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Associations of the dopamine D4 receptor gene VNTR polymorphism with drug use in adolescent psychiatric inpatients☆

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Abstract

Background: The VNTR polymorphism in the Dopamine D4 receptor gene (*DRD4*) has been associated with differential urge for substances across multiple methodologies ranging from neuroimaging to assessment in the natural environment. It is unclear whether the *DRD4* gene is a marker for an underlying propensity for greater urge or whether the *DRD4* gene differentially moderates the neuroadaptive effects of extended substance use on urge. Examination of the *DRD4* in an adolescent sample may provide evidence of a mechanism of this putative relationship.
Method: Data from a subset of 77 participants in a larger assessment study characterized adolescents for substance-related behaviors by *DRD4* genotype. The psychiatrically admitted adolescents were genotyped for the variable number of tandem repeats polymorphism in the *DRD4* gene ($L \geq 7$ [$n=25$], $S=<7$ [$n=52$]). Associations of the *DRD4* with scores on the SASSI, and ADI were examined as well as selected individual items thought to be most related to the intermediate phenotype of urge.
Results: The *DRD4* gene was not associated with any DSM-IV substance misuse diagnostic classification. Individual items related to urge were also nonsignificantly related to *DRD4* status. Carriers of the long variant of the *DRD4* polymorphism were more likely to have used hard drugs within the previous 6 months and scored higher on the self-medication subscale of the ADI compared to short variant homozygotes.
Discussion: Preliminary results provide little evidence for the *DRD4* VNTR polymorphism to be related to urge-related phenomena in hospitalized adolescents on a psychiatric inpatient unit. The association of the *DRD4* gene with hard drug use may support literature linking this gene to impulsivity. Subscale findings may suggest a role of negative affect in previous *DRD4* urge findings.

Keywords: DRD4; Adolescents; Substance misuse

1. Introduction

Alcohol and drug misuse is estimated to cost $246 billion annually and is responsible for premature mortality, morbidity, crime, traffic accidents, and liver disease (Harwood et al., 1999). The etiology of substance dependence is not entirely clear, but heritability estimates suggest that genetic factors account for 40–80% of the variance associated with this diagnosis (e.g., Kendler et al., 2005; Enoch and Goldman, 2001), with cannabis potentially less heritable (41%) and tobacco the most heritable (79%) substance. Identification of the genes contributing to substance dependence would allow for treatment efforts to be targeted on a biological basis as well as allow for more thorough gene by environment analyses (Heath et al., 2002). To that end, genes in several biological systems have been investigated in relation to substance dependence (e.g., dopamine, serotonin, GABA, glutamate, etc.), albeit with mixed results.

Although it is possible that various genes may be differentially associated with the likelihood of developing alcohol versus other drug dependence (e.g., polymorphisms in the alcohol metabolizing enzymes may impact likelihood of alcohol dependence but not tobacco dependence), dopaminergic

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function underlies all drugs of abuse (Kalivas and Volkow, 2005). Accordingly, variation in dopaminergic genes may impact dependence rates across multiple substances.

In addition to examining genes in systems identified as central to dependency for many substances, use of carefully specified phenotypes is critical. For example, the diagnostic criteria for alcohol dependence do not distinguish between persons who begin to drink alcohol problematically for different reasons (e.g., modulation of negative affect for purposes of self-medication, reactivity to cues, or drinking to avoid withdrawal). This heterogeneity may result in poorly specified phenotypic data and may account for inconsistency in results of studies designed to associate specific genes to alcohol dependence. For example, a gene variant that predicts ability to manage negative affect may influence risk for developing alcohol dependence, but this relationship might be obscured in a study of alcohol dependent persons with multiple etiologies. The use of intermediate phenotypes on the pathway between genes and diagnosis is an approach that allows far greater power to identify specific genetic risk and protective factors (Gottesman and Gould, 2003). Useful intermediate phenotypes range from those proximal to gene effects to the more distal measures of behavior associated with alcohol dependence.

