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Dopamine Receptor Gene D4 Polymorphisms and Early Sexual Onset: Gender and Environmental Moderation in a Sample of African American Youth

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Abstract

Purpose—Early sexual onset and its consequences disproportionately affect African American youth, particularly male youth. The dopamine receptor D4 gene, *DRD4*, has been linked to sexual activity and other forms of appetitive behavior, particularly for male youth and in combination with environmental factors [gene $\times$ environment ($G \times E$) effects]. The differential susceptibility perspective suggests that *DRD4* may exert this effect by amplifying the effects of both positive and negative environments. We hypothesized that *DRD4* status would amplify the influence of

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both positive and negative neighborhood environments on early sexual onset among male, but not female, African Americans.

Methods—Hypotheses were tested with self-report, biospecimen, and census data from 5 prospective studies of male and female African American youth in rural Georgia communities, $N = 1677$. Early sexual onset was defined as intercourse before age 14.

Results—No significant $G \times E$ findings emerged for female youth. Male youth with a *DRD4*-long allele were more likely than those with 2 *DRD4*-short alleles to report early sexual onset in negative community environments and not to report early onset in positive community environments.

Conclusions—Dopaminergic regulation of adolescent sexual behaviors may operate differently by gender. *DRD4* operated as an environmental amplification, rather than a vulnerability, factor.

Keywords

adolescent behavior; databases as topic; gene-environment interaction; minority groups; receptors; dopamine D4; sexual behavior

Definitions of “early” sexual onset vary, with most researchers defining early sexual debut as participation in sexual intercourse prior to age 14 or 15 [1]. Regardless of the criterion used, early sexual onset poses a significant threat to youth’s health and well-being, forecasting high numbers of sexual partners, older sexual partners, inconsistent condom use, teenage pregnancy, and acquisition of sexually transmitted infections [1]. African American youth, particularly male youth, are more likely than are their peers in other racial/ethnic groups to report sexual debut at younger ages [2]. By age 13, African American youth are more than twice as likely to have experienced sexual intercourse than are Caucasian, Latino, and Asian youth [3]. Early sexual onset places youth at risk for a number of health hazards, including multiple sexual partnerships, recent sexual intercourse under the influence of alcohol or drugs, and teenage pregnancy [1].

The biological underpinnings of early sexual onset are not fully understood. Researchers recognize, however, that the dopaminergic system plays a key role [4]. Dopamine is released in response to rewarding stimuli, including sexual activity, food, and stimulant drugs. Reward signals initiate a phasic burst of mid-brain dopamine neurons, which elicit positive emotional states and organize the learning of cues that predict future rewards [4]. In an influential review, Spears [4] proposed a “dopamine insensitivity” model of youth risk behavior and attention problems. According to this perspective, youth who experience a *reduced* incentive value from stimuli are more likely than those who do not to pursue new appetitive reinforcers. In contrast, individuals who are particularly sensitive to rewards need less of any particular stimulus to initiate a response. This perspective has increased focus on the potential of factors associated with a blunted dopamine response to predict risky or sensation-seeking behavior [5].

Variation in the gene coding for the dopamine receptor D4, *DRD4*, is one factor that may affect youth risk behavior by down-regulating dopaminergic activity [5]. *DRD4* is a variable nucleotide tandem repeat (VNTR) polymorphism composed of 16 amino acid (48 bp) repeat

polymorphisms that ranges from 2 to 11 repeats. The variations with 2, 3, 4, and 7 repeats account for about 98% of allelic variability [6]. Long (*DRD4-L*) alleles, those with 7 to 11 repeats, code less efficiently at the levels of transcription, translation, and second messenger generation than do short (*DRD4-S*) alleles, those with 6 or fewer repeats. The 7-repeat allele in particular has been associated with blunted dopamine response, reward-related ventral striatum reactivity, sensation seeking, and impulsivity [7]. Variation in *DRD4* also has been linked to a range of sexual behavior characteristics including infidelity, sexual arousal, and numbers of partners [8–10].

