

Interactive Association of Dopamine Receptor (*DRD4*) Genotype and ADHD on Alcohol Expectancies in Children

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Positive and negative alcohol expectancies (AEs) are beliefs about the consequences of alcohol use (e.g., happy, sad, lazy) and they predict patterns of adolescent and adult alcohol engagement in clinical and nonclinical samples. However, significantly less is known about predictors of AE in children, despite significant variability in AE early in and across development. To identify temporally ordered risk factors that precede AE, we evaluated the independent and interactive association of the functional 7-repeat polymorphism of the dopamine D₄ receptor (*DRD4*) genotype and attention-deficit/hyperactivity disorder (ADHD) with respect to individual differences in positive-social, negative-arousal, sedated/impaired, and wild/crazy AE in school-age children ($N = 149$) prospectively followed from 6–9 to 8–13 years of age. Controlling for age, sex, and wave, *DRD4* 7+ carriers reported more wild/crazy AE, but *DRD4* was unrelated to the remaining AE domains. ADHD symptoms independently predicted higher negative-arousal, sedated/impaired, and wild/crazy AE, but not positive-social. We also observed a significant interaction in which ADHD symptoms positively predicted wild/crazy AE only in youth with the 7-repeat *DRD4* genotype; the same interaction marginally predicted sedated/impaired AE. No interactive effects were observed for the remaining AE domains. These preliminary results suggest that, among *DRD4* youth, early ADHD symptoms predict that children will expect alcohol to have wild/crazy effects. We consider these results within a developmental framework to better understand pathways to and from youth alcohol problems.

Keywords: *DRD4*, ADHD, alcohol expectancies, children

Alcohol problems and related alcohol-use disorders are prevalent conditions with significant clinical and public health consequences. In the United States, lifetime prevalence estimates ranged from 14.0% to 16.3% and 6.0% to 6.4% for alcohol abuse and alcohol dependence, respectively, and impairment is also typically moderate to severe (Kessler et al., 2005). Further, alcohol problems cause significant economic loss due to crime, social problems, foster care, and related health services (WHO, 2004). In addition to its frequent co-occurrence with other mental health problems, alcohol problems predict violence, accidental injuries, risky behavior (e.g., sexually transmitted disease), and poor health outcomes (e.g., hypertension) (Courtney & Polich, 2009; Hingson, Heeren, & Winter, 2006; Odgers et al., 2008). To facilitate the development of innovative interventions, reliable precursors of alcohol problems, particularly early in development, must be identified. Ultimately, targeted interventions may prevent alcohol

problems, make them more amenable to treatment, and/or minimize their negative sequelae.

One potentially unique expression of alcohol problems is early-onset alcohol use. Early alcohol use has demonstrated predictive validity for later alcohol problems, alcohol-use disorders, and health impairment (Grant & Dawson, 1997; Odgers et al., 2008). Despite being implicated as a potential causal risk factor for alcohol problems and clinically significant outcomes, relatively little is known about precursors of early-onset alcohol use (Donovan & Molina, 2011). One potentially important construct is alcohol expectancies (AEs), individual differences in expectations about the consequences or effects of alcohol consumption (Chartier, Hesselbrock, & Hesselbrock, 2010). Consisting of positive (e.g., arousal, increased sociability) and negative expectations (e.g., mad, sad) about alcohol use, AEs emerge early in development (Noll, Zucker, & Greenberg, 1990) and precede explicit alcohol engagement or experimentation (Johnston, O'Malley, Bachman, & Schulenberg, 2012). Positive AE prospectively predicted increased alcohol consumption in adolescence (Brown, Christiansen, & Goldman, 1987; Chartier et al., 2010), and predicted multiple indicators of problem drinking in young adults beyond other established predictors (e.g., drinking-refusal self-efficacy; Connor et al., 2008). AE predicts alcohol engagement in clinical and nonclinical populations, suggesting that AEs represent a potential common pathway to later alcohol problems (Christiansen, Smith, Roehling, & Goldman, 1989; Young & Oei, 2000). Finally, a controlled intervention significantly reduced youth-positive and -arousing AE and concurrently raised negative AE (Cruz & Dunn, 2003). Thus, by virtue of their predictive validity

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and sensitivity to intervention effects, further understanding of youth AEs is a significant priority for the prevention of later alcohol problems.

