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Experimental Evidence for Differential Susceptibility: Dopamine D4 Receptor Polymorphism (DRD4 VNTR) Moderates Intervention Effects on Toddlers' Externalizing Behavior in a Randomized Controlled Trial

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In a randomized controlled trial we tested the role of genetic differences in explaining variability in intervention effects on child externalizing behavior. One hundred fifty-seven families with 1- to 3-year-old children screened for their relatively high levels of externalizing behavior participated in a study implementing Video-feedback Intervention to promote Positive Parenting and Sensitive Discipline (VIPP-SD), with six 1.5-hr intervention sessions focusing on maternal sensitivity and discipline. A moderating role of the dopamine D4 receptor (DRD4) variable-number tandem repeat (VNTR) exon III polymorphism was found: VIPP-SD proved to be effective in decreasing externalizing behavior in children with the DRD4 7-repeat allele, a polymorphism that is associated with motivational and reward mechanisms and Attention Deficit Hyperactivity Disorder (ADHD) in children. VIPP-SD effects were largest in children with the DRD4 7-repeat allele whose parents showed the largest increase in the use of positive discipline. The findings of this first experimental test of (measured) gene by (observed) environment interaction in human development indicate that children may be differentially susceptible to intervention effects depending on genetic differences.

Keywords: intervention, dopamine, DRD4, externalizing behavior, toddlers, sensitive parenting

Externalizing behaviors in preschoolers predict a variety of problems in later childhood (Campbell, Spieker, Burchinal, Poe, & National Institute of Child Health and Human Development, 2006; Keenan, Shaw, Delliquadri, Giovannelli, & Walsh, 1998; Romano, Tremblay, Boulerice, & Swisher, 2005), and even in toddlers externalizing behavior shows considerable stability (Alink et al., 2006). The development of externalizing problems has been associated with environmental influences, in particular inadequate parenting (e.g., Belsky, Hsieh, & Crnic, 1998; Burke, Loeber, & Birmaher, 2002; Greenberg, 1999; Patterson, 1976, 1982; Snyder, 1995), as well as with genetic factors (Boomsma, Busjahn, & Peltonen, 2002; Haberstick, Schmitz, Young, & Hewitt, 2005).

Little is known about the interplay between genetic and environmental factors in shaping externalizing behaviors. Some descriptive longitudinal studies on insensitive or harsh parenting found evidence for the importance of genetic vulnerabilities in predicting externalizing behavior in early childhood (Bakermans-Kranenburg & Van IJzendoorn, 2006) or antisocial behavior in adulthood (Caspi et al., 2002). In the current experimental intervention study we examined whether toddlers' genetic differences may explain differential effectiveness of an intervention aimed at decreasing externalizing behavior through improving parental discipline and interaction skills. To our knowledge the current study is the first experimental test of (measured) gene by (observed) environment interaction in child development.

Differential Susceptibility and Genetic Vulnerability

Almost 40 years ago, Thomas, Chess, and Birch (1968) had already noted that infant characteristics may interact with parenting to produce poorer (or better) child outcomes. Belsky (1997a, 1997b, 2005; Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007) recently emphasized the evolutionary rationale for varying susceptibility to environmental influences in siblings. In a continually changing and essentially unpredictable environment the transmission of one's genes will be facilitated by a diversification of investments, that is, offspring with a differential susceptibility to various environments. Similarly, Boyce and Ellis (2005a, 2005b) posited an evolutionary–developmental theory of varying

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biological sensitivity to context, pointing to a crucial role of gene–environment interactions. Belsky (1997a) has suggested that difficult, negatively emotional infants may be most affected by rearing influences. A growing number of studies confirm the moderating role of child negative emotionality in the association between inadequate parenting and the development of externalizing behavior, for example in the context of day care (Crockenberg & Leerkes, 2005), during family conflict (Ramos, Guérin, Gottfried, Bathurst, & Oliver, 2005), and, most importantly, in intervention contexts (Blair, 2002; Klein Velderman, Bakermans-Kranenburg, Juffer, & Van IJzendoorn, 2006).