The literature associating *DRD4* with sexual behavior, however, is inconsistent. Miller et al. [11] found no relation between *DRD4* 48 bp and age at first sex in a group of married couples, whereas Gou and Tong [12] found that genotypes including alleles with 3 or more repeats, with the exception of the 7-repeat allele, were associated with earlier first sex among a general United States population sample. This inconsistency in effects suggests that other factors could moderate behavioral expression of the *DRD4* gene. Gender and social environmental factors are hypothesized to play key roles in modulating *DRD4* expression and its influence on early-onset sexual behavior.

Studies indicate that problems associated with impulsivity and sensation seeking, including early onset of sexual intercourse, affect male youth more than they affect female youth [13]. Sex differences also may exist in dopamine regulation during adolescent development. In animal models, males experience a more pronounced reduction in receptor density during adolescence than do females as a consequence of normal developmental remodeling of the dopaminergic system [5]. In research with humans, men have shown greater dopamine release in the ventral striatum than have women in response to an amphetamine challenge paradigm [14]. Finally, studies document the influence of treatments that increase or decrease brain dopaminergic activity on changes in male sexual behavior. In contrast, no similar conclusions can be drawn from the available studies on female sexual behavior [15]. In general, few studies explicitly test sex differences in *DRD4* effects. Among the few studies we identified that examined sex differences, *DRD4* had effects on male, but not female, youth in novelty seeking [16] and externalizing problems [17]; no effects for youth of either sex emerged for alcohol craving [18]. No gender effects were detected in a meta-analysis investigating links between *DRD4-L* alleles and novelty seeking [19].

The social environment is a second mechanism hypothesized to modulate *DRD4* expression. Multiple studies on which Bakersman-Kranenberg and van IJzendoorn [20] conducted a meta-analysis indicate that exposure to stressful environments exacerbates the risks for adolescent problem behaviors associated with *DRD4*. For African Americans, residence in socioeconomically disadvantaged neighborhoods is a robust predictor of early-onset intercourse [1]; such aversive environments may combine with variability in *DRD4* to heighten sexual risks. Recent reviews of gene $\times$ environment interaction ($G \times E$) research, however, suggest a novel perspective on *DRD4* function [20]. These reviews cited studies in which the putative vulnerability allele, the *DRD4-L* allele, was linked not only to *adverse* youth outcomes in negative social environments but also to *beneficial* outcomes in positive social environments. Rather than acting as a vulnerability factor per se, the *DRD4-L* allele may amplify environmental effects for better or for worse. The weight of evidence is

inconclusive, given that (a) not all studies test for positive effects in enhanced environments, and (b) the range of environments measured may not include variability on the enhanced end of the continuum, making differential susceptibility difficult to detect [20].

The studies reviewed suggest that the combination of variability in sex, social environment, and *DRD4* status may forecast early-onset sexual activity among African American youth. We hypothesized that, for male but not female African American youth, the *DRD4-I* allele would amplify the influence of both positive and negative community environments on early sexual onset. Hypotheses were tested using the Genes, Environment, and Development Integrated Database (GEDID). GEDID is composed of environmental and genetic data on more than 2,000 African American adolescents participating in five prospective research projects in rural Georgia and Iowa. GEDID was developed to represent adequately distributions of important alleles and unique experiences in the African American population, who are underrepresented in current genetic research [21].

Method

Study hypotheses were tested with a subset of data from GEDID. Cross-project data were aggregated into GEDID for studies of G-E interplay on the basis of several commonalities, including (a) genetic information, (b) similar measures of key outcomes, and (c) focus on African American adolescents. A set of common constructs using identical or similar indicators was developed for participants who provided genetic data in the parent projects. Prior to data aggregation, preliminary analyses were conducted to determine whether participants in the parent projects who agreed to provide genetic data differed from those who did not on a range of demographic variables (e.g., poverty status, household composition, parental education). No differences emerged, suggesting that the genetically informed data in GEDID were representative of the populations sampled in the parent projects. The present study focuses on cross-study variables assessing African American adolescents' age of sexual onset, variation at *DRD4*, neighborhood environment, and two control variables: education level and single-parent status for the youths' primary caregivers.

