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Parenting Quality, DRD4, and the Prediction of Externalizing and Internalizing Behaviors in Early Childhood

ABSTRACT: *Recent research has found that the dopamine D4 receptor (DRD4) gene and maternal insensitivity may interact to predict externalizing behavior in preschoolers. The current study attempted to replicate and extend this finding in a sample of 18–30-month-old children. The current study examined two distinct dimensions of parenting (warm-responsive and negative-intrusive) as predictors of childhood externalizing and internalizing behavior. Further, race was investigated as a moderator of gene–environment relationships. Results revealed that high warm-responsive parenting was associated with decreased externalizing behavior only for African American children possessing the short polymorphism of DRD4. The data indicate that children may be differentially susceptible to different aspects of parenting depending on their genotype, and it is important to consider differences in racial composition when studying these relationships. © 2007 Wiley Periodicals, Inc.* Dev Psychobiol 49: 619–632, 2007.

Keywords: *dopamine; externalizing behavior; internalizing behavior; maternal sensitivity; parenting; gene–environment interactions*

INTRODUCTION

Behavior genetics studies have frequently examined the heritability of childhood behavior problems using twin and adoption designs (Gjone, Stevenson, Sundet, & Eilertsen, 1996; Schmitz, Cherny, Fulker, & Mrazek, 1994; van der Valk, Verhulst, Neale, & Boomsma, 1998). More recently, researchers have begun to examine the molecular genetics of childhood behavior problems. This emerging body of research has associated specific polymorphisms of the D4 dopamine receptor (DRD4) gene with externalizing behaviors, as well as related infant temperament and adult personality characteristics. The current study investigated DRD4 both alone, and in combination with parenting, as a risk factor for the emergence of internalizing and externalizing behaviors in early childhood.

Dopamine has been suggested as an underlying neurotransmitter influencing the behavioral system of approach in adults (Cloninger, 1987; Gray, 1982; Zukerman, 1994). More specifically, it has been associated with active exploration and approach toward novel stimuli as well as activation and intensity of response in reward situations (Panskepp, 1986). DRD4 is primarily expressed in the limbic areas of the brain that are involved in cognition and emotion. This gene contains a repeated sequence polymorphism (i.e., variations in DNA) within its coding sequences that changes the length of the receptor protein that has been shown to have functional significance (Asgahari et al., 1994). There is a long polymorphism (L-DRD4; 6–8 repeats *or* presence of 7-repeat allele) and a short polymorphism (S-DRD4; 2–5 repeats *or* absence of 7-repeat allele); the shorter the allele, the more efficient the receptor is in binding dopamine (Plomin & Rutter, 1998).

The relationship between the DRD4 gene and behavioral characteristics has also been examined in both

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infants and children. One group of researchers examined infants over the first year of life and found associations between DRD4 and infant temperament that were comparable to those of adult personality. At 2 weeks of age, infants possessing L-DRD4 scored higher on the orientation, motor organization, range of state, and state regulation clusters of the Brazelton Neonatal Behavioral Assessment Scale (NBAS; Brazelton & Nugent, 1995) than did the infants with S-DRD4 (Ebstein et al., 1998). At 12 months of age, infants with the L-DRD4 genotype shifted their attention more quickly and easily and received higher scores on measures of activity level, interest, and exploration of the environment (Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001). The authors discussed these infant behaviors as potentially analogous to adult stimulus-seeking behavior that have also been associated with the L-DRD4 genotype (Benjamin et al., 1996; Ebstein et al., 1996).

In children, L-DRD4 has been related to externalizing problems such as hyperactive-impulsive-inattention (LaHoste et al., 1996; Sunohara et al., 2000), oppositional defiant behaviors (Kirley et al., 2004), and aggressive behaviors (Benjamin, Ebstein, & Belmaker, 2002; Schmidt, Fox, Rubin, Hu, & Hamer, 2002). Conversely, however, many studies have failed to replicate the abovementioned links. For example, several studies have found no association between L-DRD4 and attention disorders (Hawi et al., 2000; Payton et al., 2001; Todd et al., 2001), with one study finding *S-DRD4* to be related to attention deficit hyperactivity disorder (Manor et al., 2002). Similarly, a recent study also found the opposite association between L-DRD4 and aggressive behavior in children (i.e., elevated externalizing problem scores in the *absence* of L-DRD4) at 6 years of age (Birkas et al., 2005). Consequently, although there is reason to believe that DRD4 may play a role in the development of behavioral problems, more work is needed to clearly understand this pathway and the nonreplications in the literature.

The aforementioned studies shared a common limitation, namely the adoption of a main effects modeling approach in which a DRD4 polymorphism was used as a predictor of behavioral outcomes without consideration of relevant experience. Several innovative studies have demonstrated the value of considering both genotype and early environmental stressors as predictors of later pathological outcomes (Caspi et al., 2002, 2003). To the best of our knowledge, there is only one published study that investigated the joint contribution of DRD4 and environmental influences in the development of childhood behavioral problems (Bakermans-Kranenburg & van IJzendoorn, 2006). This study examined the interplay of DRD4 and observed parental insensitivity as predictors of problem behaviors at 39 months of age. Findings revealed no significant effects on internalizing behavior. However, those children possessing L-DRD4 and who were exposed to insensitive parenting exhibited a sixfold increase in externalizing behavior over those children with L-DRD4 and sensitive parenting, as well as over those that possessed S-DRD4. These results suggest that children may be differentially susceptible to insensitive parenting partly as a function of the DRD4 polymorphism. Moreover, they suggest that inconsistencies in previous studies regarding the relationship between DRD4 polymorphisms and behavioral outcomes may be resolved by considering parenting as one experience that coacts with the polymorphism to affect externalizing behavior.