A complementary approach is the search for "genetic vulnerabilities" to negative child rearing experiences that enhance the risk for negative developmental outcomes (Fox et al., 2005; Rutter, 2006). Studies examining the influence of (measured) gene by (measured) environment interactions have illustrated that genes are involved in both the dynamics and the outcome of development (Rutter, Moffitt, & Caspi, 2006), although much of the processes are still unknown. In a pioneering study, Caspi et al. (2002) found a measured gene (Monoamine oxidase A, or MAO-A; see Brunner, 1996) by measured environment (maltreatment) interaction for antisocial behaviors in adult males. Maltreated children with a genotype conferring low levels of MAO-A expression were more likely to develop antisocial problems in adulthood than comparisons. Bakermans-Kranenburg and Van IJzendoorn (2006) targeted the dopamine D4 receptor (DRD4) gene in relation to insensitive parenting as predictive of toddlers' externalizing behaviors. The exon III DRD4 7-repeat allele has been associated with several forms of externalizing problems across the life span, such as aggression and Attention Deficit Hyperactivity Disorder (ADHD; Ebstein, Benjamin, & Belmaker, 2002; Schmidt, Fox, Rubin, Hu, & Hamer, 2002). The 7-repeat allele has been linked to lower dopamine reception efficiency; the dopaminergic system is engaged in attentional, motivational, and reward mechanisms (Robbins & Everitt, 1999). Parental insensitivity was found to be associated with externalizing behaviors in preschoolers, but only in the presence of the DRD4 7-repeat polymorphism. The increase in externalizing behaviors in children with the 7-repeat allele exposed to insensitive care compared with children without these combined risks was six fold. The results were replicated in the second half of the sample (Bakermans-Kranenburg & Van IJzendoorn, 2006). The dopamine system may therefore affect the susceptibility to environmental influences and may thus play an important role in gene–environment interactions.

VIPP-SD and Externalizing Behaviors

From a meta-analysis on 70 attachment-based intervention studies, it was concluded that rather brief and focused interventions proved to be most effective in enhancing the quality of parenting (a "less is more" approach: Bakermans-Kranenburg, Van IJzendoorn, & Juffer, 2003). Video-feedback Intervention to promote Positive Parenting (VIPP; Juffer, Bakermans-Kranenburg, & Van IJzendoorn, 2007) is a brief and focused program in which parent and child are videotaped during daily situations at home, and feedback is provided to stimulate parents' interactive skills. To prevent the development of externalizing problem behaviors, the VIPP approach has been extended with a focus on parental sensitive discipline (VIPP-SD). Sensitive discipline includes child-oriented discipline methods, such as induction (Hoffman, 1984), empathy for the child when frustrated or angry (Lieberman, 2004), and avoidance of coercive cycles (Patterson, 1982).

Studies using the VIPP approach showed positive effects on parental sensitivity and/or attachment security in nonclinical groups, for example in adoptive families (Juffer, Bakermans-Kranenburg, & Van IJzendoorn, 2005), and in at-risk and clinical groups, such as mothers with an insecure representation of attachment (Klein Velderman et al., 2006) and mothers with eating disorders and their infants (Stein et al., 2006). In a previous report on the current sample, Van Zeijl, Mesman, Van IJzendoorn, et al. (2006) showed that VIPP-SD was effective in promoting sensitive discipline interactions in the intervention group as compared with the control group. Molecular genetic information on this sample, however, became available just recently, and the current study examines the role of DRD4 polymorphisms in explaining differential effectiveness of VIPP-SD.

Hypotheses

In a randomized controlled trial, the VIPP-SD intervention program was tested in 157 families screened for their children's relatively high levels of externalizing behavior. The first question was whether the intervention effects are moderated by the variable-number tandem repeat (VNTR) polymorphism in exon III of the DRD4 in that the children with the 7-repeat allele show the largest decrease of externalizing behaviors. The second question was whether maternal positive discipline (significantly enhanced by VIPP-SD; Van Zeijl, Mesman, Van IJzendoorn, et al., 2006) interacts with DRD4 to shape developmental outcome. The answer to the latter question might provide insight into the mechanism of an experimentally induced Gene × Environment interaction.

Method

The SCRIPT Study

The SCRIPT study (Screening and Intervention of Problem behavior in Toddlerhood) investigated the effectiveness of an early intervention program aimed at reducing externalizing behavior in 1- to 3-year-old children by enhancing maternal sensitivity and adequate discipline strategies. It consisted of a screening phase in a general population sample and a randomized case-control intervention phase in a selected subsample of children with relatively high levels of externalizing behavior.