Procedures

Most participants in the five projects were recruited from rural communities and small towns in Georgia. A subsample of youth in one project was recruited from Iowa; these youth were excluded from the present study to avoid confounding factors in interpretation. In each project, participants were recruited randomly from public school lists; participation rates ranged from 58% to 79% of eligible participants screened. Across projects, youth age at baseline varied based on the goals of the individuals projects. Youth provided data beginning in 6th grade (age 11) in three projects [22–24], beginning in 10th grade (age 15) in one project [25], and beginning in 12th grade (age 17) in one project [26]. All self-report data were collected in participants' homes by African American research staff using either researcher-administered or self-administered computer-assisted interviews. Parents and youth completed their interviews separately, and both parents and youth were informed that parents would not have access to youth's data. The projects used a common protocol for biospecimen collection, and all assays were conducted at a single laboratory. Youth's DNA

was obtained using Oragene DNA kits (DNA Genotek, Kanata, Ontario, Canada). Youths rinsed their mouths with tap water and then deposited 4 ml of saliva in the Oragene sample vial. The vial was sealed, inverted, and shipped via courier to the University of Iowa's Psychiatric Genetics Lab in Iowa City, IA, where samples were prepared according to the manufacturer's specifications. For all waves of survey data collection and for biospecimen collection, parents consented to minor youth's participation and youth assented to their own participation. All studies received appropriate institutional approval.

Measures

Early onset of sexual intercourse—We defined early sexual onset as intercourse prior to age 14. In each project, youth were asked if they “ever had sexual intercourse,” with minor variations in wording (“Have you ever had sex?” “Have you ever had sex with a boy/girl?”). If participants responded yes, they reported the age in years at which they first had sex. To develop an indicator of sexual onset prior to age 14, we implemented an iterative process beginning with the first wave of data provided in each project and using each successive wave as necessary. This involved first determining whether youth reported ever having sexual intercourse and then coding their stated age at first intercourse as early (< 14) or not early (≥ 14). If participants reported never having sexual intercourse, and age at the time of data collection was 14 years or older, they were coded *not early*. For participants younger than 14 years who reported never having intercourse, we coded their status based on their response to the same question in the next wave of data.

Control variables—Demographic interviews in each project included assessments of primary caregivers' education levels. Although the exact Likert scale varied among projects, the information that each provided made it possible to determine whether or not the caregivers had received a high school diploma or GED. Primary caregivers also reported their families' composition, which was coded to identify single or dual parent households.

Neighborhood environment—At the baseline assessment for each project, participant addresses were linked to census tracts; 172 census tracts were identified. Using census data from 2000, each tract was characterized by the proportions of (a) households on public assistance, (b) single-mother-headed households, (c) adults without a high school diploma, (d) African Americans living below the federal poverty level, and (e) unemployed adults. The sixth census-based indicator was per capita income in the census tract. We developed an aggregate neighborhood environment score using a principal components analysis (PCA). The PCA indicated one factor with an eigenvalue greater than 1 that explained 71.25% of the variance. The six indicators loaded significantly ($p < .01$) on the factor, and all factor loadings exceeded .75. A factor score from these variables was estimated using the regression method and was used as a continuous assessment of neighborhood environment in subsequent analyses. High scores on the composite indicated a negative neighborhood environment, and low scores indicated a positive environment. Cronbach's alpha for this composite score was .92.

Genotyping

Genotype at *DRD4* was determined for each adolescent using the primers F- CGCGACTACGTGGTCTACTCG and R-AGGACCCTCATGGCCTTG, standard Taq polymerase and buffer, standard dNTPs with the addition of 100 mol/L 7-deaza GTP, and 10% DMSO. The resulting PCR products were electrophoresed on a 6% nondenaturing polyacrylamide gel and the products visualized using silver staining. Genotype was then called by two individuals blind to the study hypotheses and other information about the participants. *DRD4* status was dummy coded using a minor allele strategy; participants carrying at least one *l* allele were assigned a code of 1 (48.28% of the sample), and participants carrying two *s* alleles were assigned a code of 0 (51.72% of the sample). None of the alleles deviated from Hardy-Weinberg equilibrium, $\chi^2(1) = .258, p = .61$.

