaman, DiMatteo, & Stacy, 1987; Needle, Su, & Lavee, 1989; Newcomb & Bentler, 1988; Wills et al., 2007). Cronbach's alpha for the scale was .65.

Genotyping—Youths' DNA was obtained using Oragene™ DNA kits (Genetek; Calgary, Alberta, Canada). Youths rinsed their mouths with tap water, 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 youth as described by Lichter et al. (1993). Genotype at the 5-HTTLPR was determined for each sample as described previously

(Bradley, Dodelzon, Sandhu, & Philibert, 2005). Genotype was then called by two individuals blind to study hypotheses or other information about the participants.

Results

Descriptive Statistics

At the first data collection session, youths' mean age was 11.65 years ($SD = 0.35$) and caregivers' mean age was 36.7 years ($SD = 7.1$). Of the mothers, 32.6% were married and living with their husbands, 2.4% were married but separated, 7.1% were cohabiting with a significant other, 25.2% were in a significant relationship but not cohabiting, and 32.7% were not in a significant relationship. Mean household monthly income was \$2,082. Although 75% of the mothers were employed outside the home, 44.5% of the families lived below federal poverty standards and another 29.6% lived within 150% of the poverty threshold.

As expected, prevalence rates for drug use at pretest, when the youths were 11 years old, were low: 15% for any alcohol use, 1.2% for binge drinking, and 0.0% for marijuana use. Lifetime prevalence rates increased over time; at the long-term follow-up, when the youths were 14 years old, lifetime rates were 39.2% for alcohol use, 4.6% for binge drinking, and 4.3% for marijuana use. Likewise, average past-month substance use was low at pretest ($M = .07$, $SD = .42$) but increased across waves to long-term follow-up ($M = .17$, $SD = .73$). These rates for African American youths are consistent with data from other studies (Johnston, O'Malley, Bachman, & Schulenberg, 2007).

Hardy-Weinberg equilibrium was examined for youth genotype distribution; $\chi^2 = .91$, $p = 0.34$. The non-significant chi-square indicates that the distribution of heterozygotes (4-R with non-4-R) was consistent with the distribution of homozygotes (4-R, 4-R), indicating no differential allele dropout.

Plan of Analysis

We used multilevel modeling (Bryk & Raudenbush, 1992) with HLM 6.08 software to examine the data. Two levels of analysis were conducted. First, there were 337×4 observations, accounting for the repeated measures within individuals. Second, there were 337 individuals. Because the outcome variable of past-month substance use consisted of count data (number of times using substances) with many zeros (non-consumption) and had a sample variance (.69) greater than the sample mean (.32), we conducted nonlinear analysis using a negative binomial regression for this dependent variable. Models examined the impact of youth genotype at both *DRD4* and *5HTT*, intervention condition, and the interaction of each genetic polymorphism with treatment. We used a similar approach to examine effects on intervention-targeted parenting but did not use the negative binomial distribution to model the data because the parenting measure was not composed of count data and did not include any zeroes. In the follow-up analyses to rule out passive effects, we focus only on parent *DRD4*.

Tests of Hypotheses

Effect of youth *DRD4* and SAAF on intervention-targeted parenting—First, we determined whether youth *DRD4* status interacted with condition to produce differential change in parenting behavior as a function of intervention. Using the analytic framework outlined previously, we found a main effect of participation in SAAF ($\gamma_{SAAF} = .89$, $p < 0.01$), but no significant effect for youth genotype for either *DRD4* ($\gamma_g = 0.08$, ns) or *5HTT* ($\gamma_g = 0.14$, ns), and no interaction of intervention with youth genotype at *DRD4* ($\gamma_{S \times G} = -0.38$, ns). A significant interaction of youth genotype at *5HTT* with SAAF ($\gamma_{S \times G} = 1.65$, $p < .05$) emerged. The results are summarized in Table 2. As can be seen, SAAF produced expected gains in

intervention-targeted parenting behavior for all participants regardless of youth genotype at *DRD4*.