Sample

Participants were recruited from community records of several cities and towns in the western region of the Netherlands (see Van Zeijl, Mesman, Van IJzendoorn, et al., 2006). Parents of 4,615 1-, 2-, and 3-year-old children were sent questionnaires by mail (screening phase). We obtained 2,408 questionnaires from primary caregivers (response rate 52%). There were no child age or child sex differences between responding and nonresponding families ($p = .11$ and $p = .38$, respectively). Children with scores above the 75th percentile on the Child Behavior Checklist (CBCL) Externalizing Problems scale (age 1 year: scores ≥ 13; age 2 years: scores ≥ 19; age 3 years: scores ≥ 20) were selected for the intervention study. About 2 years after the intervention, the intervention study sample ($N = 237$) was contacted to take part in the collection of DNA material. Cheek cells were collected from 171 children; 157 of them had complete follow-up data. 94% of the mothers were Caucasian, and the majority of the parents were well educated ($M = 3.72$ on a scale ranging from 1 = elementary school to 5 = university degree). These children and their families did not significantly differ from the intervention study sample on experimental group membership (intervention vs. control), maternal age, child age, gender, number of siblings, and level of externalizing behavior at any of the assessments ($ps = .09–.98$). Thus, the children in the current subsample did not react differently to the intervention compared to the total sample.

Procedure

Four months after the screening, families were invited for a pretest in the laboratory. Mother and child completed several tasks (coded afterwards from videotapes by independent coders, unaware of experimental condition and other data concerning the participants) and mothers were asked to fill out some questionnaires. After the pretest, a computer-generated list randomly assigned families, stratified for age group, to either the control group ($n = 83$) or the intervention group ($n = 74$). There were no differences between groups regarding initial level of child externalizing behavior, DRD4 genotype, parental educational level, or child and maternal age ($ps > .23$). The only statistically significant difference was the percentage of boys, which was higher in the control group (64%) compared with the intervention group (47%; see Table 1). Gender was however unrelated to the presence of the DRD4 7-repeat allele ($p = .77$). Families in the intervention group received six home visits and, parallel in timing, families in the control group received six telephone calls. Approximately 1 year after the pretest, families from both the intervention and control

Table 1
Background Variables, Maternal Positive Discipline, and Externalizing Behavior in Intervention and Control Groups

	Total ($N = 157$)		Intervention group ($n = 83$)		Control group ($n = 74$)	
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*
Parental educational level	3.72	1.03	3.69	1.02	3.76	1.03
Maternal age at screening (years)	33.5	3.94	33.5	4.02	33.5	3.88
Boys*[a]	86 (55%)		39 (47%)		47 (64%)	
DRD4 7-repeat allele[a]	49 (31%)		28 (34%)		21 (28%)	
Screening						
Child age (months)	23.1	10.28	23.3	10.31	23.0	10.31
Child externalizing behavior	23.76	6.82	24.30	6.95	23.16	6.65
Overactive	3.93	1.54	3.95	1.66	3.91	1.42
Oppositional	15.17	4.95	15.53	4.78	14.76	5.15
Aggressive	4.67	2.63	4.82	2.85	4.50	2.38
Pretest						
Child age (months)	27.0	10.20	27.2	10.28	26.8	10.17
Child externalizing behavior	25.24	8.19	25.72	7.97	24.72	8.45
Overactive	4.36	1.67	4.25	1.72	4.47	1.62
Oppositional	15.94	5.70	16.36	5.50	15.47	5.93
Aggressive	4.95	2.67	5.11	3.01	4.77	2.25
Maternal positive discipline	−0.02	2.09	−0.00	2.29	−0.05	1.84
Posttest						
Child age (months)	39.3	10.34	39.5	10.43	39.1	10.30
Child externalizing behavior	23.17	8.67	22.93	8.21	23.43	9.20
Overactive	3.80	1.91	3.61	1.87	4.00	1.96
Oppositional	14.66	5.57	14.58	5.25	14.74	5.95
Aggressive	4.71	3.03	4.73	2.98	4.69	3.10
Maternal positive discipline**	0.13	2.15	0.62	2.45	−0.43	1.60
Follow-up						
Child age (months)	52.2	10.54	53.5	10.46	51.1	10.60
Child externalizing behavior	21.47	8.84	21.55	9.08	21.36	8.62
Overactive	3.50	1.80	3.43	1.87	3.57	1.73
Oppositional	14.15	6.07	14.23	6.00	14.07	6.18
Aggressive	3.82	2.59	3.89	2.71	3.73	2.47

Note. DRD4 = dopamine D4 receptor.
[a] Values are *n* (%).
* $p < .05$. ** $p < .01$. (Significance level for difference between intervention and control groups.)

group visited the laboratory for the posttest, using the same procedures as the pretest. One year after the posttest mothers completed the CBCL as part of the follow-up.