Analytic Sample and Plan of Analysis

Of the youth from Georgia who provided data for GEDID, 0.8% were missing data needed to link them to a census tract; these youth did not differ from those providing census data on any demographic variables ($p > .40$). These youth were deleted listwise from additional analyses, resulting in a final sample of 1677 participants (740 male and 937 female youth). Study hypotheses were tested using hierarchical logistic regression with complex designs as implemented in Mplus [27]. This program adjusts parameter estimates for standard errors to account for the non-independence of the data that occurred because some participants lived in the same census tracts. We first regressed early sexual onset on gender, *DRD4*, and neighborhood environment, followed by inclusion of 2-way (Gender $\times$ *DRD4*) and 3-way (Gender $\times$ *DRD4* $\times$ Neighborhood environment) interactions terms. We calculated p values adjusting for the false discovery rate [28]. We planned post hoc tests of the hypothesized interaction effects to interpret them more easily and to determine whether they conformed to a diathesis-stress or an environmental amplification model. Following recent recommendations for $G \times E$ research [29], we conducted a simple slope test, a regions of significance test, and a proportion of interaction (PoI) test.

Results

Participants' baseline demographic, genetic, and sexual onset characteristics and characteristics of the census tracts in which they lived are summarized in Table 1. Approximately one fifth of primary caregivers did not complete high school or obtain a GED; this proportion was slightly higher for the caregivers of female youth. The majority of youth (79.6%) lived in single-parent households. A majority of youth (55%) carried two copies of *DRD4-s*. Among the total sample, 23.2% of youth reported sexual onset prior to age 14. This proportion was significantly higher for male (34.1%) than for female (14.6%) youth.

We first regressed early-onset sexual activity on gender, *DRD4*, and neighborhood environment, controlling for single-parent household status and parent education. Only gender revealed a main effect; male youth were almost twice as likely as female youth to evince early onset (odds ratio = 1.914 [95% CI, 1.695–2.160], $p = .001$). The 2-way interaction between *DRD4* and gender included in the model was not significant ($p = .129$).

In the final step, we included a 3-way *DRD4* × Gender × Neighborhood environment interaction term. Consistent with our expectations, the 3-way interaction term was significant ($p = .040$); Table 2 provides a summary of the regression effects conducted separately for male and female youth. We were unable to predict female youths' early onset of sexual activity using *DRD4* × neighborhood environment. The combination of neighborhood environment and *DRD4* for male youth, however, significantly predicted the likelihood of early-onset sexual activity (odds ratio = 1.322 [95% CI, 1.123–1.555], $p = .005$).

Figure 1 depicts the effect of *DRD4* on sexual onset for levels of neighborhood disadvantage that range from -2 to $+2$ standard deviations from the mean. A simple slope test indicated that the association between quality of the neighborhood environment and early sexual onset was significantly steeper for male youth who carried the *l* allele ($b = .18$ [95% CI, .02–.34], $p = .039$) than for those who did not ($b = -.10$ [95% CI, $-.25$ –.06], $p = .317$). This suggests a robust influence of neighborhood environment on the early sexual onset of youth with the *l* allele, whereas neighborhood environment did not influence early sexual onset for youth without the *l* allele.

The slopes in Figure 1 demonstrate a cross-over pattern consistent with an environmental amplification rather than a diathesis-stress model; the *DRD4-l* allele influenced youth in both negative and positive neighborhood environments. The shaded portions of Figure 1 represent the regions of significance for the interaction. Significant effects emerged at both ends of the neighborhood environment measure, consistent with an environmental amplification model. The PoI index was .57. The score's proximity to .50 suggests equal significance on both sides of the interaction.