Effect of youth *DRD4* and SAAF on past-month substance use—We examined the effect of youth *DRD4* status on susceptibility to the intervention. Analysis of the unconditional model showed that the largest share of the variance in past-month substance use was within individuals (21%), reinforcing the importance of within- individual variation. As Table 2 shows, a significant overall treatment effect on past-month substance use emerged ($\gamma_{SAAF} = -.20, p < 0.05$). Main effects for both the *DRD4* 7-repeat allele ($\gamma_g = .16, p < .10$) and the short *5HTT* allele ($\gamma_g = .20, p < .10$) approached significance. A significant gene $\times$ intervention interaction emerged for *DRD4* ($\gamma_{S \times G} = -1.04, p < .01$) but not for *5HTT* ($\gamma_{S \times G} = -0.18, NS$). To explicate the significant interaction with *DRD4*, we plotted the means across time for past-month substance use for each of the four subgroups. As Figure 1 shows, SAAF reduced growth in past-month substance use only for youths with one or two copies of the 7-repeat allele for *DRD4*. The effect size of 0.26 for the interaction of genotype with intervention accounted for 2% of the explained variance in outcomes. Within-group analyses indicated a significant protective effect of SAAF only for those with the 7-repeat allele of *DRD4* ($\gamma_{SAAF} = -.69, p < 0.01$). For those with the 4-repeat allele, the effect was in the opposite direction ($\gamma_{SAAF} = .33, p < 0.01$).

Ruling out passive genetic effects—Because, in most cases, a biological relationship existed between the youth and caregiver, it is possible that the observed interaction effect between youth genotype and intervention actually resulted from the effect of parent genotype youth response to treatment. Confirming the potential for such an effect, a chi-square analysis indicated a significant association between caregiver and youth genotypes ($\chi^2_{(1)} = 45.25, p < .01, N = 258$). The number of parent-youth dyads with similar *DRD4* status was 91 for those with 4-repeat alleles only and 92 for those with at least one 7-repeat allele; the numbers, however, were significantly lower for those in the off diagonals: 36 for those in which only the parent, and 39 for those in which only the youth, had a 7-repeat allele.

Effect of caregiver *DRD4* on youth substance use—To rule out caregiver genotype as a source of passive genetic effects in response to intervention, the analysis of change in youth past-month substance use was repeated using caregiver rather than youth genotype as both a main effect and a moderator of intervention effects. Because there was no effect for youth genotype at *5HTT*, parent genotype at *5HTT* was not included in the analysis. All parents who provided genetic material and could be assigned to either the 7-repeat allele or the two 4-repeat allele group were included in the analyses ($N = 344$); the results are presented in Table 3. In this model, the effect of caregiver genotype on youth past-month substance use was not significant as a main effect ($\gamma_g = -.03, NS$) or in interaction with intervention ($\gamma_{S \times G} = -.13, NS$). Thus, youths' own genetic variation at *DRD4* and not genetic similarity to the caregiver was responsible for the observed intervention $\times$ genotype interaction.

Exploratory examination of caregiver *DRD4* on intervention-targeted parenting

—Given the association of *DRD4* with attentional processes, caregiver genotype could be consequential for degree of change in intervention-targeted parenting. To test this possibility, we conducted an exploratory examination of parents' own genotypes as a factor in their response to the intervention. The results are summarized in Table 3. Significant main effects emerged for both participation in SAAF ($\gamma_{SAAF} = .82, p < .05$) and parent genotype ($\gamma_g = -1.10, p < .01$). The interaction of SAAF with parent genotype approached significance ($\gamma_{S \times G} = -1.31, p < .10$). As Figure 1 shows, caregivers with the 7-repeat allele reported less change in intervention-targeted parenting behavior than did caregivers with two copies of the 4-repeat allele. The marginal interaction was driven by the significant impact of SAAF on the slope of

change among parents with 4-repeat alleles ($\gamma_{\text{SAAF}} = 1.40, p < .01$), with no significant effect for parents with a 7-repeat allele ($\gamma_{\text{SAAF}} = .19, \text{NS}$).