VIPP-SD Intervention Program

The SCRIPT study applied the video-feedback method known as VIPP-Sensitive Discipline (VIPP-SD), aimed at parental sensitivity and sensitive parental discipline (Juffer et al., 2007). A female intervener went into the families' homes to provide personal feedback on parenting, using videotaped mother–child interactions as well as information on the development of young children in general (see Van Zeijl, Mesman, Van IJzendoorn, et al., 2006). The duration of each home visit was approximately 1.5 hr. The first four intervention sessions took place every month, the last two sessions every other month. In between home visits, the interveners selected specific video fragments and prepared comments based on the themes of each specific intervention session. Themes of the intervention included the importance of adequate and prompt responses to the child's signals, sharing emotions, distraction and induction as noncoercive responses to difficult child behavior, positive reinforcement, the use of a "sensitive time-out," and consistent and adequate discipline strategies. Sessions 5 and 6 were "booster sessions," aimed at consolidating intervention effects by integrating the tips and feedback given in the previous sessions. At the end of the program, the mothers received a brochure with tips and exercises on the key issues of the intervention.

Parallel to the intervention sessions, the mothers in the control group received six telephone calls as a dummy intervention, to ensure comparable motivation and attention in the intervention and control group and to prevent selective attrition. During these telephone calls mothers were asked to talk about general child development issues (e.g., sleeping, eating, playing), but no advice was given at any time.

Instruments

Externalizing behavior. The Child Behavior Checklist for 1.5- to 5-year-old children (CBCL/1.5–5; Achenbach & Rescorla, 2000) was completed by the mothers during the screening phase, the pretest, posttest and follow-up. Van Zeijl, Mesman, Stolk, et al. (2006) showed that the broadband Externalizing Problems scale was also applicable to 1-year-old children. We focused on the Externalizing Problems scale and its constituent syndrome scales Overactive (5 items), Oppositional (17 items), and Aggressive (9 items). The internal consistencies (Cronbach's alpha) were .66, .89, and .75, respectively ($N = 2{,}408$).

Maternal discipline. Maternal discipline strategies were observed in the laboratory sessions during a 10-min "don't" task. The child was shown a treat, which was subsequently given to the mother with the (written) instruction to refrain from giving the treat to the child until the end of the session, 10 min later. The following positive maternal discipline strategies were observed: distraction, induction, and understanding. The average intraclass correlation (single rater, absolute agreement) for intercoder reliability (for all separate pairs of five coders) was .85 (range .61–.95; $n = 30$). An overall positive discipline score was computed by adding the standardized frequencies of the three positive discipline strategies (factor loadings .79, .57, and .78, Van Zeijl, Mesman, Van IJzendoorn, et al., 2006).

Genotyping. DNA samples were incubated in lysis buffer and genomic DNA was isolated using the Chemagic buccal swab kit (Chemagen Biopolymer-Technologie; Baesweiler, Germany). The average yield of DNA was 4 μg per sample. For amplification primers 5′-GCGACTACGTGGTCTACTCG-3′ and 5′-AGGACCCTCATGGCCTTG-3′ were used. The DRD4 exon III fragments were amplified by an initial denaturation step of 5 min at 95 °C, followed by 38 cycles of 45 s 95 °C, 30 s 60 °C, 1 min 72 °C, and a final extension step of 5 min 72 °C. The number of repeats for each sample was determined by size, fractionating the exon III PCR products on a 2% agarose gel. The main DRD4 genotypes in the sample (2/4, 4/4, 4/7, 7/7) were in Hardy-Weinberg equilibrium, χ^2 ($df = 3$, $N = 131$) = 2.85, $p = .42$. Children were grouped in subgroups with long DRD4 (at least one 7 repeat) versus short DRD4 (both alleles shorter than 7 repeat). Long DRD4 was present in 31% of our sample.