Despite evidence that AE is a potential causal risk factor for alcohol engagement and alcohol problems, “there has been relatively little research on antecedents of AE” (Donovan, Molina, & Kelly, 2009; p. 249). That is, individual differences in AE are typically treated as predictors of alcohol outcomes, whereas far less is known about predictors of AE. Moreover, to distinguish simple correlates from potential risk factors for AE, temporally ordered designs are necessary (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001), given that replicated risk factors for AE represent logical targets for intervention. Preliminary work on youth AE has emphasized familial and socialization influences, including parental alcohol use (Molina, Pelham, & Lang, 1997). However, the acquired preparedness model proposed the centrality of trait disinhibition to the development of positive AE, which in turn predicted alcohol use (Smith & Anderson, 2001). In other words, positive AE mediated the association of trait disinhibition and alcohol problems. This model has been substantiated in young adult samples (Anderson, Schweinsburg, Paulus, Brown, & Tapert, 2005), although nonreplications have also been reported, including in children (Anderson, Smith, McCarthy, Fister, Grodin, Boerner, & Hill, 2005). Given that dopamine neurotransmission and frontostriatal circuitry are associated with correlates of disinhibition, including loss aversion (Tom, Fox, Trepel, & Poldrack, 2007), gambling (Chambers, Taylor, & Potenza, 2003), and substance disorders (Volkow, Fowler, Wang, Swanson, & Telang, 2007), functional genetic variants regulating dopamine are plausible candidate genes for AE. Among alcohol-dependent patients, AE partially mediated the association between the A1 allele of the dopamine (D2) receptor gene and alcohol problems, suggesting that AEs were sensitive to genetic influences. In another study, AEs were sensitive to GABA-ergic, but not dopaminergic variants (Young, Lawford, Feeney, Ritchie, & Noble, 2004). A critical limitation of this literature is that studies have been limited exclusively to adults, despite the fact that there are individual differences in AE in childhood. This limitation is problematic given that early alcohol use may reflect *unique* genetic influences (and causal risk factors more generally), relative to later onset alcohol use (Connor et al., 2002). Therefore, future studies consisting of predictions of *youth* AE must be developmentally sensitive (e.g., conducting research on a narrow age band of youth participants prior to alcohol engagement) and genetically informative.

The dopamine D₄ receptor (*DRD4*) gene is located on chromosome 11p15.5 and contains a 48 base-pair, variable-number, tandem-repeat polymorphism in Exon 3. This locus consists of 2 to 11 repeats, although 4 and 7 repeats are the most common. *DRD4* genotypes produce variation in the third cytoplasmic loop of the receptor protein that affects D₄-receptor functioning and mediates signal transduction through changes in intracellular cyclic adenosine monophosphate levels. Broadly, genetic variation at this locus is thought to underlie individual differences in risk taking, reward sensitivity, and perhaps reactivity to both positive and negative environmental experiences. For example, the 7-repeat allele (7+) predicted increased novelty seeking in adults (Benjamin et al., 1996) and nonhuman primates (Bailey, Breidenthal, Jorgensen, McCracken, & Fairbanks, 2007), as well as sexual promiscuity and sexual infidelity (Garcia et al., 2010), although meta-analytic findings suggested 7+ and adult-personality

“approach” traits were only modestly associated (Munafò et al., 2003). These associations are biologically plausible given that *DRD4* 7+ differentially activated ventral striatum during a reward task (Forbes et al., 2009), as well as orbitofrontal cortex and striatum in response to alcohol cues (Filbey et al., 2008). Therefore, we conceptualized the functional *DRD4* 7+ polymorphism within the larger framework of the acquired preparedness model because it may represent an “upstream” causal influence by which dopamine neurotransmission influences reward sensitivity, reward-based learning, and disinhibition. In other words, whereas the acquired preparedness model *begins* with disinhibition (Smith & Anderson, 2001), *DRD4* may extend this causal model by testing etiological influences *on* disinhibition.

Genetic influences on complex phenotypes are likely to include interactive effects with other constructs; thus, developmental models of AE should explicitly consider both independent and transactional effects. One factor that may alter predictions of AE from *DRD4* 7+ is attention-deficit/hyperactivity disorder (ADHD). Defined by extreme and impairing levels of inattention and/or hyperactivity, ADHD may be related to youth AE for several reasons. First, there is meta-analytic evidence that childhood ADHD prospectively predicts adolescent and adult alcohol problems, including alcohol abuse and dependence (Lee, Humphreys, Flory, Liu, & Glass, 2011; Charach, Yeung, Climans, & Lillie, 2011). Second, dopamine dysregulation, deficient inhibitory control and executive functioning, as well as sensitivity to reward are central to theories of ADHD and alcohol problems (Nigg, 2001; Smith & Anderson, 2001). A recent study of young adults found that the combination of elevated ADHD and positive AEs was particularly predictive of alcohol problems (e.g., social dysfunction; Dattilo, Murphy, Van Eck, & Flory, 2013), suggesting that interactive effects with respect to ADHD and AE are plausible. Similarly, in a sample of young adult drinkers, whereas risk taking and poor behavioral inhibition were positively associated with alcohol consumption, deficient attentional inhibition was *uniquely* associated with heavy drinking in adults with ADHD (Weafer, Milich, & Fillmore, 2011); also, adults with ADHD demonstrated more alcohol-induced, impaired inhibitory control than did non-ADHD controls (Weafer, Fillmore, & Milich, 2009). However, we know of no published study of the independent and interactive association between childhood ADHD and the *DRD4* 7+ genotype with respect to individual differences in youth AE. Moreover, given that alcohol use predicts altered neurocognitive performance (e.g., executive functioning; Squeglia, Spadoni, Infante, Myers, & Tapert, 2009), temporally ordered measures of childhood ADHD are valuable for strengthening the inference that ADHD symptoms are risk factors for AE, rather than simple correlates of AE and/or potential reflections of their effects on alcohol problems. Taken together, these studies suggest that ADHD sufferers designate a unique group with respect to pathways to and from alcohol problems and related phenotypes.