The choice of parenting as a key experience makes good sense given the well established relationship in the literature between parenting quality and the prediction of childhood externalizing behaviors, irrespective of genetic influences. For example, some of the most powerful predictors of later externalizing behaviors are harsh or insensitive parenting (Booth, Rose-Krasnor, McKinnon, & Rubin, 1994), parental rejection (Loeber & Southamer-Loeber, 1986), maternal depression and interaction style (Leadbeater, Bishop, & Raver, 1996), nonaffection (McFadyen-Ketchum, Bates, Dodge, & Pettit, 1996), and parent–child relationships that are relatively low in warmth and affective enjoyment (Olson, Bates, Sandy, & Lanthier, 2000). Caregiving as early as infancy has been significantly associated with externalizing problems, such as conduct and oppositional disorders, at school entry (Shaw, Owens, Giovannelli, & Winslow, 2001). Similarly, internalizing problems in children have been associated with early parenting variables such as negative maternal attitudes towards the child, manifested in hostile behavior, low warmth, and inconsistent availability (Cicchetti & Toth, 1995; Hammen & Rudolph, 1996). Children that are biologically vulnerable to psychopathology may be at increased risk after exposure to this type of parenting. To this end, the current study investigates the infant-caregiver relationship at 6 and 12 months of age and polymorphisms of the DRD4 gene as potential coactional factors contributing to externalizing and internalizing outcomes in early childhood.

Although extant findings have consistently supported the importance of parenting for child outcomes, it is typically examined as one overarching variable, and thus several studies have advocated breaking down this broad construct to examine more specific dimensions of parenting (Ainsworth, 1973; DeWolff & van IJzendoorn, 1997; Kochanska, Forman, & Coy, 1999). Consistent with this goal, the current study will examine ''negative-intrusive'' and ''warm-responsive'' maternal behavior as two unique dimensions of parenting. Maternal negative-intrusive parenting includes behavior that is negative or intrusive, but also inappropriate, nonresponsive, and not child-centered. On the other hand, warm-responsive

parents are warm and responsive, but also actively involved with their children through the use of activities and conversation to stimulate child development, and they display behaviors that are animated, positive, and energetic. The inclusion of these two distinct dimensions of parenting in the current study will give us further insight into the specific style of parenting that is most relevant in the development of later childhood behavioral problems.

Furthermore, a significant limitation of the genetic studies described above is that for the most part, they each investigated primarily European American children. This is a significant limitation for many reasons, but of particular relevance here is the possibility that genetic contributions to behavior may not consistently generalize across racial groups. The current study investigates whether the previously reported relationship between parenting style, DRD4, and childhood problem behaviors may vary by race. There are several possible reasons we expect that this may be the case.

First, a recent study provided evidence that the effect of one specific gene may be dependent on race (Williams et al., 2003). Findings revealed that the S/S polymorphism of a serotonin gene (5-HTTLPR) was associated with the production of *higher* levels of serotonergic function in the central nervous system of African American participants and *lower* levels of serotonergic function among European American participants. The authors suggest that their findings may help to clarify the abundance of non-replications in the literature; associations made between the S/S genotype and personality factors may differ as a function of race. Although the mechanisms underlying these differential effects are not yet clear, the authors suggest that this variation may be due to a genetic difference, such as linkage disequilibrium. However, a second possible explanation is that this difference stems from the dissimilar life experiences of each group. For example, studies have found that African American children experience a disproportionate amount of poverty and economic hardship (McLoyd, 1998; Myers & King, 1983). Poverty has been found to increase stress and limit parents' support systems, potentially resulting in less parental warmth and emotional availability for their children (Bakermans-Kranenburg, van IJzendoorn, & Kroonenberg, 2004; McLoyd, 1990). Therefore, African American children may be exposed to a higher risk environment than European American children which, in conjunction with genotype, may yield different biological and behavioral consequences. And finally, there is evidence that differential effects of parenting may depend on race (Deater-Deckard & Dodge, 1997). Cultural variations may influence both the way in which an individual parent behaves as well as the way in which that behavior is interpreted (Deater-Deckard, Dodge, Bates, & Pettit, 1996). Therefore, race may play a significant role in understanding genes, parenting, and childhood behavioral outcomes as well as their relationship. Due to the limited number of studies that have investigated race as a moderator of this relationship, the current study will include race with no a priori hypotheses.

In sum, the current study will attempt to replicate the findings of Bakermans-Kranenburg and van IJzendoorn (2006) by testing DRD4 polymorphisms, observed parenting quality, and their interaction in the prediction of externalizing and internalizing outcomes. We will extend the previous research by considering: (1) race as a moderator of expected relationships, (2) two subdimensions of parenting (i.e., negative-intrusive and warm-responsive) and (3) aggregates of parenting quality and child behaviors across multiple assessments in order to create more reliable predictors and outcomes.

MATERIALS AND METHODS

Participants

Participants were drawn from the Durham Child Health and Development Study, a longitudinal sample consisting of 206 healthy, full-term infants recruited at 3 months of age. The current sample includes 169 of these infants (those that had complete genetic data) and their mothers seen at approximately 6, 12, 18, 24, and 30 months of infant age. Mothers' mean age at the 6-month visit was 28.75 ($SD = 5.68$). Of the infants in the analysis sample, 84 (50%) were male, 85 (50%) were female, 97 (57%) were African American, and 72 (43%) were European American. Eighty-five families (50%) were defined as being below poverty and 84 (50%) were defined as being above poverty.

Procedure

Dyads were part of a longitudinal study from 3 months to 3 years of age. The current analyses will examine observational and questionnaire data from laboratory visits that occurred when the infants were 6, 12, 18, 24, and 30 months of age. At each of these visits, infants and their mothers participated in several joint and individual tasks followed by a standardized interview and completion of demographic questionnaires by the mother.