Results

A repeated measures ANOVA with experimental condition and long versus short allele of the DRD4 gene as between-subjects factors and time as within-subjects factor was performed to assess the development of externalizing behavior across screening, pretest, posttest, and follow-up assessments. The three-way interaction of Experimental condition × DRD4 × Time was significant, $F(1, 153) = 4.46$, $p = .04$, partial $\eta^2 = .03$. For children with the 7-repeat DRD4 allele, the intervention was effective in decreasing externalizing behavior, particularly at follow-up, $F(1, 47) = 4.47$, $p = .04$, partial $\eta^2 = .09$, whereas for children without the 7-repeat DRD4 allele the intervention was not effective, $F(1, 106) = 0.24$, $p = .63$, partial $\eta^2 = .00$ (see Figure 1). A priori contrasts of the mean change scores from pretest to follow-up showed a significant difference between the 7-repeat intervention group

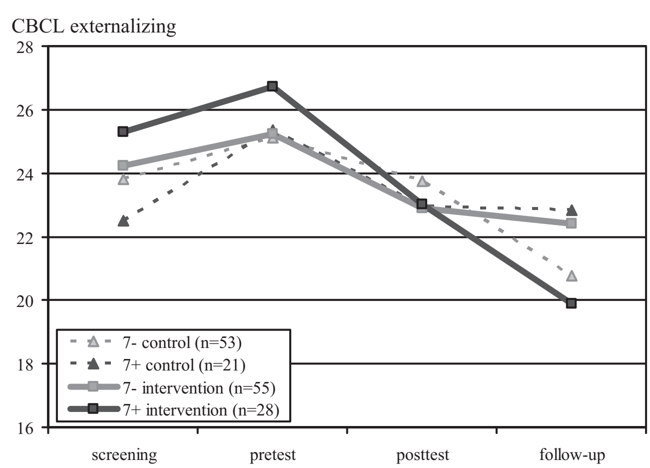

Figure 1. Development of externalizing behavior (as indicated by scores on the Child Behavior Checklist [CBCL] Externalizing Problems scale) across screening, pretest, posttest, and follow-up for intervention and control groups with (7+) and without (7−) the dopamine D4 receptor (DRD4) 7-repeat allele.

and the other groups, $t(153) = -2.06$, $p = .04$. None of the other groups showed significant contrasts, underscoring the susceptibility of the 7-repeat group to the intervention. Exploring whether the intervention affected any specific type of externalizing problems (overactive, oppositional, or aggressive behaviors), we found a significant three-way interaction effect for oppositional behavior, $F(1, 153) = 4.34$, $p = .04$, partial $\eta^2 = .03$, but not for overactive ($p = .39$) or aggressive ($p = .14$) behavior. The intervention produced a decrease of oppositional behavior, but only in children with the 7-repeat allele of the DRD4 gene. No main or interaction effects for gender were found.

Because in a previous report we found that VIPP-SD significantly improved maternal use of positive discipline strategies (Van Zeijl, Mesman, Van IJzendoorn, et al., 2006), we tested whether this intervention effect on parenting was a significant factor explaining the decrease in externalizing behavior in intervention children with the long DRD4 allele. It should be noted that the intervention significantly improved maternal use of positive discipline strategies also in the current sample, $F(1, 155) = 7.76$, $p < .01$, partial $\eta^2 = .05$, but that the intervention did not differentially impact mothers of children with versus without the long DRD4 allele, $F(1, 153) = 0.88$, $p = .35$. For externalizing behavior, the four-way interaction of Experimental condition × DRD4 × Mothers' increased use of positive discipline (change in positive discipline, i.e., posttest residuals controlled for positive discipline at the pretest, dichotomized with a median split) × Time was significant, $F(2, 149) = 3.16$, $p = .045$, partial $\eta^2 = .04$ ($d = 0.47$). Intervention children with the 7-repeat DRD4 allele showed a decrease in externalizing behavior at follow-up (but not at the immediate posttest), particularly when their mothers improved more in the use of sensitive discipline strategies between pretest and posttest assessments (see Figure 2). For control children, such decreases in externalizing behavior were not found (see Figure 3). Surprisingly, control children without the 7-repeat allele whose mothers did not improve much in the use of sensitive discipline showed a decline in externalizing behavior at follow-up, but the decline was not significant.