By virtue of their predictive validity, AE is a potentially important precursor of alcohol problems for both clinical and nonclinical populations (Connor et al., 2008). Despite being implicated as a potential causal risk factor for early-onset alcohol use and alcohol problems, virtually nothing is known about risk factors for individual differences in AE (Donovan et al., 2009). Given the centrality of deficient dopamine neurotransmission and disinhibition

to theories of ADHD and alcohol problems, we examined the independent and interactive association of the *DRD4* genotype and childhood ADHD with respect to emergent AE (i.e., positive-social, negative-sedative, sedated/impaired, wild/crazy). Based on 149 ethnically diverse children with and without *DSM-IV* ADHD followed prospectively from 6–9 years old to 8–13 years old, we tested whether the youth *DRD4* 7+ genotype and initial ADHD independently and interactively predicted emergent individual differences in positive-social, negative-arousal, sedated/impaired, and wild/crazy AE at a 2-year follow-up. Given that ADHD and AE are temporally ordered, the current study is well-positioned to differentiate correlates versus risk factors for youth AE, and to identify potentially important targets for intervention.

Method

Participants

At baseline (i.e., Wave 1), participants were 219 children (68% boys) with ($n = 119$) and without ($n = 110$) *DSM-IV* ADHD. Children were 6–9 years old ($M = 7.89$, $SD = 1.19$) and 49% of the sample was Caucasian, 8% African American, 9% Hispanic, 3% Asian, 22% mixed, and 10% other or missing (see Table 1 for demographic characteristics). Participants were recruited using presentations to self-help groups for ADHD, advertisements mailed to local elementary schools, pediatric offices, clinical service providers, and some referrals from mental health clinics. English fluency was required for parents and children. Exclusion criteria for all participants consisted of a full-scale IQ < 70 or pervasive developmental, seizure, or neurological disorders that prevented full participation in the study. Characteristics of participants at Wave 1 have been described elsewhere (Humphreys, Aguirre, & Lee, 2012; Lee, Falk, & Aguirre, 2012). Examiners obtained written consent from all parents and written assent from all children. Children were reminded that participation was optional, and that they could stop at any time. All procedures were approved by the institutional review board.

Procedures

At Wave 1, families who contacted the study completed a telephone screener to determine their eligibility based on the inclusion and exclusion criteria listed above. Eligible families were then invited to the research laboratory for in-person assessments. Following signed parental consent and child assent, clinical psychology graduate students or bachelor's-level extensively trained staff separately assessed children and parents. All interviewers were initially blind to the child's diagnostic status, although the blindness could not be guaranteed, given the amount of information gathered about the child. Approximately 85% of children were assessed during their laboratory visits without medication. Parents were asked to rate each child based on his or her unmedicated behavior.

Approximately 2 years after their original evaluations, families were invited back to the laboratory to participate in a follow-up study (i.e., Wave 2; ages 8–13), which consisted of highly parallel procedures to Wave 1 (e.g., structured diagnostic interviews), but also included the assessment of children's AEs using the *Memory-Model Based Expectancy Questionnaire (MMBEQ; Dunn, 1999)*. Overall, at Wave 2, 91% of the total Wave-1 sample was ascertained to have no significant demographic (i.e., age, sex) or clinical (i.e., number of oppositional defiant disorder or conduct disorder symptoms) differences between the overall Wave 2 sample and the participants who did not participate at Wave 2. However, for the current study, AE data were available for 149 participants.

Measures

Diagnostic Interview Schedule for Children (4th ed.; DISC-IV). At Wave 1 and Wave 2, we administered the computerized *DISC-IV* (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) to each participant's parent using graduate students and advanced undergraduates who had completed intensive assessment training. This fully structured interview probes required symptom levels, duration/persistence, age of onset, and functional impairment. The total number of ADHD symptoms at each wave was used in these analyses. Test-retest reliability for ADHD from

Table 1
Demographic Characteristics of the Sample Based on Wave-1 ADHD Diagnostic Status

Variable	ADHD ($n = 119$); Mean (SD)	No ADHD ($n = 110$); Mean (SD)	F or χ^2
Age at Wave 1	7.77 (1.16)	8.01 (1.22)	2.27
Sex (% male)	74%	62%	3.87*
Race (% White)	51%	53%	0.13
<i>DRD4</i> genotype (% any 7)	36%	37%	0.85
DISC ADHD symptoms, Wave 1	12.28 (3.20)	3.11 (2.87)	522.39***
DBD ADHD symptoms, Wave 1	30.56 (10.00)	10.42 (8.91)	250.22***
DISC ADHD symptoms, Wave 2	10.34 (4.57)	2.95 (3.60)	158.83***
DBD ADHD symptoms, Wave 2	25.57 (11.97)	9.30 (9.73)	105.69***
Positive-social AE	18.64 (8.02)	20.38 (8.35)	1.63
Negative-arousal AE	12.78 (5.38)	11.94 (4.28)	1.04
Sedated/impaired AE	11.96 (4.50)	11.89 (3.41)	0.01
Wild/crazy AE	10.65 (2.94)	10.02 (2.98)	1.62

Note. *DRD4* = dopamine D_4 receptor; DISC = Diagnostic Interview Schedule for Children; DBD = Disruptive Behavior Disorder rating scale; AE = alcohol expectancies.

* $p < .05$. *** $p < .001$.

the DISC ranged from .51 and .64 in the *DSM-IV* field trials (Lahey et al., 1994) and diagnostic designations from the DISC showed predictive validity in other studies of children with versus without ADHD (Lee, Lahey, Owens, & Hinshaw, 2008).