Although cellular research on the potential functional consequences of the VNTR polymorphism of the dopamine D4 receptor gene (*DRD4*) has yielded mixed results (e.g., some evidence for functional differences in 7 repeat receptors compared with 2 or 4-repeat receptors (Asghari et al., 1995) and some evidence suggesting differences between the 2-repeat and the 4 and 7 repeat receptors (Czermak et al., 2006)), clinical research across multiple intermediate phenotypes and substances suggest a consistent pattern of results. Functional neuroimaging of recently detoxified alcoholics suggests that participants who carry the 7 or more repeats in the *DRD4* VNTR (*DRD4L*) show increased activation to alcohol-related stimuli in the anterior cingulate and associated prefrontal cortical areas compared with participants who carry only shorter variants (*DRD4S*) (Smolka et al., 2005, manuscript under review). Laboratory studies of reactivity to associated cues have shown greater subjective urges reported by *DRD4L* participants compared to *DRD4S* participants in smoking and alcohol studies (Hutchison et al., 2002a,b; McGeary et al., 2001), a study of heroin addicts (Shao et al., 2006), and even a study related to food craving (Sobik et al., 2005). Pharmacogenetic studies suggest the differential subjective urge for alcohol may be attenuated by a D4 receptor antagonist relative to active placebo (Hutchison et al., 2003). A behavior economics study found that *DRD4L* participants valued alcohol more highly than *DRD4S* participants (Mackillop et al., under review). Finally, the examination of urges in the natural environment through the use of palm-top computers suggests that *DRD4L* carriers report greater urges to drink alcohol than *DRD4S* participants (McGeary et al., 2004; Monti et al., 2004).

Although this pattern of results across multiple studies suggest that the *DRD4* VNTR polymorphism is consistently related to urge phenomenology across substances of abuse, it is not clear if the long variant is associated with an underlying liability to greater desire or if the *DRD4* gene moderates the neuroadaptive changes that occur with extended use. A direct test of these possibilities is difficult as it requires either administering drugs or alcohol to adolescents prior to their becoming regular users (presenting obvious ethical problems) or attempting to assess responses to drug or alcohol use early in the experimentation stage. The cue reactivity studies described above cannot inform this question due to their reliance on associative learning over repeated exposures.

Despite these ethical and practical difficulties, examination of the *DRD4* VNTR polymorphism in adolescents may have utility. Although adolescents may have a history of alcohol and other drug use, it is likely that this history will be shorter than the histories of the participants in the studies described above. Positive associations of the *DRD4* gene and alcohol and drug use behaviors would suggest that either relatively shorter consumption histories still manifest the expected differences or that indeed the *DRD4* VNTR is related to some underlying vulnerability. Moreover, positive results might suggest the possibility of matching pharmacological treatments to genetic background as has been suggested in the adult literature (Oslin et al., 2003). Previous research has demonstrated the potential utility of naltrexone in teens (Deas et al., 2005) but has not examined potential genetic moderators. Accordingly, in this study we examine a subset of adolescents from a larger assessment study that characterizes alcohol and drug use in a sample of youth at high risk for the development of alcohol and drug dependence, seriously mentally ill adolescents hospitalized on a psychiatric inpatient unit.

2. Method

2.1. Participants

One hundred and one adolescents hospitalized on an acute adolescent psychiatric inpatient unit and their parents/guardians were asked to participate in this study on a voluntary basis. The large majority of adolescents were hospitalized due to suicidal thoughts or behavior. Adolescents were recruited from the major child psychiatric hospital in the state which accepts Medicaid, uninsured, and privately insured youth. Of those approached for participation, 77 (76%) were successfully recruited. Adolescents ranged in age from 13 to 18 years, with a mean age of 14.9 years (SD = 1.3). Participants were 71% female and were 88% White, 1.3% African American, 1.3% Asian, 3.9% Native American and 5.2% other ethnicity and approximately 14% of the sample was of Hispanic/Latino ethnicity.

2.2. Procedure

Adolescents admitted to an adolescent psychiatric inpatient unit over the course of a two year period as part of a larger NIMH funded (MH065885) assessment study were eligible for participation. Adolescents met inclusion criteria for participation if they: (1) were English speaking; (2) adolescent assent and parental consent were provided; (3) had a Verbal IQ estimate $\geq$ 70; and (4) the adolescent met criteria for a mood,

anxiety, or disruptive behavior disorder. Exclusion criteria included current psychosis or full placement in DCYF custody, as documented in the inpatient admission materials.