A racial admixture variable was developed using the Structure program version 2.3.4 [30] with a panel of 24 ancestrally informative markers. The racial admixture variable was used as a covariate in the analyses described previously. The results did not change, indicating that population stratification did not affect the analyses.

Discussion

In the present study, we hypothesized that allelic variation in the dopamine receptor D4 gene would combine with characteristics of the social environment to influence the timing of African American male youths' sexual debut. Results were consistent with this hypothesis. We found no *DRD4* × neighborhood interaction effect for female youth. In contrast, for male youth, the *DRD4-l* allele predicted early sexual onset contingent on the social environment. For male youth living in negative neighborhood environments, *DRD4-l* predicted an elevated likelihood of early sexual onset. Conversely, for male youth living in positive neighborhood environments, *DRD4-l* predicted a diminished likelihood of early sexual onset. These effects are consistent with an environmental amplification hypothesis, suggesting that *DRD4-l* increases sensitivity to both negative and positive environmental stimuli.

The present study contributes to an accumulating body of research suggesting that sex differences exist in the dopaminergic modulation of adolescent sexual onset and other forms of problem behavior. Sex differences in *DRD4* effects, both direct and interactive, have been detected in a number of studies on a range of phenotypes involved in risky behaviors [17, 31]. The precise biological mechanisms involved constitute an important target for future research. Potential directions for research that informs these sex differences may include (a) hormonal factors that modulate dopaminergic activity [32], (b) sex-specific chromosomes, (c) differences in DNA methylation, and (d) differences in autosomal genes [33]. Sex differences in *DRD4* effects may also be a function of differential exposure to neighborhood contextual risk factors [17]. Study findings also support the potential of $G \times E$ studies to inform the routine non-replication of single genetic polymorphism effects on complex behavioral phenotypes [34]. Specifically, it may prove untenable to identify uniquely “genetic” effects without considering the substantial heterogeneity of the environments in which genes are expressed.

Study results also are consistent with the perspective that, for African American male youth, *DRD4* confers increased sensitivity to environmental input, for better or worse. This perspective suggests that considering *DRD4* a genetic risk factor is less than accurate. Rather, with supportive contexts, *DRD4* appears to promote positive outcomes, whereas in risky contexts, it fosters negative outcomes. Although evidence for the mechanisms of these environmental amplification effects is sparse, a plausible hypothesis has been advanced. The dopaminergic system is engaged in attentional, motivational, and reward mechanisms, and lower dopaminergic signaling impedes learning based on negative feedback; this in turn may lead to a relative insensitivity to environmental cues and rewarding stimuli [5]. This results in a strong preference for immediate reinforcement from the environment and elevated reactivity to high-intensity environmental cues. High-intensity environments that clearly reinforce both negative and positive behavior exert a heightened influence on behavioral development among reward-deficient children and youth. Rather than withdrawing from the environment or carefully processing environmental cues, such young people are likely to be hyper-reactive to the environment and reflect the positive or negative input from their immediate surroundings [20].

Study results underscore the importance of screening and preventive measures for African American male youth residing in disadvantaged neighborhoods. More than 1 in 3 male youth in this sample reported sexual onset prior to age 14; this prevalence is elevated among youth in the most socioeconomically disadvantaged areas. Recent evidence suggests that the environmental amplification processes found among *DRD4-l* carriers also may affect their response to preventive interventions [35] as well as to treatment for alcohol problems [36]. The prevention studies suggest that, although *DRD4-l* may be associated in negative contexts with risk for early sexual onset and other problem behaviors, young people who carry this allele also may benefit the most from preventive interventions. Beach et al. [37] found that African American male youth with the *DRD4-l* allele who participated in a family-centered prevention program were more likely than youth with two *s* alleles to experience alcohol prevention effects. Similar findings have emerged from studies in which *DRD4-l* was associated with enhanced sensitivity to intervention among toddlers [35].