Measures

Mother–Infant Free-Play (6- and 12-Month Visit). To evaluate maternal behavior during interactions with infants, mothers were instructed to interact with their children as they normally would if they were playing with them during some free time on a typical day. Dyads were seated on a blanket and given a standard set of toys to use if

they so chose. The experimenter then left the dyad alone in the room for the duration of the task and returned after 10 min. The task was videotaped for later coding.

Free play interactions were coded by two independent coders who were unaware of the study's hypotheses. Coders were trained to reliability using selected video recorded free play episodes that had been previously coded by criterion coders. To reach inter-rater agreement, coders continued training until an intra-class correlation coefficient of .80 was reached for each coder on each construct with the criterion coders. Once reliability was met, coders continued to code in pairs and coded at least 20% of cases with a criterion coder. Training was ongoing throughout entire coding process as all cases were double coded and conferenced for final scores weekly. Overall, coders' inter-rater reliability on all subscales remained above .80 and reliability among coders (within pairs and with criterion coders) was monitored to ensure they remained this way for each construct.

Seven subscales were used to evaluate maternal behavior during the free play task for a global rating of maternal behavior. The following qualitative ratings have been used in previous studies (e.g., National Institute of Child Health and Human Development [NICHD] Study of Early Child Care, 1997) to assess parent–child interaction during long free play sessions and include: sensitivity/responsiveness, detachment/disengagement, positive regard, intrusiveness, animation, stimulation of development, and negative regard. For each subscale, mothers received a score between 1 and 5 with '1' being not at all characteristic of their behavior during the dyadic interaction and '5' being highly characteristic of this interaction. Factor analyses suggested two composite measures of maternal behavior at each timepoint. The composite score for maternal *negative-intrusive* behavior was created by summing the scale scores for intrusiveness, negative regard, and reverse scored sensitivity/responsiveness (6-month factor loadings were .92, .77, and .73; 12-month factor loadings were .89, .76, and .76). Similarly, the composite score for maternal *warm-responsive* behavior was created by summing the scale scores for positive regard, animation, stimulation of development, and reverse coded detachment/disengagement (6-month factor loadings were .89, .71, .85, and .88; 12-month factor loadings were .89, .70, .85, and .86). Negative-intrusive and warm-responsive parenting behaviors were negatively correlated at 6 months of age ($r = -.31$, $p < .05$) and 12 months of age ($r = -.50$, $p < .05$).

Bivariate correlations for the same measures across assessments indicated reasonable stability. Because our hypotheses were not specific to time period, we created aggregate scores. Specifically, both parenting variables were individually standardized to $M = 0$ and $SD = 1$ within each assessment period. An aggregate score was then created, which consisted of the mean score across time periods (e.g., negative-intrusive aggregate = mean of negative-intrusive behavior observed at 6 and 12 months). These aggregate scores served the effect of reducing the amount of missing data. For example, whereas 152 and 143 parent–child interactions were coded at the 6- and 12-month visits, respectively, a total of 167 parent–child dyads were observed during at least one of the assessments (see Tab. 2). The aggregate scores for warm-responsive parenting and negative-intrusive parenting were also negatively correlated ($r = -.44$, $p < .05$).

Child Behavior Checklist: 1½-5 Years (18-, 24-, and 30-Month Visit). Mothers were given the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2000) within a packet of questionnaires to complete at home prior to each lab visit. The CBCL is a standardized assessment that obtains a parental rating of children's behavioral/emotional problems and provides an overall behavioral index of seven subscales. Mothers rate their child on each item that describes the child currently or within the last 2 months. This version of the CBCL consists of 99 items describing behavioral/emotional problems, plus an open-ended item for additional problems. The seven syndromes for the CBCL are: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior. Withdrawn, somatic problems, emotionally reactive problems, and anxious/depressed syndromes were combined to form an internalizing broad-band score, and attention and aggressive problems were combined to form an externalizing broad-band score.

Bivariate correlations for the same measures across assessments indicated reasonable stability (see Tab. 2). Because our hypotheses were not specific to time period, we created aggregate scores. Specifically, behavioral variables were individually standardized to $M = 0$ and $SD = 1$ within each assessment period. An aggregate score was then created, which consisted of the mean score across time periods. Similar to the description of aggregating the parent scores (see above), these new scores served the effect of reducing the amount of missing data.

Buccal Cell Collection (12-Month Visit). DNA was obtained through the collection of infant buccal cells (i.e., cheek cells). The experimenter began collection by putting on a pair of latex gloves before handling any supplies, ensuring that the experimenter's own skin cells would not come into contact with the collection materials. The experimenter rubbed the inside of the infants' inner cheek and gums for at least 20 s with a Q-tip. The Q-tip was then immediately placed into a pint-sized zip-loc bag,

sealed, and put into a storage freezer where it remained until cells were sent to the laboratory for processing. Cheek cells for DNA isolation and analysis were sent to a genetics laboratory at North Carolina State University, Raleigh, North Carolina. All of the genotyping was done blind to the studies hypotheses and outcomes.