Adolescents and their parents/guardians were approached for recruitment by a trained bachelor level research assistant after family meetings or during family visits on the adolescent inpatient unit. If parental consent and adolescent assent were provided, the family was enrolled in this assessment study. Adolescents and their parent/guardian completed the assessments while the adolescent was hospitalized on the inpatient unit. The research assistant administered the assessment battery with the exception of the diagnostic interview which was administered by masters and doctoral level clinicians who completed training in this interview provided by CES. Parent and adolescent assessments were conducted separately. The parent version of the diagnostic interview and assessments was administered in a two hour session. The child version of the diagnostic interview and intelligence test was administered in a separate two hour session.

All adolescents received four movie tickets and their parent/guardian received a $50 money order for their participation. A feedback form summarizing responses to clinical measures (with the exception of substance related information) was placed in each adolescent's inpatient file upon completion of the full assessment battery so that it could be reviewed by the adolescent's inpatient treatment team to aid in treatment and discharge planning. Substance related information was not shared because teens' self-reported substance use has been shown to be accurate and reliable under conditions of confidentiality (Needle et al., 1983). This study was approved by the affiliated University and Hospital Institutional Review Boards.

2.3. Measures

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) is a widely used semi-structured diagnostic interview that provides a reliable and valid measurement of DSM-IV psychopathology in children and adolescents. Interrater agreement for scoring screens and diagnoses is high (range: 93% to 100%). Test–retest reliability and kappa coefficients are in the excellent range for diagnoses of major depressive, bipolar, generalized anxiety, conduct, and oppositional defiant disorders (.77 to 1.00) and in the good range for other diagnoses (.63 to .67) (Kaufman et al., 1997). Only the *current* mood, anxiety, disruptive behavior, alcohol/substance use, and eating disorder sections were administered to both the adolescent and parent.

A best-estimate clinical consensus procedure, which has been shown to yield good to excellent reliability (Klein et al., 1994, 2001), was used to resolve discrepancies across parent and adolescent report. The clinical consensus team included the second author and the masters and doctoral level clinical interviewers. In decision making, more weight was given to youth report of internalizing and alcohol/substance symptoms, and to parent report of externalizing symptoms, to maximize detection of psychopathology (Cantwell et al., 1997).

Kaufman Brief Intelligence Test (K-BIT; Kaufman and Kaufman, 1990) provides a brief estimate of intelligence for individuals 4–90 years of age. It contains 2 subtests, Vocabulary and Matrices, which provide estimated Verbal IQ and Performance IQ, respectively. Split half reliability and test–retest reliability estimates for the subtests are acceptable and the IQ scores have demonstrated adequate convergent validity with other measures of verbal intelligence and achievement (Spreen and Strauss, 1998). Only the Vocabulary subtests were administered in the present study as a screening tool.

Adolescent Drinking Index (ADI). The ADI (Harrell and Wirtz, 1989a) is a 24 item self-report questionnaire that provides an index of severity of problem drinking among adolescents referred for emotional or behavioral disorders. Adolescents are asked to indicate the degree to which statements related to drinking apply to them using a 3-point Likert scale. The latter 14 questions ask the adolescent to indicate the frequency with which they have experienced various problem drinking behaviors using a 4-point Likert scale. Higher scores reflect increasing levels of alcohol-related problem behaviors. The ADI contains a total severity index, as well as two subscales based on patterns associated with problem drinking. A self-medication drinking subscale assesses the degree to which drinking is used to alter mood. A rebelliousness subscale is an indicator of the degree to which aggressive, rebellious behavior is related to drinking. Adequate internal consistency and validity have been demonstrated. A cutoff score of 16 or greater suggests a clinical need for alcohol treatment services (Harrell and Wirtz, 1989b). In the present study, the ADI total score, the self-medication subscale and a one item reflective of subjective urge for alcohol (item #1 "I often think about drinking") were examined.

Personal Experiences Screening Questionnaire (PESQ; Winters, 1992) is a 40-item instrument designed to assess adolescent drug use problem severity, drug use history, and related psychosocial problems. Norms have been established for normative samples, juvenile offenders, and drug abusing populations. Excellent psychometric properties and diagnostic sensitivity have been reported (Winters, 1992). Only Part III of this questionnaire, which assesses frequency of substance use, was administered. Participants were asked to indicate frequency of alcohol, marijuana, and other drugs use over the course of the prior 6 months, using a 7-point Likert scale ranging from "never" to "40+ times".