Discussion

The results supported the hypotheses that participation in the SAAF prevention program would increase intervention-targeted parenting regardless of youth genotype at *DRD4* and that youths with the *DRD4* 7-repeat allele would be more responsive to the intervention than would youth with two copies of the *DRD4* 4-repeat allele. A main effect of intervention on change in past-month substance use over time emerged; main effects for both *DRD4* and *5HTT* approached significance. As the susceptibility hypothesis (Belsky & Pluess, 2009) and research with toddlers (Bakermans-Kranenburg et al., 2008) suggested, youths with the 7-repeat allele were more responsive than those without it to a parenting-focused intervention. Among youths with the 7-repeat allele, those in the control group increased past-month substance use at a substantially greater rate than did those in SAAF. Conversely, for youths with 4-repeat alleles, no evidence indicated that participation in the intervention reduced age-related increases in past-month substance use. The net result was greater differential change in the predicted direction between intervention and control youth for those with the 7-repeat allele relative to those with two 4-repeat alleles. In the context of the susceptibility hypothesis, the results indicated that SAAF interacted with presence of the 7-repeat polymorphism in *DRD4* to change a potentially deleterious genetic factor into a potentially positive one. It is important to note, however, that the results are based on youth self-reported substance use and are not corroborated by biological tests. In addition, in other exploratory analyses, we found no evidence of similar moderation by *DRD4* for parent-reported delinquency outcomes, suggesting that genetic moderation of the effect of *DRD4* is specific to increases in substance use or that parent report may yield a different pattern of results.

We examined caregiver genotype, and its association with youth genotype was highly significant. Caregiver genotype did not, however, account for the observed susceptibility effect among youth. Interestingly, however, parents carrying the 7-repeat allele showed less change over time in intervention-targeted parenting behavior. Together with the observed susceptibility effect for youth with the 7-repeat allele, this suggests the potential need to craft intervention delivery methods that enhance changes in intervention-targeted parenting for caregivers carrying the 7-repeat allele, particularly when they are caregivers for youth with the same allele. In addition, the results suggest that the explication of the caregiver genotype $\times$ child genotype $\times$ intervention interaction may prove interesting and important when larger samples permit adequately powered examination of higher-order effects.

The differential impact of SAAF was not attributable to different ending points for intervention-targeted parenting as a function of youth genotype at *DRD4*. Rather, the SAAF program was designed to equalize the parenting environments for youth with differing genotypes. Caregivers showed equivalent changes in response to intervention regardless of youth genotype at *DRD4* and showed significantly greater changes in SAAF than in the control condition. Accordingly, the effects support a susceptibility hypotheses and not simply a genetic risk explanation for the impact of the 7-repeat allele of *DRD4*. This finding has the potential to change understanding of the nature of vulnerability to early substance use and strengthens the argument for provision of preventive programming focused on substance use outcomes.

The effect of genotype on outcomes of interest may have been missed had we not examined the susceptibility hypothesis. Belsky and Pluess (2009) point to the susceptibility hypothesis as a compelling account of the manner in which genetic variability may exert its influence, one that does not require genotypic main effects and fits with broader evolutionary theorizing (Belsky, 1997, 2005). In the case of *DRD4*, increased susceptibility to variation in parenting

behavior and decreased responsiveness of the dopaminergic reward pathway may have been particularly adaptive in contexts of deprivation (Campbell & Eisenberg, 2007), which characterized much of human evolutionary history. At a minimum, some advantages of the *DRD4* 7-repeat allele seem likely because it appears to have arisen as a rare variant that increased substantially through positive selection over the past 40,000-50,000 years (Ding et al., 2002).

Finally, it is important to note that, in the current study, we found effects of the SAAF intervention on escalation of risk behavior whereas in prior work we have focused primarily on its initiation (e.g. Brody, Murry, Gerrard et al., 2006; Brody, Beach, Philibert, Chen, & Murry, 2009). The emergence of different genetic moderators for initiation (e.g. *5HTT*) than for escalation (e.g. *DRD4*) of risk behavior across adolescence may inform developmental models of youth substance use. In particular, the distinct phases of substance use initiation, substance use escalation, and substance use maintenance into young adulthood may constitute separable processes with differing genetic substrates.