Genomic DNA was extracted from each salivary sample using the Puregene DNA extraction kit by following the manufacturer's protocol for DNA isolation from 1 ml of body fluid. Saliva samples yielded DNA in adequate quantities for genotyping (approximately 200 μg/ml). Genotyping of the 48-bp repeat in exon III of the DRD4 gene was performed using AmpliTaq Gold DNA Polymerase purchased from Applied Biosystems (Foster City, CA) by touch-down PCR amplification using the forward and the reverse primers: 5'-AGGACCCT-CATGGCCTTG (D4DR-Fwd) and 5'-GCGACTACG-TGGTCTACTCG (D4DR-Rev) (Benjamin et al., 1996). Primers were purchased from MWG Biotech (High Point, NC). The PCR products were run on a 3% agarose gel stained with ethidium-bromide, imaged with the Bio-Rad ChemiDoc System PC RS-170 using Quantity One (version 4.2.1) software, and manually genotyped. This protocol results in short alleles of 379–571 bp (2–6 repeats) or in long alleles of greater than 619 bp (7 or more repeats). The genotypes ss, sl, or ll were assigned to each individual where s is the short allele and l is the long allele. Based on previous results (Anchordoquy, McGeary, Liu, Krauter, & Smolen, 2003; Benjamin et al., 1996; Schmidt et al., 2002), polymorphisms made up of homogeneous short alleles (s/s) were classified as Short (S-DRD4) and heterogeneous polymorphisms (s/l and l/l) were classified as Long (L-DRD4). The distribution of DRD4 genotypes (s/l = 30%, s/s = 62%, l/l = 8%) conformed to Hardy–Weinberg equilibrium (see Tab. 1 for allelic frequencies).

Analytic Strategy

The overall goal of this study was to investigate how two dimensions of parenting behavior, warm-responsive and negative-intrusive, relate to children's externalizing and internalizing behaviors with a specific interest in testing whether these relationships were moderated by child genotype (DRD4) and/or race. These questions were tested using a series of regression models of the following form:

$$\begin{aligned} Y = {} & b_0 + b_1\ \text{male} + b_2\ \text{AA} + b_3\ \text{negative} - \text{intrusive} \\ & + b_4\ \text{warm} - \text{responsive} + b_5\ \text{DRD4} + b_6\ \text{DRD4\_AA} \\ & + b_7\ \text{warm} - \text{responsive\_DRD4} + b_8\ \text{negative} \\ & - \text{intrusive\_DRD4} + b_9\ \text{warm} - \text{responsive\_AA} \\ & + b_{10}\ \text{negative} - \text{intrusive\_AA} + b_{11}\ \text{warm} \\ & - \text{responsive\_DRD4\_AA} + b_{12}\ \text{negative} \\ & - \text{intrusive\_DRD4\_AA} \end{aligned}$$

Table 1. Sample Description

		% (*n*)		
Variable (time period)	Categories/unit	EA, *n* = 71–72	AA, *n* = 83–97	Total, *n* = 154–169
Child gender	Male	54 (39)	46 (45)	50 (84)
	Female	46 (33)	54 (52)	50 (85)
Child D4 polymorphism	s/s	64 (46)	61 (59)	62 (105)
	s/l	32 (23)	29 (28)	30 (51)
	l/l	4 (3)	10 (10)	8 (13)
Marital status (6 months)	Married	76 (54)	43 (36)	58 (90)
	Separated	4 (3)	1 (1)	3 (4)
	Living w/someone	10 (7)	13 (11)	12 (18)
	Single	10 (7)	42 (35)	27 (42)
Poverty level (recruitment)	Below poverty line	38 (27)	60 (58)	50 (85)
	Above poverty line	63 (45)	40 (39)	50 (84)
Variable (time period)	Categories/unit	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Mother age (6 months)	Years	29.5 (5.7)	28.1 (5.7)	28.8 (5.7)
Family income (aggregate)	Total $/persons supported	17,677 (12,462)	10,092 (9958)	13,397 (11,707)
Negative-intrusive parent (aggregate)	Standardized (*M* = 0)	−.5 (.6)	.3 (.8)	.0 (.8)
Warm-responsive parent (aggregate)	Standardized (*M* = 0)	.3 (.8)	−.2 (.9)	.0 (−.9)
Externalizing (aggregate)	Standardized (*M* = 0)	.0 (.8)	−.0 (.9)	.0 (.9)
Internalizing (aggregate)	Standardized (*M* = 0)	−.2 (.5)	.2 (1.0)	.0 (.9)

Note: AA, African American; EA, European American; % may not sum to 100 given rounding error.

Table 2. Pairwise Correlations for Repeated Measures Data

Construct	Assessment (months)		1.	2.	3.		*n*
Negative-intrusive parenting	6	1.	1.0	—	—		152
	12	2.	.38	1.0	—		143
	Aggregate	3.	.85	.84	1.0		167
Warm-responsive parenting	6	1.	1.0	—	—		152
	12	2.	.36	1.0	—		143
	Aggregate	3.	.86	.85	1.0		167
Construct	Assessment (months)		1.	2.	3.	4.	*n*
Externalizing	18	1.	1.0	—	—	—	160
	24	2.	.61	1.0	—	—	162
	30	3.	.51	.63	1.0	—	160
	Aggregate	4.	.84	.88	.84	1.0	167
Internalizing	18	1.	1.0	—	—	—	160
	24	2.	.61	1.0	—	—	162
	30	3.	.58	.54	1.0	—	160
	Aggregate	4.	.87	.85	.84	1.0	167

Note: All $p < .0001$; all scores were standardized within assessment to $M = 0$ and $SD = 1$. Aggregate scores refer to mean scores across assessments.

where AA indexes African American children, DRD4 is a dummy variable indexing the long polymorphism, and warm-responsive and negative-intrusive refer to different forms of observed parenting behavior. Significance tests of the two- and three-way interaction terms involving the DRD4 gene provided a test of our hypotheses. Final models retained only those interaction terms that were significant. Model assumptions were investigated using graphical techniques that are available in SAS® version 9.1.

RESULTS

Although our original sample at 3 months of age included 206 dyads, the current analyses include only those dyads in which infants had complete genetic data (82%; $n = 169$). χ^2 and *t*-tests were conducted to examine patterns of missing data. No systematic differences were found between dyads included in the analyses and those that were not on such demographic variables as gender, race, and income or on measures of parenting or infant behavior.