Disruptive Behavior Disorder rating scale (DBD). At Wave 1 and Wave 2, parents completed the DBD (Pelham, Gnagy, Green-slade, & Milich, 1992), the 45-item rating scale of *DSM-IV* child ADHD symptoms. Ratings ranged from 0 for *not at all* to 3 for *very much*, resulting in total ADHD symptom counts. This measure has excellent psychometric properties and is widely considered an evidence-based assessment measure of ADHD and disruptive behavior disorders (Pelham, Fabiano, & Massetti, 2005). We used the total number of ADHD symptoms.

AEs. At Wave 2, children were interviewed using the 41-item *MMBEQ* (Dunn, 1999; Dunn & Goldman, 1996). Children were first read the definition of a single AE word (e.g., talkative, cool, sleepy) and then reported how often people experienced that word following alcohol consumption. With the help of a graphic anchor (i.e., rectangular boxes differentiated by varying levels of being “filled”), children rated their expectancies according to a 4-point scale (i.e., *never, sometimes, usually, always*). The reliability of the *MMBEQ* has been established across development, with coefficient alphas of .76 for 2nd–5th graders, .81 for 3rd, 6th, 9th, and 12th graders, and .83 for college undergraduates (Dunn & Goldman, 1996, 1998). Scoring reflected four separable expectancy factors: positive-social (e.g., happy, fun), negative-arousal (e.g., mad, sad), sedated/impaired (e.g., sleepy, stupid), and wild/crazy (e.g., goofy, hyper). Cronbach’s alphas for the subscales were adequate to good (positive-social: .82, negative-arousal: .79, sedated/impaired: .70, wild/crazy: .77). Although the precise age range at which AEs peak is unknown (see Miller, Smith, & Goldman, 1990 and Donovan, Molina, & Kelly, 2009 for divergent reports), we contend that the age range of the participants at Wave 2 represent a unique period in development given that only seven children (less than 5% of the sample) endorsed alcohol use in the past 6 months greater than a sip. Thus, the vast majority of the sample is alcohol naïve.

DRD4 genotype. DNA was extracted from saliva using Genotek Oragene Self-Collection (DNA Genotek, Inc., Ottawa, CA). Genomic DNA was isolated from buccal cells using standard methods. The 48-base pair element in the third exon was determined in two separate polymerase chain reaction (PCR) amplifications. The distribution was as follows: 2/2 ($n = 2$), 2/3 ($n = 1$), 2/4 ($n = 23$), 2/7 ($n = 6$), 2/8 ($n = 1$), 3/4 ($n = 10$), 3/7 ($n = 4$), 4/4 ($n = 78$), 4/5 ($n = 2$), 4/6 ($n = 4$), 4/7 ($n = 46$), 4/8 ($n = 3$), 7/7 ($n = 8$), and 7/8 ($n = 2$). *DRD4* genotypes were in Hardy–Weinberg equilibrium (Fisher’s exact test, $p = .91$). Population stratification is a threat to the internal validity of genetic association studies. However, given that race/ethnicity was unrelated to *DRD4* ($\chi^2 = .09$, $p = .76$), a necessary condition for population stratification (Hutchison, Stallings, McGeary, & Bryan, 2004), it is unlikely that the effects reported herein are spurious.

Data Analysis

We used linear mixed modeling (LMM) in SPSS (Version 20) to examine the independent association of *DRD4* genotype, the total number of Wave 1 and Wave 2 ADHD symptoms, and their interaction (i.e., *DRD4* \times ADHD) with respect to individual dif-

ferences in each of the four AE domains (i.e., positive-social, negative-arousal, sedated/impaired, wild/crazy). LMM is appropriate for nested data given that it creates a two-level hierarchical model with repeated data (i.e., ADHD symptoms from both dimensions across two time points) within individuals and flexibly accommodates missing data. A dummy variable was created for *DRD4* (i.e., one or more 7+ alleles vs. individuals without this allele, 7–). Given that *DRD4* was unrelated to ADHD diagnostic status and the total number of ADHD symptoms (chi-square = .25, $p = .62$, $r = -.04$, $p = .62$, respectively), (see Table 2), *DRD4* and ADHD were interpreted as independent predictors.

Separate LMMs were created for each AE domain to estimate the independent and interactive association between *DRD4* and ADHD. ADHD symptoms were based on inattention and hyperactivity across Wave 1 and Wave 2. To capitalize on the multiple measures of ADHD, we used LMM to estimate time-varying predictions of ADHD measured from the DISC-IV at Wave 1 and Wave 2 (i.e., Wave 1 inattention and hyperactivity plus Wave 2 inattention and hyperactivity). This process was identically reconstructed in separate models consisting of ADHD from the DBD rating scale. Each model controlled for the effects of wave of assessment, sex, and age, and specified fixed effects for all variables. The potential differential interaction between ADHD and AE based on wave of data collection was examined for all outcomes, and removed from the model following a nonsignificant interaction ($p > .10$).