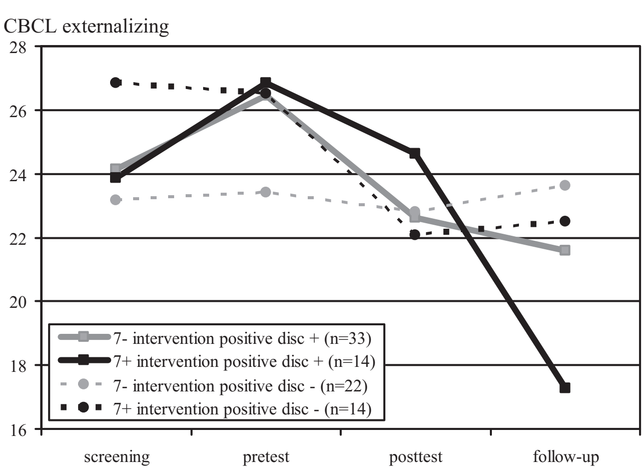

Figure 2. Development of externalizing behavior (as indicated by scores on the Child Behavior Checklist [CBCL] Externalizing Problems scale) across screening, pretest, posttest, and follow-up for intervention groups with more (+) or less (−) increased use of positive discipline (disc) after the intervention, for children with (7+) and without (7−) the dopamine D4 receptor (DRD4) 7-repeat allele.

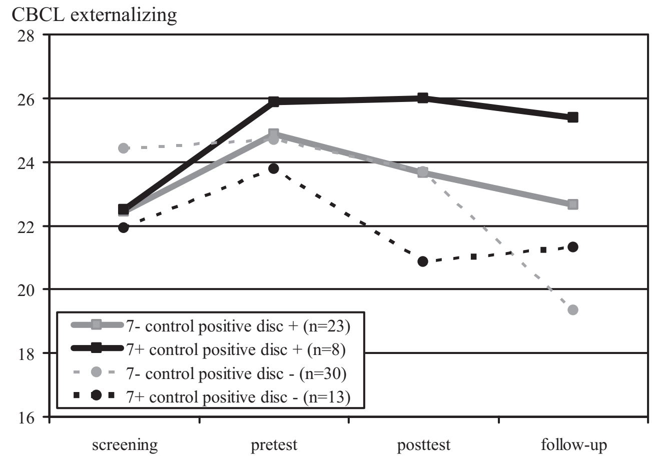

Figure 3. Development of externalizing behavior (as indicated by scores on the Child Behavior Checklist [CBCL] Externalizing Problems scale) across screening, pretest, posttest, and follow-up for control groups with more (+) or less (−) increased use of positive discipline (disc) after the intervention, for children with (7+) and without (7−) the dopamine D4 receptor (DRD4) 7-repeat allele.

For oppositional behavior the four-way interaction was also significant, $F(2, 149) = 3.76$, $p = .03$, partial $\eta^2 = .05$. Intervention children with the 7-repeat DRD4 allele whose mothers improved most in the use of sensitive discipline strategies between pretest and posttest assessments showed the lowest levels of oppositional behavior at follow-up.

Discussion

Gene–environment interactions may play an important role in explaining differential effectiveness of interventions. We found evidence for a larger intervention effect on externalizing behaviors in toddlers with a 7-repeat allele of the DRD4 gene. Children with the 7-repeat allele showed the largest decrease of externalizing behaviors after the intervention, in particular when their parents showed the largest increase in the use of positive discipline. It should be noted that these effects were not apparent at the first posttest assessment, immediately after the intervention, but became manifest at the follow-up, about 1 year later. Although we had expected lower levels of externalizing behavior immediately after the intervention, we already had suggested increasing long-term effectiveness of VIPP-like interventions because of the family system dynamics involved in this type of interventions (see Van IJzendoorn, Bakermans-Kranenburg, & Juffer, 2005). Our findings indicate that children are differentially susceptible to experimentally induced changes in the environment depending on genetic differences. In our case children who varied in the presence of the DRD4 7-repeat allele were differentially susceptible to experimentally induced changes in maternal discipline with respect to externalizing behavior outcomes. Experimentally manipulated gene–environment interactions leave little room for alternative interpretations in terms of passive or evocative gene–environment correlations.

Gene–environment interactions may be crucial for understanding the differential susceptibility of vulnerable versus resilient individuals to inadequate or changing environments. In the medical sciences the search for gene–environment interactions with implications for treatment has started some years ago, for example in the area of essential hypertension (Imumorin et al., 2005). The outcomes of these studies are suggested to lead to more effective primary and secondary prevention programs involving lifestyle interventions in which the role of stress is taken into account, particularly for individuals at increased genetic risk for the disease.