Mean Differences

Prior to testing our hypotheses, we tested for differences in parenting variables, as well as family income, using a 2 (race) × 2 (DRD4 genotype) ANOVA (see Tab. 3). The goals of these analyses were primarily descriptive. Thus, although our hypotheses were centered on questions about the covariance between parenting and behavioral outcomes as a function of genotype and race, we also wanted to explore whether there were mean level differences in parenting variables as a function of genotype and race too. There was no evidence for race by genotype interactions. With the exception of warm-responsive parenting, where children with long polymorphisms were rated as having less warm-responsive parents than children with the short polymorphism (standardized scores: L-DRD4, $M = -.24$, $SD = .87$ vs. S-DRD4, $M = .15$, $SD = .85$), there was no indication of main effects by genotype. There was

Table 3. Mean Differences in Income, Parenting, and Child Behavior by Child Race and DRD4

	Race	D4	Race × D4
Construct	$F(1, 163)$	$F(1, 163)$	$F(1, 163)$
Family income	14.6^{***}	2.2	1.4
Negative-intrusive parenting	50.8^{****}	.01	1.1
Warm-responsive parenting	16.2^{****}	8.7^{**}	.4
Externalizing	.2	.5	.7
Internalizing	6.1^{*}	1.5	.1

Note: $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$; $^{****}p < .0001$; All outcomes are standardized aggregates; descriptive statistics by race are summarized in Table 1.

consistent evidence of race differences for both parenting variables, as well as for total family income and internalizing (but not externalizing) behavior. Relative to European American families, African American parents were rated as exhibiting higher levels of negative-intrusiveness and lower levels of warm-responsiveness during free play with their infants, self-reported substantially less total family income, and rated their children as having more internalizing problems (see Tab. 1 for descriptive statistics). Consistent with self-reported total family income, 38% (27/72) of European American families versus 60% (58/97) of African American families reported to be at or below the Federal poverty line for a given household size at the time of study entry.

Correlations

As a preliminary step in the data analyses, we computed correlations to investigate the relationship between the two dimensions of parenting and child externalizing and internalizing behaviors for the overall sample. As expected, the results of these analyses revealed several significant correlations. Internalizing behavior correlated significantly with warm-responsive parenting ($r = -.29$, $p < .0001$) as well as negative-intrusive parenting ($r = .33$, $p < .0001$). Similarly, externalizing behavior correlated significantly with warm-responsive parenting ($r = -.18$, $p < .02$) as well as negative-intrusive parenting ($r = .27$, $p < .0005$).

Regression Models

Externalizing Behaviors. The model predicting externalizing behavior was significant, $F(10, 150) = 3.0$, $p = .0018$, Adjusted $R^2 = .11$. However, negative-intrusive parenting ($b = .37$, $p = .0004$) was the only significant effect. An evaluation of model assumptions using graphical procedures (Fox, 1991) resulted in the identification of four potential outliers (i.e., cases with appreciably larger Cooks D values relative to others). After removal of the four outliers, the above correlations were recalculated to examine relationships between externalizing behavior (minus the outliers) and the two parenting dimensions. There continued to be a significant correlation between externalizing behavior and warm-responsive parenting ($r = -.20, p < .01$) as well as negative-intrusive parenting ($r = .31, p < .0001$). Furthermore, we looked more closely at the correlations between externalizing behavior and parenting within each *genotype* (L-DRD4 vs. S-DRD4) and *race* (African American (AA) vs. European American (EA)) group (e.g., L-DRD4/EA, S-DRD4/AA). A significant correlation was obtained between externalizing behavior and warm-responsive parenting only in the S-DRD4/AA group ($r = -.46$, $p < .0003$). However, several significant correlations were found between externalizing behavior and negative-intrusive parenting within genotype/race groups (S-DRD4/AA: $r = .39$, $p < .002$; S-DRD4/EA: $r = .35$, $p < .02$; L-DRD4/EA: $r = .45$, $p < .02$; L-DRD4/AA: $r = .29$, $p < .10$). See Figure 1 for scatterplots of the relationship between externalizing behavior and warm-responsive parenting (minus the four outliers) by genotype/race group.

The model was re-estimated excluding the four outlier cases. The overall model continued to be significant, $F(10, 146) = 3.86$, $p = .0001$, with a slight increase in overall prediction (Adjusted $R^2 = .16$ vs. .11). Negative-intrusive parenting continued to exert a significant main effect ($b = .40$, $p < .0001$). However, there was now also now evidence of significant two-way interaction for warm-responsive parenting and race ($b = -.46$, $p = .03$) and a three-way interaction for warm-responsive parenting, race, and DRD4 ($b = .66$, $p = .059$). Given that there is typically limited statistical power to adequate test interaction terms (McClellan & Judd, 1993) we explored this effect despite the fact that it was marginally significant (see Tab. 4).

The significant three-way interaction was probed following procedures recommended by Aiken and West (1991). Because child gender and family income were not significant predictors in either model, they were omitted when probing interactions in order to avoid having to condition the three-way interaction on them. As shown in Figure 2, increasing levels of warm-responsive parenting resulted in decreasing race differences in externalizing behavior among individuals with L-DRD4 but increasing race differences among individuals with S-DRD4. Inspection of simple slopes indicated that warm-responsive parenting was only significantly associated with reductions in externalizing behavior for African American children with the S-DRD4 polymorphism ($b = -.42$, $p = .004$). The simple slopes for externalizing on warm-responsive parenting were not significantly different than zero for any of the remaining three groups (L-DRD4/EA: $b = -.07$, $p = .75$; L-DRD4/AA: $b = .12$, $p = .45$; S-DRD4/EA: $b = .07$, $p = .62$).