Results

Association of *DRD4* and ADHD With Positive-Social AEs

Controlling for wave of assessment, age, and sex, ADHD symptoms from the DISC, $F(1, 489.00) = 2.67$, $p = .10$, and *DRD4* genotype, $F(1, 495.96) = 1.31$, $p = .25$, were unrelated to positive-social AEs. The *DRD4* \times ADHD symptom (from the DISC interaction was also nonsignificant, $F(1, 493.43) = 0.18$, $p = .68$). Similarly, based on the DBD scale, neither *DRD4* genotype, $F(1, 488.00) = 1.80$, $p = .18$, nor DBD ADHD symptoms, $F(1, 480.62) = 0.66$, $p = .42$, significantly predicted positive-social AE. Finally, the *DRD4* \times ADHD (from the DBD) interaction was unrelated to positive-social AE, $F(1, 484.49) = 0.003$, $p = .96$. Time did not significantly moderate the association of *DRD4* or ADHD with positive AE.

Association of *DRD4* and ADHD With Negative-Arousal AEs

We observed a significant main effect of the total number of ADHD symptoms from the DISC, $F(1, 489.50) = 9.41$, $p = .002$,

Table 2
DRD4 Genotype by ADHD Diagnosis at Wave 1

Diagnosis	<i>DRD4</i> 7+ ($n = 66$)	<i>DRD4</i> 7– ($n = 124$)	χ^2
ADHD ($n = 94$)	47% ($n = 31$)	51% ($n = 63$)	0.25 _{ns}
No ADHD ($n = 96$)	53% ($n = 35$)	49% ($n = 61$)	

Note. *DRD4* = dopamine D₄ receptor.

and a marginal association of *DRD4* genotype, $F(1, 495.94) = 3.02, p = .08$, with negative-arousal AE, again controlling for wave of assessment, age, and sex. Specifically, the number of ADHD symptoms from the DISC was positively associated with negative AE (est. = 0.22, 0.07), and the *DRD4* 7- group had marginally lower negative AE than the 7+ group (12.19, 0.03, vs. 12.99, 0.38). The *DRD4* × DISC ADHD-Symptoms interaction marginally incremented predictions of negative-arousal AE, $F(1, 483.75) = 3.23, p = .07$. We then reproduced the same model but used the number of ADHD symptoms from the DBD rating scale. Once again, there was a significant main effect of ADHD symptoms, $F(1, 479.33) = 9.57, p = .002$, and a marginal effect for *DRD4* genotype, $F(1, 487.94) = 3.39, p = .066$. The *DRD4* 7- group reported lower negative AE than the 7+ group (12.17, 0.30, vs. 13.02, 0.38), and negative AE increased with more DBD ADHD symptoms (est. = 0.09, 0.03). The *DRD4* × ADHD interaction was unrelated to negative-arousal AE, $F(1, 483.57) = 0.04, p = .85$. Time did not significantly moderate the prediction of negative AE from *DRD4* and ADHD.

Association of *DRD4* and ADHD With Sedated/Impaired AEs

Neither *DRD4* genotype, $F(1, 496.00) = 0.03, p = .87$, DISC ADHD symptoms, $F(1, 489.80) = 1.89, p = .17$, nor their interaction, $F(1, 493.98) = 0.15, p = .70$, significantly predicted sedated/impaired AE. However, based on ADHD symptoms from the DBD, we observed a significant main effect, $F(1, 480.09) = 9.00, p = .003$, where ADHD positively predicted sedated/impaired AE (est. = 0.07, 0.02). There was no significant effect of *DRD4* genotype, $F(1, 487.90) = 0.05, p = .83$, however. The *DRD4* × ADHD (from the DBD) interaction was marginally significant, $F(1, 483.75) = 3.23, p = .07$. Because detecting significant interactions in nonexperimental designs is difficult (McClelland & Judd, 1993), we probed the interaction in an exploratory spirit. Whereas ADHD symptoms on the DBD were unrelated to sedative AE in the *DRD4* 7- group (est. = 0.04, 0.03, $p = .23$), they positively predicted sedative AE in the *DRD4* 7+ group (est. = 0.15, 0.04, $p < .001$; see Figure 1). Time did not significantly moderate the prediction of sedated/impaired AE from *DRD4* and ADHD.

Association of *DRD4* and ADHD With Wild/Crazy AEs

For wild/crazy AE, there were significant main effects for *DRD4* genotype, $F(1, 491.96) = 14.88, p < .001$, and DISC ADHD symptoms, $F(1, 484.67) = 8.89, p = .003$. The *DRD4* 7+ group had greater expectancies that alcohol would have wilder/crazier effects than *DRD4* 7- youth (11.08, 0.23, vs. 9.98, 0.18) and wild/crazy expectancies increased linearly with the number of DISC ADHD symptoms (est. = 0.13, 0.04). A significant *DRD4* × ADHD interaction was also found, $F(1, 489.27) = 3.94, p = .048$, such that ADHD symptoms on the DISC were unrelated to wild/crazy AE in the *DRD4* 7- group, but ADHD symptoms robustly predicted wild/crazy AE in the *DRD4* 7+ group (see Figure 2). These results were replicated with significant main effects for *DRD4*, $F(1, 483.96) = 15.16, p < .001$, and DBD ADHD symptoms, $F(1, 475.62) = 14.97, p < .001$. Once again, the ADHD ×