Substance Abuse Subtle Screening Inventory Adolescent Version 2 (SASSI A-2; Miller and Lazowski, 2001) contains 72 true–false items and 28 multiple choice questions that assess frequency of substance misuse, problems associated with substance misuse, attitudes toward substance misuse, and related contextual factors. This instrument contains 9 subscales: face valid alcohol scale, face valid other drug scale, family-friends risk scale, attitudes scale, symptoms scale, obvious attributes scale, supplemental addiction measure, subtle attributes scale, and defensiveness scale. This instrument was developed and cross validated with 1244 adolescents and has excellent psychometric properties (Miller and Lazowski, 2001). In the present study, the total score from the face valid alcohol

scale, total score from the face valid other drug scale, and one individual item from the face valid alcohol scale reflective of a subjective urge for alcohol (item #4 "had more to drink that you intended to") were examined.

2.4. Candidate genotyping

After obtaining secondary consent for DNA collection for genetic testing, DNA collection was performed at the final visit in the parent study. Genomic DNA was collected and isolated from buccal swabs using published procedures (Freeman et al., 1997; Lench et al., 1988). The 48 basepair VNTR in exon 3 of the *DRD4* gene was assayed using modifications of previously reported methods (Sander et al., 1997). Participants were grouped by number of repeats in the VNTR by conventional methods with *DRD4* long (*DRD4L*) comprised of those with at least one copy of the 7 or greater repeats, and those in the *DRD4* short group (*DRD4S*) being those who had neither copy being greater than 6 repeats (Hutchison et al., 2002a,b, 2003). All genotyping was performed by technicians blinded to participant characteristics. Quality control procedures for genotyping included separate genotype calls by two independent lab technicians, and rerunning ten percent (randomly determined) of samples to check for reliability. Successful calls were made for all samples and there was full agreement in genotyping calls made by both raters.

2.4.1. Data analysis methods

All analyses used the SPSS statistical package. Variables were first checked for distributional assumptions. As the PESQ frequency items and the individual items of interest selected from the SASSI and ADI were highly skewed, we dichotomized these variables into "never used" versus "any use." Chi square analyses were utilized to test for associations of the *DRD4* gene (*DRD4L* vs. *DRD4S*) for each variable of interest. The ADI total score, ADI self-medication subscale, SASSI face valid alcohol scale, and SASSI face valid other drug scale were analyzed as continuous variables. *T*-tests were used to examine associations between the *DRD4* gene and these continuous variables.

2.5. Results

2.5.1. Participant characteristics

The 77 participants were characterized for alcohol and drug use using the frequency items from the PESQ. Fifty-two percent of participants reported alcohol use in the last six months, with 39% of the total sample reporting that they had consumed five or more drinks when drinking. Forty-eight percent reported marijuana use, and 23% reported use of hard drugs. Thirty-one percent reported that they had used alcohol and drugs at the same time in the last six months. On the ADI, twenty-six percent of participants met the criteria for clinically significant alcohol problems (ADI score ≥ 16). Single items from the ADI and SASSI that were identified a priori as potentially more direct measures of urge-related phenomenon revealed that 39% of the sample endorsed the item "I often think about drinking" (ADI, item #1) and 30% answered that they had "had more to drink than they intended to" (SASSI, FVA scale, item #4).

Table 1
Means, standard deviations, and *t* values for *DRD4S* and *DRD4L* participants

Measure	*DRD4S* *M* (SD)	*n*	*DRD4L* M (SD)	*n*	t
ADI total score	8.6 (10.8)	52	10.4 (15.6)	25	.599
ADI self-medication subscale[a]	2.7 (2.1)	14	6.3 (1.9)	6	3.70**
SASSI face valid alcohol total	3.2 (5.2)	52	3.5 (6.6)	25	.208
SASSI face valid other drugs total	6.5 (9.1)	52	10.1(13.9)	25	1.36

Note. ADI=Adolescent Drinking Index; SASSI=Substance Abuse Subtle Screening Inventory Adolescent Version 2. [a]Only the 20 participants who reported clinically significant alcohol problems on the ADI were included in this analysis. **$p>.01$.