The current results are also of interest from a practical perspective in light of studies of pharmacotherapy for ADHD that have focused on the role of the *DRD4* genotype in predicting response to treatment. These studies have found preferential response to treatment among youth with the 4-repeat genotype compared with those carrying the 7-repeat allele (e.g. Cheon, Kim, & Cho, 2007; Hamarman, Fossella, Ulger, Brimacombe, & Dermody, 2004). Combined with the present results and those of Bakermans-Kranenburg et al. (2008), this suggests the intriguing possibility of differential effectiveness of various intervention modalities for some problems in childhood and early adolescence as a function of genotype or associated behavioral characteristics (i.e., pharmacological intervention for some allelic variants or phenotypes and psychosocial interventions for others). Although additional research is necessary, youths with the 7-repeat allele may be particularly responsive to parenting-based intervention whereas those with two 4-repeat alleles are not. This may provide opportunities to enhance universal, community-based interventions by making special efforts to recruit those most likely to show the greatest response. Likewise, the current results suggest that caregivers of some youth with 7-repeat alleles may be less likely to change their parenting styles if they also carry the 7-repeat allele of *DRD4*. If so, this may constitute an important opportunity to enhance treatment for a subgroup that is particularly likely to show positive effects: parent-child dyads concordant for the 7-repeat allele.

Acknowledgments

This research was supported by Awards Numbers 5R01AA012768-08 and 3R01AA012768-08S1 from the National Institute on Alcohol Abuse and Alcoholism, and by Awards Numbers 5R01DA01923-04S1 and 1P30DA027827 from the National Institute on Drug Abuse. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, or the National Institutes of Health.

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Figure 1.
Youth genotype at *DRD4* moderates SAAF effects on past-month substance use and parent genotype at *DRD4* influences SAAF effects on intervention-targeted parenting

Table 1

Equivalence of Demographic Variables for Groups Based on Youth Genotype

Descriptive Measure	<i>DRD4</i> , youths					
	Any 7-repeat allele (<i>n</i> = 169)			Two 4-repeat alleles (<i>n</i> = 168)		
	<i>M</i>	<i>SD</i>	%	<i>M</i>	<i>SD</i>	<i>t</i> -value
Per capita income, \$/mo.	524.23	388.48		497.23	354.61	0.66
Female, youths			51.5			-0.27
Single-mother-headed families			62.7			1.15
Baseline intervention-targeted parenting	66.81	8.73		66.33	10.12	0.46
Baseline past month substance use	0.10	0.53		0.05	0.29	1.14

Table 2

Effect of SAAF Intervention, Child DRD4 or 5HTT Genotype, and Intervention $\times$ Genotype Interaction on Growth in Youth Past Month Substance Use, and Intervention Targeted Parenting ($N = 337$)

	Past-Month Substance Use			Intervention-Targeted Parenting		
	Model 1a	Model 1b	Model 1c	Model 2a	Model 2b	Model 2c
Intercept	-1.89	-1.91**	-1.92**	67.38*	67.38**	67.38*
Slope	0.21**	0.19**	-0.22*	1.04*	0.41	0.68 [†]
SAAF		-0.20*	0.44**		0.89**	0.41
DRD4, youth (1 = 7-repeat alleles)		0.16 [†]	0.80**		0.08	0.36
5HTTLPR, youth (1 = s allele)		0.20 [†]	0.26*		0.14	-0.87 [†]
Two-way interaction						
SAAF $\times$ DRD4, youth			-1.04**			-0.38
SAAF $\times$ 5HTTLPR, youth			-0.18			1.65*

Note. Population-average model with robust standard errors; past-month substance use used negative binomial HLM regression model.

[†] $p < .10$.

* $p < .05$.

** $p < .01$.

Effect of SAAF Intervention, Parent DRD4 Genotype, and Intervention $\times$ Genotype Interaction on Growth in Youth Past Month Substance Use, and Intervention Targeted Parenting ($N = 344$)

Table 3

	Past-Month Substance Use			Intervention-Targeted Parenting		
	Model 1a	Model 1b	Model 1c	Model 2a	Model 2b	Model 2c
Intercept	-1.93**	-1.94**	-1.94**	66.89**	66.89**	66.89**
Slope	0.17*	0.31**	0.28*	1.09**	1.19**	0.79*
SAAF		-0.22†	-0.15		0.82*	1.50**
DRD4, parent (1 = 7-repeat alleles)		-0.03	0.04		-1.10**	-0.35
Two-way interaction						
SAAF $\times$ DRD4, parent			-0.13			-1.31†

Note. Population-average model with robust standard errors; past-month substance use used negative binomial HLM regression model.

† $p < .10$.
* $p < .05$.
** $p < .01$.