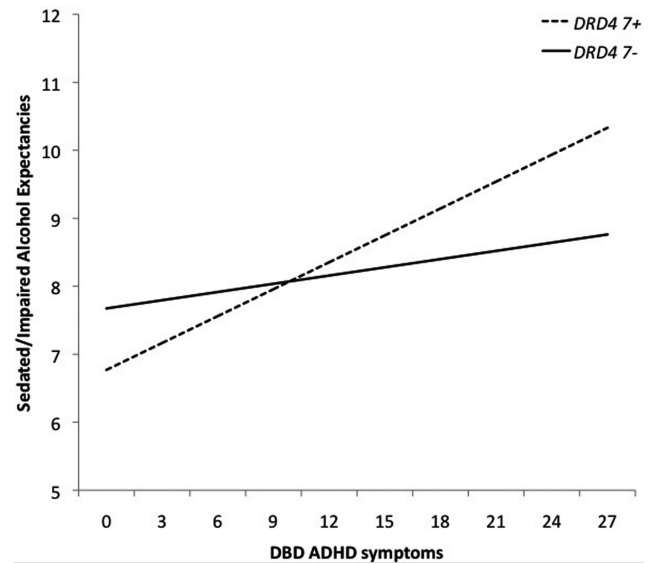


Figure 1. Interaction of Youth *DRD4* × DISC ADHD symptoms on sedated/impaired AEs.

DRD4 interaction was significant, $F(1, 479.27) = 10.55, p < .001$, where ADHD symptoms on the DBD were unrelated to wild/crazy AE in the 7- group, but positively predicted wild/crazy AE in the 7+ group (see Figure 3). Time did not significantly moderate the prediction of wild/crazy from *DRD4* and ADHD.

DRD4 × ADHD × Sex Interaction: Prediction of AEs

Given sex differences in ADHD (Barkley, 2006), we conducted exploratory analyses of sex as a moderator of the *DRD4* × ADHD interaction described above. The *DRD4* × ADHD × Sex interaction was unrelated to positive, sedative, and wild/crazy AE. However, with respect to negative AE, there was a significant *DRD4* effect, $F(1, 162.34) = 4.09, p = .045$, where *DRD4* 7+ girls had significantly more negative AE than *DRD4* 7- girls, (12.66, 0.57, vs. 12.10, 0.53); there was also a significant effect of ADHD symptoms according to the DISC, $F(1, 155.99) = 4.34, p = .039$. We also observed a significant *DRD4* × DISC ADHD × Sex interaction, $F(1, 157.83) = 4.60, p = .034$. Specifically, among girls with the *DRD4* 7- genotype, DISC ADHD symptoms predicted more negative AE. The patterns of association were highly similar when ADHD was estimated from the DBD rating scale. No significant *DRD4* × ADHD interaction was detected for boys, however, for any AE domain using both the DBD and DISC.

Discussion

Developmental perspectives on alcohol problems are recognized (Brown et al., 2008), but many studies have focused on narrow developmental periods (e.g., adolescence) and explicit alcohol use and alcohol problems. Although childhood AEs predict adolescent and adult alcohol engagement, relatively little is known about factors contributing to the development of AEs in children (Donovan et al., 2009). In particular, prospective longitudinal designs are necessary to temporally disentangle simple correlates of AE from genuine risk factors for AE that represent logical targets for

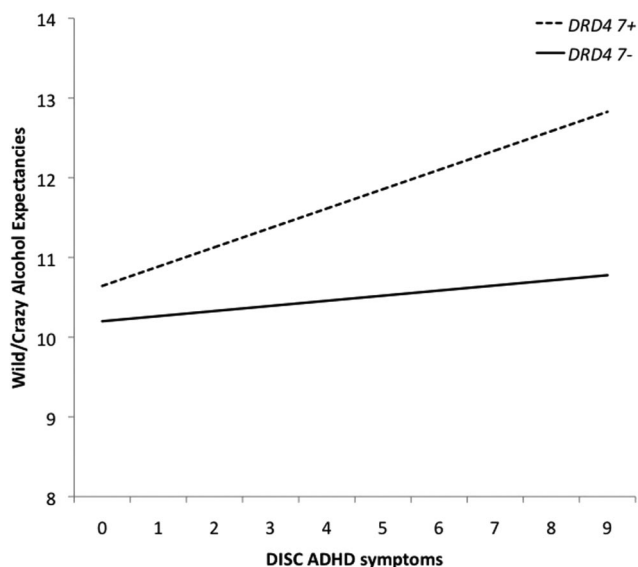


Figure 2. Interaction of Youth *DRD4* × DISC ADHD symptoms on wild/crazy AEs.

intervention. Controlling for age, sex, and study wave, we examined the independent and interactive association of youth *DRD4* genotype and ADHD symptoms with respect to emergent positive-social, negative-arousal, sedated/impaired, and wild/crazy AEs in 6–9 year-old children followed prospectively to 8–13 years of age. First, *DRD4* 7+ youth reported higher expectations that alcohol would have wild/crazy effects, but no other AE domains were sensitive to a main effect of *DRD4*. Second, ADHD positively predicted more negative-arousal, sedated/impaired, and wild/crazy AEs. Finally, an interaction was detected such that ADHD symptoms positively predicted the wild/crazy AE, but only among *DRD4* 7+ youth. These preliminary findings suggest that *DRD4* 7+ status and ADHD are independent risk factors for individual differences in multiple AE domains; the interaction of *DRD4* 7+ and ADHD symptoms specifically predicted children's expectations that alcohol would have wild/crazy effects.