In the psychiatric and behavioral sciences the study of (measured) gene by (measured) environment interactions still is in a perinatal stage (Caspi & Moffitt, 2006). At this point only one replicated and robust finding has been established, namely the moderating role of MAOA for the impact of childhood maltreatment on antisocial behavior. A meta-analysis of five independent studies with varying outcomes demonstrated that the association between maltreatment and externalizing problems is significantly stronger in the group of males with the genotype conferring low versus high MAOA activity (Kim-Cohen et al., 2006).

The dopamine D4 receptor gene appears to be another promising gene in the search for differential susceptibility. In one of the few psychiatric studies on gene–environment interactions, Levitan et al. (2006) suggested that DRD4 is an excellent candidate for genetic association studies, as it has a number of functionally different VNTR polymorphisms. They found a significant interaction between season of birth and DRD4 7 repeat increasing the risk for obesity in seasonal affective disorder. The reward value of food is supposed to be different for individuals with or without the 7-repeat allele. In vitro studies suggest that the 7-repeat allele has decreased affinity for dopamine, which results in a weaker transmission of the intracellular signals in comparison to other alleles (Levitan et al., 2006). Ding et al. (2002) found that the 7-repeat allele originated as a rare mutational event that nevertheless increased to high frequency in human populations by positive selection. This may imply rather strong evolutionary advantages of the phenotypes related to this polymorphism.

In the first developmental study on the role of DRD4 in differential susceptibility to observed rearing influences Bakermans-Kranenburg and Van IJzendoorn (2006) found that children with the 7-repeat DRD4 allele and insensitive mothers displayed significantly more externalizing behaviors than children without the DRD4 7-repeat allele. To test the “favorable side” of the differential susceptibility hypothesis (Belsky et al., 2007), children with the long DRD4 alleles reared by sensitive mothers were contrasted with the other groups, and they showed the lowest levels of externalizing behavior. Thus, children with the 7-repeat DRD4 allele were more susceptible to both sensitive and insensitive parenting (Bakermans-Kranenburg & Van IJzendoorn, 2007).

Why would DRD4 moderate the effects of an attachment-based intervention on externalizing behaviors? The VIPP-SD focuses on increasing parental sensitive responses to the children’s signals and prompt reactions to disciplinary transgressions. In fact, the VIPP-SD can be conceptualized as an intervention that enhances the reward value of parental stimuli (or perhaps more generally: the reward value of the parent) by creating a more concordant and prompt interplay between the child’s and the parent’s communicative signals. Parents learn to read the child’s signals more accurately and are enabled to broaden their repertoire of novel stimuli that trigger the child’s attention and that fulfill its motivational interests. A sensitive parent may be better able to address any novelty-seeking orientation of the child.

Results from animal research suggest that the D4 receptor could play a key role in the dopaminergic modulation of the perception of environmental stimuli (Falzone et al., 2002). We submit that children with the 7-repeat allele are genetically less sensitive to environmental stimuli because of their hypodopaminergic DRD4 functioning and thus need more sensitive environments to feel connected and responsible for changes in the environment. Seeger, Schloss, Schmidt, Rüter-Jungfleisch, & Henn (2004) suggest that the DRD4 7-repeat allele is associated with a reward deficiency syndrome. If children are less sensitive to the reward or reinforcement value of their parents’ interactions, the relation between the child’s actions and the parent’s responses needs more emphasis in order to make the child aware of the communicative link. As children with DRD4 7-repeat alleles need this emphasis on the reward value of parental responses most, they may be the ones who gain most from experimentally enhanced parental sensitivity.

Current findings should be independently replicated. Although gene–environment interactions are usually moderate in size and may be elusive, Evans (1985) stated that even moderate effects explaining as little as 1% of the total variance should be considered important—whereas we found 4% of the variance explained. The reported moderate effect size ($d = 0.47$) indicates a substantial change in the development of externalizing behavior for children with DRD4 7-repeat alleles as a result of the intervention. Because we built our study on an earlier correlational investigation in a different sample (Bakermans-Kranenburg & Van IJzendoorn, 2006; see also Sheese, Voelker, Rothbart, & Posner, 2007), we only tested DRD4 polymorphisms as a potential moderator of the effects of the increased use of positive discipline, thus preventing capitalization on chance. Control children without the 7-repeat allele also showed some decline in externalizing behavior at follow-up, pointing to a potential protective effect of the short DRD4 variants that might be confirmed in a replication study with more power. Replication and—in a later stage—meta-analyses are strongly recommended as strategies for rigorously testing the validity of reported gene to behavior associations (e.g., Ioannidis, 2003).