Internalizing Behaviors. First, correlational analyses were conducted to examine the relationship between internalizing behaviors and the two dimensions of parenting within each genotype/race combination (as described above). Two significant relationships were found between internalizing behavior and warm-involved parenting (S-DRD4/AA: $r = -.40$, $p < .002$; L-DRD4/AA: $r = -.34$, $p < .05$), and one significant correlation was found between internalizing behavior and negative-intrusive parenting (S-DRD4/AA: $r = .36, p < .006$). The regression model predicting internalizing behavior was significant, $F(7, 153) = 6.08$, $p < .0001$, Adjusted

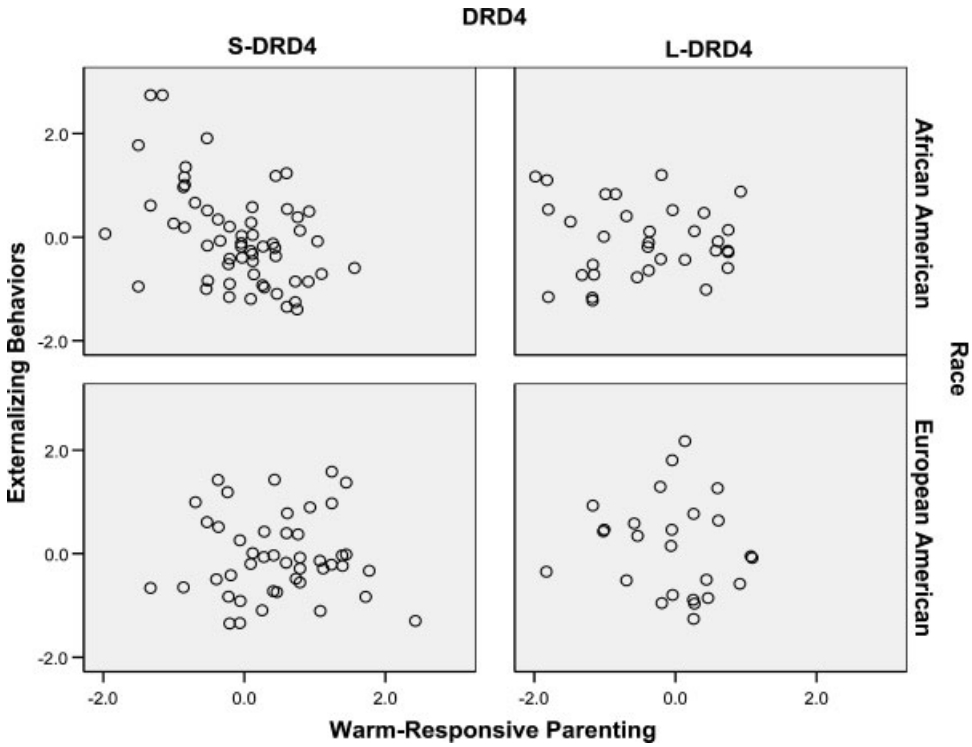

FIGURE 1 Warm-responsive parenting and externalizing behavior (minus four outliers) by race and DRD4 group.

$R^2 = .18$. Consistent with the model predicting externalizing behaviors, there was a significant main effect of negative-intrusive parenting on internalizing behavior ($b = .27$, $p = .005$). Moreover, the two-way interaction for warm-responsive parenting and race was significant ($b = -.52$, $p = .001$). Because child gender and family income were not significant predictors in the model, they were omitted when probing interactions in order to avoid having to condition the two-way interaction on them. As shown in Figure 3, increasing levels of warm-responsive parenting were associated with significant reductions in internalizing behaviors for African American ($b = -.38$; $p = .0002$) but not European American ($b = .16$; $p = .1994$) children. Notably, neither the negative-intrusive or warm-responsive parenting effects were moderated by the DRD4 polymorphism.

Table 4. Summary of Regression Models

	Ext (full sample)	Ext (less four outliers)	Int (full sample)
Intercept	−.03639	.04539	−.06806
Male	.24814	.16845	−.08090
Family Income	−.00531	−.03076	−.06153
African American (AA)	−.24482	−.28495	.04602
Warm-responsive parenting	.08644	.08780	.16511
Negative-intrusive parenting	.36923***	.40479****	.27327**
L-DRD4	.25353	.17520	.09246
L-DRD4 × AA	−.19947	−.08853	—
Warm-responsive × L-DRD4	−.02877	−.16298	—
Warm-responsive × AA	−.34128	−.45890*	−.51881**
Warm-responsive × L-DRD4 × AA	.24653	.66254†	—
F(ndf, ddf)	3.0 (10,150)**	3.9 (10,146)**	6.1 (7,153)****
Adjusted r^2	.11	.16	.18

Note: $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$; $^{****}p < .0001$; $^{\dagger}p < .10$; Ext, externalizing; Int, internalizing; ndf, numerator degrees of freedom; ddf, denominator degrees of freedom.

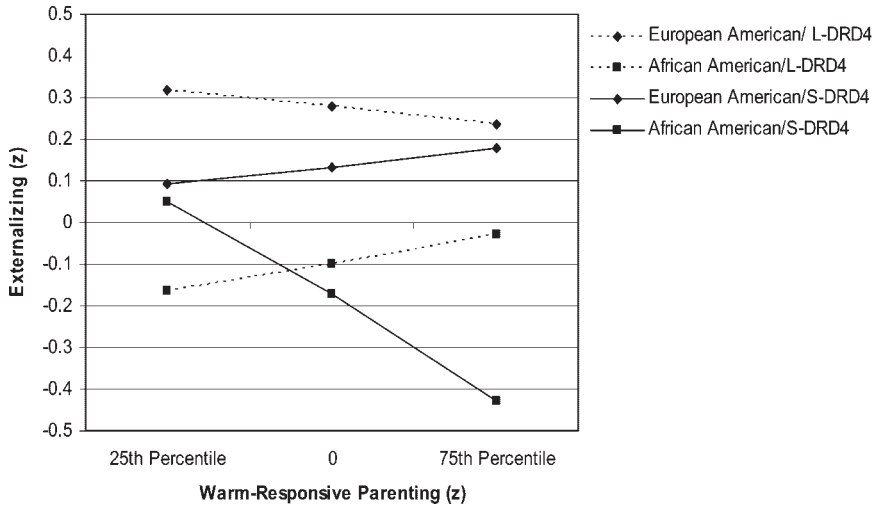

FIGURE 2 Model-implied relationship between warm-responsive parenting and externalizing by race and DRD4 group.