Although genetic association studies of AE are rare (Connor et al., 2008; Young et al., 2004), dopamine neurotransmission is plausibly related to AE for several reasons. In this study, *DRD4* 7+ carriers, independent of ADHD symptoms and demographic factors, specifically reported more wild/crazy AEs. The wild/crazy AE may be part of a broad phenotypic constellation, including reward sensitivity and risk taking, reflecting the consequence of genetic variation regulating dopamine. Functional dopamine polymorphisms, including *DRD4* 7+, differentially activated reward circuitry (Stice, Yokum, Burger, Epstein, & Smolen, 2012) and uniquely accounted for nearly 11% of variance in ventral striatum reactivity (Nikolova, Ferrell, Manuck, & Hariri, 2011). *DRD4* 7+ status may also underlie exposure to putative environmental correlates of AE (e.g., parental alcohol consumption; Molina et al., 1997) through evocative, active, and passive gene–environment correlation (Jaffee & Price, 2007). Alternatively, wild/crazy AEs may disproportionately reflect executive and/or inhibitory processes rather than reward per se. Because *DRD4* 7+ is associated with executive dysfunction (Froehlich et al., 2007), wild/crazy

AEs may reflect deficits in attention, working memory, and planning. However, a recent twin study found that AEs predicted alcohol use largely through shared environmental influences (controlling for genetic influences; Samek, Keyes, Iacono, & McGue, 2013). Finally, AEs in youth reflect a 2 × 2 dimension of good–bad and arousal–sedation, which is sensitive to developmental influences. For example, whereas identical descriptions of “wild and dangerous” AEs were endorsed across 2nd- and 5th-grade children, the association of those terms differed dramatically. Whereas the former group associated wild and dangerous negatively, the latter group identified them favorably (Dunn & Goldman, 1996). Thus, studies must separately examine positive and negative AEs, given that they may be differentially sensitive to reward-based learning, emotion regulation, and inhibitory control, all of which are changing dynamically with development (Malter, Cohen, Tottenham, & Casey, 2013). Overall, there is a critical shortage of integrative explanatory models underlying the development of childhood positive and negative AE, despite their centrality to emergent alcohol engagement.

The positive association in this study of childhood ADHD symptoms with AE (e.g., wild/crazy), independent of *DRD4* 7+ genotype, may reflect several important processes. First, ADHD predictions of AE may result from shared or correlated risk factors for childhood ADHD and AEs, including parental alcohol use and disinhibition (Molina et al., 1997; Smith & Anderson, 2001). Next, two independent meta-analyses have established the predictive validity of early ADHD with respect to alcohol outcomes (e.g., abuse/dependence; Lee et al., 2011; Charach et al., 2011). Future research must elucidate the mechanisms underlying the prediction of alcohol use from early ADHD, given that risk-factor research does not inherently identify risk processes. A key exception to this: Molina et al. (2012) reported that ADHD symptom persistence, related functional impairment, and parental monitoring mediated predictions of escalating alcohol use. Although speculative, it may be that positive AE similarly mediates and/or moderates predic-

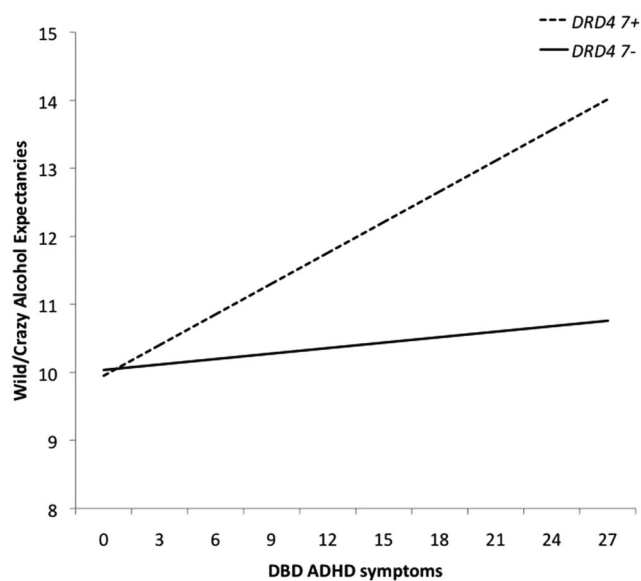


Figure 3. Interaction of Youth *DRD4* × DBD ADHD symptoms on wild/crazy AEs.

tions of alcohol problems from ADHD. In one study, lower positive AE partially mediated the inverse association of high parental respect and alcohol use (Shih, Miles, Tucker, Zhou, & D'Amico, 2012), although this was evident only in specific cultural groups. Also, although impulsivity (a defining feature of ADHD) predicted alcohol quantity, frequency, and binge drinking in college students, this association was evident among those with average and elevated positive AEs only (Carlson & Johnson, 2012). Finally, although negative AEs may protect against alcohol use, there is also evidence that negative AEs positively predicted alcohol problems (Mann, Chassin, & Sher, 1987; McMahon, Jones, & O'Donnell, 1994). Furthermore, among individuals with *high* impulsivity and poor inhibitory control (e.g., ADHD), negative AEs predicted *more* alcohol consumption (Finn, Bobova, Wehner, Fargo, & Rickert, 2005). These findings collectively suggest the need to replicate and extend the association of childhood ADHD with separate measures of positive and negative AEs and their ultimate associations with alcohol use.