Consideration of limitations is necessary when interpreting the results of this study. First, we used self-report data to index early sexual onset. The potential for self-presentation and other forms of bias are mitigated to some extent by allowing participants to respond privately through standardized computer-assisted protocols. Second, studies are needed that describe more precisely the characteristics of advantaged or disadvantaged communities that affect *DRD4* expression. Such studies should examine the ways in which communities affect proximal family interactions, which have been shown to interact with *DRD4* to predict adolescent outcomes [20]. Furthermore, the present study does not rule out the possibility that other developmental environments interact with female youth's *DRD4* status. For example, some studies have found that female youth are more sensitive than are male youth to family environments as predictors of risk behavior [38, 39]. Finally, genetics researchers have found that multiple replications are essential in reducing false positive findings. Nevertheless, the present study provides information on the effects of the interaction of gender, social environment, and genotype on the early initiation of sexual activity among African American youth. These findings may be useful in directing future research and in designing interventions to delay the onset of sexual intercourse during adolescence.

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Implications and Contribution

Social environments play a key role in young men's early sexual onset; however, men are differentially susceptible to environmental influences. Variation at the dopamine receptor gene may increase young men's sensitivity to the environment.

Figure 1.

Interaction of *DRD4* and neighborhood disadvantage, with regions of significance. Shaded areas indicate the regions of significance for the interaction effect, the point at which the regression lines differ significantly.

Table 1

Sample and Census Tract Characteristics

Variables	Frequency (%)		Gender difference (χ^2)
	Males <i>n</i> = 740	Females <i>n</i> = 937	
Sample variables			
Primary caregiver educational attainment			3.873*
< HS diploma/GED	142 (19.2)	217 (23.2)	
high school or above	598 (80.8)	720 (76.8)	
Family composition			0.704
Single-parent household	511 (69.1)	629 (67.1)	
Two-parent household	229 (30.9)	308 (32.9)	
Sexual onset			87.643**
Early onset	252 (34.1)	137 (14.6)	
Non-early onset	488 (65.9)	800 (85.4)	
<i>DRD4</i> ^a			0.468
1 or 2 copies of the <i>l</i> allele	333 (45.0)	406 (43.3)	
2 copies of the <i>s</i> allele	407 (55.0)	531 (56.7)	
Census tract variables (<i>N</i> = 172 tracts)		Mean (<i>SD</i>)	
Percentage on public assistance		4.9 (2.7)	
Single-mother-headed households		11.9 (4.4)	
Adults without a high school degree		32.4 (8.5)	
African Americans living below federal poverty level		17.1 (8.6)	
Unemployment		7.93 (4.0)	
Per capita income (U.S. dollars)		15,722.2 (4,167.6)	

^aSpecific allele frequencies are available from the first author upon request.

* $p < .05$.

** $p < .01$.

Table 2
Adjusted Logistic Regression of Early Sexual Onset on *DRD4* and Neighborhood Environment

	Male Youth			Female Youth		
	<i>B</i> (SE)	OR (95% CI)	<i>p</i>	<i>B</i> (SE)	OR (95% CI)	<i>p</i>
Gene effect						
<i>DRD4</i>	.040 (.082)	1.041 (.886–1.222)	.629	–.194 (.101)	.824 (.676–1.004)	.055
Neighborhood effect						
Neighborhood disadvantage	–.095 (.080)	.909 (.777–1.064)	.235	.051 (.076)	1.052 (.907–1.221)	.504
Gene by neighborhood effect						
<i>DRD4</i> × Neighborhood disadvantage	.277 (.082)	1.319 (1.123–1.549)	.001	.016 (.087)	1.016 (.857–1.205)	.856
Constant	.496 (.112)	1.642 (1.318–2.045)	.000	1.042 (.114)	2.835 (2.267–3.545)	.000
R ²	.027			.017		

Note: Primary caregiver educational status and family composition are controlled. The analysis included 740 male youth from 128 neighborhoods and 937 female youth from 147 neighborhoods. SE = standard error. OR = odds ratio. CI = confidence interval.