Chi-square analyses used to test for associations between *DRD4* status and the aforementioned dichotomous variables yielded a significant relationship between *DRD4* status and hard drug use in the past 6 months (χ^2 (1, $N=77$)=8.79, $p<.01$, $\eta^2=.09$). Only 14% of *DRD4S* participants had used hard drugs within the last 6 months whereas 61% of *DRD4L* carriers had. To partially address concerns of population stratification, a re-analysis of only participants who self-identified themselves as "White" was conducted with similar results (χ^2 (1, $N=68$)= 6.33, $p<.05$, $\eta^2=.09$). No other relationships between *DRD4* status and alcohol/substance use variables were significant.

The mean ADI score for the sample was 9.2 (SD=12.5), the mean SASSI face valid alcohol total score was 3.3 (SD=5.6), and the mean SASSI face valid other drugs total score was 7.6 (SD=10.9). A *t*-test revealed a significant effect of *DRD4* status on the self medication subscale of the ADI among youth with clinically significant alcohol problems, $t(20)=3.70$, $p<.001$, $r=.67$ with *DRD4L* carriers reporting a mean of 6.3 (SD=1.9) compared with DRD4S homozygotes level of 2.7 (SD=2.1). A re-analysis of "White" participants (see above) yielded similar results $t(15)=2.98$, $p<.01$, $r=.63$. No other differences were found across these variables (see Table 1).

Tests for Hardy Weinberg Equilibrium (HWE) were performed using the Exact Test of Hardy–Weinberg Proportion for Multiple Alleles (Guo and Thompson, 1992). Proportions did not vary from HWE ($p>.05$).

3. Discussion

The first aim of this study was to investigate whether the *DRD4* VNTR polymorphism was associated with substance use behavior in a group of seriously mentally ill adolescents. The second aim was to examine the relationship of this polymorphism with single items and subscales thought to be related to the intermediate phenotype of urge for use of substances. Despite low power to detect effects and a psychiatrically heterogeneous sample, two findings were of significance. The first finding was that *DRD4* status was associated with use of hard drugs within the previous 6 months with carriers of 7 or more repeats more likely to have used hard drugs compared to those who were homozygous for fewer than 7 repeats. However, this was not found to be true for alcohol or marijuana use. The second was that *DRD4* status was associated with self medication sub-scores

on the ADI with *DRD4* long carriers endorsing more items that are consistent with the self medication hypothesis of drug use as compared to *DRD4S* homozygotes.

These results provide limited support for the hypothesis that the associations of the *DRD4* gene with urge in studies of heavy substance users may be due to an underlying propensity to experience greater urges. This study utilized a sample of convenience and is by no means an authoritative examination of this possibility but the lack of evidence for binge drinking or increased frequency of substance use raises the possibility that *DRD4* findings in more drug-experienced populations may be more related to neuroadaptive changes associated with extended drug exposure or some third variable (e.g., impulsivity). The relationship of *DRD4* to recent hard drug use may be due to greater impulsivity (e.g., Frank et al., 2004) as impulsive adolescents may be more likely to seek out and use hard drugs, but the results for the *DRD4* and self medication may suggest an alternative explanation (see also Zalsman et al., 2004). Urge to use substances may be elicited not only by exposure to priming doses and associated cues but also with negative affect induction procedures (Sinha and O'Malley, 1999). Indeed, negative affect may be the predominant determinant of urge in users experiencing active withdrawal states (e.g., Zinser et al., 1992). Since no measures of negative affect are included in previously published studies of the *DRD4* gene and urge, it is possible that negative affect associated with the urge state is underlying the association. Use of lab-based studies of cue reactivity and mood (e.g., Rubonis et al., 1994) that include candidate genes could be used in an economical fashion to examine this possibility in adolescents (see also Curtin et al., 2005).

This study has several limitations including: low power to detect effects, only indirect assessments of urge for substances (i.e., single items related to thinking about drinking and of drinking more than intended that may be a behavioral manifestation of increased urge), and a reliance on retrospective self report. The standard disclaimers for genetic association studies regarding population stratification and linkage disequilibrium also apply (e.g., Hutchison et al., 2004). Nevertheless, this preliminary study provides additional evidence of a relationship between *DRD4* status and negative affect and suggests the need for further characterization of the role of the *DRD4* gene in adolescent samples. However, no study with adolescents has assessed cue reactivity while examining candidate genes, thus a gene by environment lab illustration might be indicated as the next step.

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