Perhaps the most interesting finding in the current study was the positive prediction of the wild/crazy AE from childhood ADHD symptoms, but only among *DRD4 7+* individuals. Although childhood ADHD was measured dimensionally, rather than diagnostically, these findings substantiate previous reports that *DRD4 7+* status predicted a more persistent and stable pattern of ADHD among children and adults with ADHD (Biederman et al., 2009). Similarly, among children and adolescents with ADHD, the *DRD4 7+* genotype differentially predicted individual differences in response to treatment with methylphenidate (McGough et al., 2009). These studies suggest that the considerable *within-group* heterogeneity frequently associated with ADHD, ranging from comorbidity (e.g., conduct problems) to long-term outcomes (e.g., alcohol- and substance-use disorders), may be usefully prosecuted based on genetic markers. For example, Caspi et al. (2008) reported that antisocial behavior, a frequent concomitant feature of ADHD, was partly the result of genetic heterogeneity within ADHD. By extension, perhaps the sensitivity of wild/crazy AEs to the interactive effect of *DRD4 7+* and elevated ADHD symptoms reflects an empirically distinct subgroup and/or pathway to important alcohol phenotypes. However, this is speculative until genetically informative, prospective designs mature into adolescence with careful ascertainment of ADHD, AE, and alcohol engagement (e.g., age of onset, frequency, amount). Finally, given that there are multiple pathways to and from adaptive and negative outcomes (e.g., alcohol problems; Cicchetti & Rogosch, 1996), we contend that post hoc mediational tests secondary to significant interactions underlying AE be investigated. That is, if the interaction of *DRD4 7+* status and childhood ADHD symptoms is replicated with respect to wild/crazy AEs, we await follow-up studies of plausible mediational constructs *within* that subgroup (i.e., elevated ADHD symptoms and *DRD4 7+*) to more fully identify the development of these specific cognitive expectations.

We also emphasize that the development of positive-social, negative-arousal, sedated/impaired, and wild/crazy AEs in children remains poorly understood (Donovan, Molina, & Kelly, 2009). Not only are there likely to be multiple risk factors for AEs in childhood, the consequences of individual differences in AE are likely to be similarly diverse (i.e., multifinality; Cicchetti & Rogosch, 1996). We contend that developmentally sensitive studies are necessary given that AE may function differentially across

development. This is particularly true with respect to developmental aspects of alcohol use, including the progression from use to heavy use and to eventual alcohol problems, as well as reciprocal associations with other important influences. For example, a cross-lagged study of college students found that AEs predicted the frequency of alcohol use, but alcohol use did not affect AEs; however, alcohol use did affect perceived norms around alcohol use (Wardell & Read, 2013). Further underscoring the potential that AEs are sensitive to developmental influences, the positive AE for sociability was central to alcohol use in 18–24 year-olds, whereas expectations around the tension-reducing properties of alcohol were more predictive of adult alcohol use (Pabst, Kraus, Piontek, Mueller, & Demmel, 2013). Collectively, these studies reinforced the notion that prospective longitudinal studies are necessary to fully understand the multiple ways in which AEs are likely to influence and develop patterns of alcohol engagement that are empirically distinct, and are also highly sensitive to development (e.g., early-onset alcohol use; Odgers et al., 2008).

Although this study is strengthened by its prospective design and relatively large and ethnically diverse sample, we noted several important limitations. First, linkages between ADHD symptoms and AE were combined across inattention and hyperactivity dimensions, potentially masking differential patterns of association with respect to alcohol and substance outcomes (Molina & Pelham, 2003). Second, parental alcohol use is an important aspect of AEs (Molina et al., 1997), but these data are not available in the current study. Third, ADHD frequently co-occurs with other disruptive behavior, mood, and anxiety disorders. Thus, the specificity of AE predictions from ADHD must be made cautiously. Third, less than 5% ($n = 7$) of the sample self-reported recent alcohol use greater than a sip. Although detailed information on frequency and quantity was not queried, we cannot be certain that these findings completely generalize to other alcohol-naïve samples. Fourth, unmeasured interactions with other *DRD4* variants (e.g., linkage disequilibrium) and other environmental factors (e.g., parental alcohol use) were not investigated, once again reinforcing the preliminary nature of these results; related, candidate gene studies of individual-difference traits often do not replicate. We readily acknowledge that the associations reported herein must be interpreted cautiously, that they necessitate cross-validation in independent samples, and that they may reflect atypical effect sizes, given the statistical significance in a small study according to the standards of genetic epidemiology.

Based on an ethnically diverse sample of 6–9-year-old children with and without ADHD followed prospectively to 8–13 years of age, we observed a reliable positive association of childhood ADHD symptoms with multiple AE dimensions; *DRD4 7+* genotype also independently and positively predicted wild/crazy AE. Moreover, we detected a significant interaction in which ADHD symptoms predicted elevated levels of expectations that alcohol would have wild/crazy effects, but this association was limited to individuals with the *DRD4 7+* genotype. Although AEs predict individual differences in alcohol engagement in adults and related special populations (e.g., college students), there remains a substantial gap in knowledge about AE in children generally and their precursors more specifically. This preliminary study suggests that genetic variation-regulation dopamine neurotransmission and ADHD are two potential sources of influence for child AEs. Future studies of emergent AEs in children must prioritize developmental

theories and related methods, including the centrality of disinhibition (Smith & Anderson, 2001), to more fully understand their association with the onset, progression, and escalation of alcohol use and alcohol problems.

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