DISCUSSION

Our results indicate that the association between warm-responsive parenting and externalizing behavior is conditional on child's DRD4 genotype and race. Specifically, higher parental warm-responsiveness was associated with less externalizing behavior only for African American children with the S-DRD4 polymorphism. The lack of a direct genetic effect, yet a significant moderating one, further highlights the importance of moving beyond bivariate associations and towards the examination of genes as only one of multiple interacting factors that contribute to the development of complex behavioral characteristics.

The current study is the first, to our knowledge, to find race differences moderating the relationship between DRD4, parenting, and childhood behaviors. We suggest three possible explanations for this finding. First, from a biological perspective, studies and reviews have suggested that the same allele may function differently in various racial groups (Myers & King, 1983; Schraufnagel, Wagner, Miranda, Peter, & Roy-Byrne, 2006). Most of the

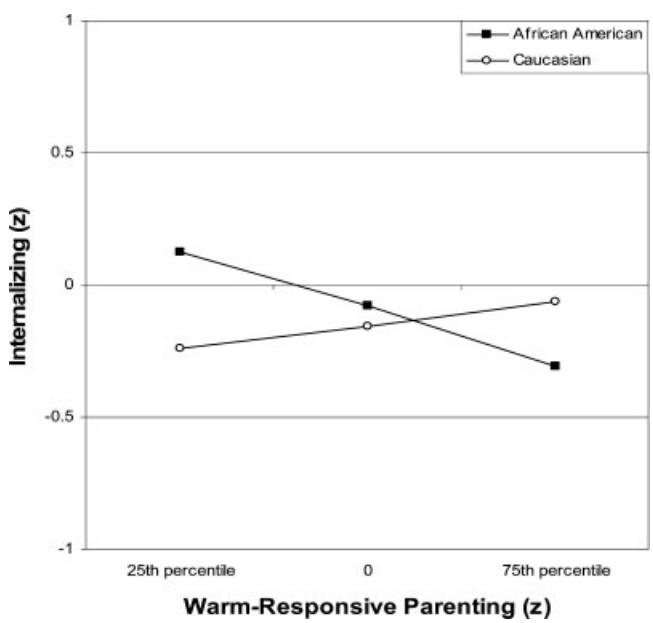

FIGURE 3 Model-implied relationship between warm-responsive parenting and internalizing by race.

studies in this area have consisted of primarily European American samples, while our sample has a higher number of African American than European American families. Thus, the findings of the current study may not replicate those of previous studies due to differences in racial composition.

Second, although the influence of parenting is more effective at reducing externalizing problems for infants with the S-DRD4 genotype, this is only the case for African American families in this sample. Thus, beyond a genetic difference as described above, this effect may be environmental in nature with race acting as a proxy for broader cultural factors. The meaning, interpretation, and response to specific parental behaviors may vary between different cultural groups (Deater-Deckard et al., 1996). For example, one study found a positive correlation between physical discipline and child aggression for European American children, but a nonsignificant (or sometimes negative) correlation between the same variables was found for African American children (Deater-Deckard et al., 1996). These results provide support for the hypothesis that not all groups of children respond the same way to their environment. Thus, it may be the case that African American children exhibit a different response than European American children to the same style of maternal behavior. Or, on the other hand, there may be a cultural difference in the way in which African American mothers respond to their children as compared to European American mothers. In other words, children's reactivity (which may be due to genotype) may elicit a different response from parents based on cultural norms. Although in the current study we did not examine the differential response of infants to parenting as a function of race, these possibilities fit with existing work and lead to exciting directions for future work.

Third, the race × gene × parenting effect may be interpreted from the broader perspective of differential susceptibility to environmental influences due to infant (including genetic) characteristics. Belsky (1997a) has suggested that perhaps not all children are similarly affected by the same rearing experience, and even more specifically ''. . .children in a family vary in terms of their susceptibility to particular influences – for genetic reasons'' (Belsky, 1997b, p. 185). In an empirical study of this hypothesis, Belsky and colleagues found that parenting was indeed a stronger predictor of externalizing problems and inhibition at 3 years of age for a specific group of children—those that were considered highly negative as infants (Belsky, Hseih, & Crnic, 1998). This finding suggests that highly negative infants may be more developmentally responsive and susceptible to the care that they receive than those infants that are less negative. The authors proposed that future research should look more closely at these infants and their vulnerability to rearing influences, and the current analyses provide evidence that this direction may be a fruitful one to pursue. Extant research on the molecular genetics of infant temperament has found that infants possessing S-DRD4 exhibit more difficulty adapting to change in objects, food, or clothes at 1 month of age (DeLuca et al., 2001), lower levels of state regulation and motor organization at 2 weeks of age (Ebstein et al., 1998), more anger-related negative emotionality and shorter reaction time to an anger-inducing situation at 12 months of age (Auerbach et al., 2001), and higher intensity of reaction scores at 3 years of age (DeLuca et al., 2003). Although the current analyses do not include measures of infant behavior over the first months of life in order to confirm these associations, previous research suggests that it is likely that those infants possessing the S-DRD4 allele may be more prone to higher reactivity and negativity. Thus, in the present study, the stronger response of infants carrying the S-DRD4 allele to parenting behavior provides further support for Belsky's hypothesis.

The current analyses also indicate that the interaction between race and warm-responsive parenting significantly predicted reported internalizing behavior in children. Although further examination of the finding that African American children in our sample displayed decreased levels of internalizing behavior in response to warm-responsive parenting compared to European American children is beyond the scope of this study, these results provide interesting data for future research. More interesting, however, is that DRD4 did not contribute to this relationship either independently or in conjunction with parenting or race variables, confirming our (and others) hypotheses. Whereas polymorphisms of the DRD4 gene have been related to externalizing behaviors such as approach, aggression, and novelty seeking (Auerbach et al., 1999; Cloninger, 1987; Ebstein et al., 1998; Zukerman, 1994), it is the presence of other genetic polymorphisms (i.e., serotonin transporter gene), as well as their interaction with environmental factors, that have been related to internalizing problems such as anxiety, depression, and withdrawal in adults and shyness in children (Arbelle et al., 2003; Caspi et al., 2003; Fox et al., 2005; Kaufman et al., 2004; Lesch et al., 1996). Thus, our findings support existing research on the specificity of the association between DRD4 and externalizing behaviors (Bakermans-Kranenburg & van IJzendoorn, 2006), even in children as young as the current sample.

The two dimensions of parenting that we examined were related to child outcomes in different ways. Consistent with existing research, we found a main effect of *negative-intrusive* parenting on maternal report of children's behavior (Booth et al., 1994; Shaw et al., 2001). Children of parents displaying less negative-intrusive

behavior during laboratory assessments were rated by their mothers as exhibiting significantly less externalizing and internalizing behavior at this age than those with highly negative-intrusive parents. However, *negative-intrusive* parenting was not found to be a significant predictor of externalizing behavior when it was examined in conjunction with DRD4, although this was the case with *warm-responsive* parenting. These results are consistent with previous findings that various styles of maternal behavior may exert a range of influences on individual children depending on their genotype or temperament (Kochanska, 1997).

Although these results did not replicate the findings of Bakermans-Kranenburg and van IJzendoorn (2006) the current study contributed to this line of research in at least three important ways. First, we distinguished between two forms of parenting and documented that DRD4 interacted with parental warm-responsive behavior but not negative-intrusive behavior. Importantly, both parenting measures were based on observational coding of parent-child interactions across two points in time (6 and 12 months). Second, we provided additional evidence for the specificity of the association between DRD4 and externalizing behaviors rather than internalizing behaviors. And third, we demonstrated that the relationship between DRD4 and warm-responsive parenting in prediction of externalizing problems was further moderated by race. Together, these results help clarify nonreplications and inconsistent results in previous studies that adopted a main effects strategy for investigating the relationship between DRD4 and childhood behavioral problems.

This study also had at least four limitations. First, despite the strength of our longitudinal measure of child behavior, it is important to note that these data were solely collected via maternal report. Future studies should include observational measures of child behavior, or additional informants (i.e., teachers, other caregivers), in order to provide more convincing evidence of cross-setting consistency of behavior. Second, our sample size is relatively small. Although it was sufficient to detect a three-way interaction, our tests of simple slopes for parent involvement in the prediction of externalizing behaviors separately for race and DRD4 groups were based on relatively small samples which may have increased type II errors. Future studies based on larger samples would allow for more complex models that can incorporate multiple genes as well as multiple environments to more precisely explain behavioral phenotypes. Third, the significant three-way interaction found between parenting, race, and DRD4 in predicting childhood externalizing behaviors was contingent on the removal of four outliers. We identified these anomalous cases using well-established graphical measures (Fox, 1991) and reported results that were obtained both with and without these cases, however, it is still important to note that the interaction was not significant when these four outliers remained in the analyses.

The final limitation concerns the observation of a significant association between children with L-DRD4 and mothers that were rated as less warm-responsive. This relationship indicates the presence of a gene–environment correlation (rGE), or an individual difference in the likelihood of exposure to risky or protective environments due to genotype (Rutter & Silberg, 2002). There are two types of rGE that may be present in the current study (Rutter, 2006). From the perspective of ''evocative'' rGE, children that are genetically predisposed to exhibit more externalizing-type behaviors may also be more difficult to care for which may lead to less warm and sensitive maternal behavior. Alternatively, from the perspective of ''passive'' rGE, mothers with risk genes may pass them on to their children while also providing them with negative environments (due to this same genotype), thus transmitting both genetic and environmental risk which may subsequently lead to behavioral problems. Previous studies have attempted to address evocative and passive correlations using genetically sensitive designs such as adoption or twin studies (for evocative rGE) and twin studies of parents (for passive rGE) (Rutter, Moffit, & Caspi, 2006). Other studies have used analytical methods to adequately test for such correlations, thus ruling them out or properly controlling for them (e.g., Belsky et al., 1998; Kim-Cohen et al., 2006). Unfortunately, the design and assessment protocol of the present study did not permit us to fully investigate (in case of passive) or rule out (in case of evocative) rGE effects. Hence, although we are confident in the presence of the three-way interaction, we acknowledge that the theoretical implications of this effect are open to some debate. Future examinations of gene–environment interactions should design studies with this issue in mind.

In summary, these findings contribute to a growing body of research that implicates the conditional relationship of genes and environment in the prediction of behavioral phenotypes. The current study provides evidence of a gene–environment coaction that predicts early childhood behaviors. More specifically, the S-DRD4 genotype coacted with warm-responsive parenting to influence externalizing behaviors in African American children, but not European American children, early in childhood.

NOTES

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