Focused search for relevant genes and pertinent environments that constitute interaction effects is needed to enhance the chance of replication. In the current study the subgroup of children with the DRD4 7-repeat allele was substantial ($n = 49$) but too small to allow for a formal test of mediation explaining the decrease in child externalizing behavior through changes in parenting in this specific subgroup. Building on the current findings, intervention studies with samples selected for a more balanced presence of the DRD4 7-repeat allele may provide more insight into the processes that render interventions differentially effective (J. Belsky, personal communication, February 7, 2007).

The moderating role of DRD4 in our study does not imply immediate practical applications. We know that children respond differently to the intervention and that this differential susceptibility is partly based on genetic differences. Our study supports the concept of differential susceptibility as linked to gene–environment interaction. What is needed now is more insight into the endophenotypes related to DRD4 (Kieling, Roman, Doyle, Hutz, & Rohde, 2006), for example, problems with sustained attention to environmental stimuli, that may be used for screening families with children who are anticipated to profit most from the intervention efforts.

References

Achenbach, T. M., & Rescorla, L. A. (2000). *Manual for the ASEBA Preschool Forms & Profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Alink, L. R. A., Mesman, J., Van Zeijl, J., Stolk, M. N., Juffer, F., Koot, H. M., et al. (2006). The early childhood aggression curve: Development of physical aggression in 10- to 50-month-old children. *Child Development, 77,* 954–966.

Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2006). Gene-environment interaction of the Dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48,* 406–409.

Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2007). Genetic vulnerability or differential susceptibility in child development: The case of attachment. *Journal of Child Psychology & Psychiatry, 48,* 1160–1173.

Bakermans-Kranenburg, M. J., Van IJzendoorn, M. H., & Juffer, F. (2003). Less is more: Meta-analyses of sensitivity and attachment interventions in early childhood. *Psychological Bulletin, 129,* 195–215.

Belsky, J. (1997a). Theory testing, effect-size evaluation, and differential susceptibility to rearing influence: The case of mothering and attachment. *Child Development, 64,* 598–600.

Belsky, J. (1997b). Variation in susceptibility to environmental influence: An evolutionary argument. *Psychological Inquiry, 8,* 182–186.

Belsky, J. (2005). Differential susceptibility to rearing influence: An evolutionary hypothesis and some evidence. In B. Ellis & D. Bjorklund (Eds.), *Origins of the social mind: Evolutionary psychology and child development* (pp. 139–163). New York: Guildford.

Belsky, J., Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2007). For better *and* for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16,* 300–304.

Belsky, J., Hsieh, K., & Crnic, K. (1998). Mothering, fathering, and infant negativity as antecedents of boys' externalizing problems and inhibition at age 3 years: Differential susceptibility to rearing experience? *Development and Psychopathology, 10,* 301–319.

Blair, C. (2002). Early intervention for low birth weight, preterm infants: The role of negative emotionality in the specification of effects. *Development and Psychopathology, 14,* 311–332.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics, 3,* 872–882.

Boyce, W. T., & Ellis, B. J. (2005a). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17,* 271–301.

Boyce, W. T., & Ellis, B. J. (2005b). Biological sensitivity to context: II. Empirical explorations of an evolutionary-developmental theory. *Development and Psychopathology, 17,* 303–328.

Brunner, H. G. (1996). MAOA deficiency and abnormal behaviour: Perspectives on an association. *Genetics of Criminal and Antisocial Behaviour, 194,* 155–164.

Burke, J. D., Loeber, R., & Birmaher, B. (2002). Oppositional defiant disorder and conduct disorder: A review of the past 10 years, part II. *Journal of the American Academy of Child and Adolescent Psychiatry, 41,* 1275–1293.

Campbell, S. B., Spieker, S., Burchinal, M., Poe, M. D., & National Institute of Child Health and Human Development (2006). Trajectories of aggression from toddlerhood to age 9 predict academic and social functioning through age 12. *Journal of Child Psychology and Psychiatry, 47,* 791–800.

Caspi, A., McClay, J., Moffitt, T., Mill, J., Martin, J., Craig, I., et al. (2002, August 2). Role of genotype in the cycle of violence in maltreated children. *Science, 297,* 851–854.

Caspi, A., & Moffitt, T. E. (2006). Opinion: Gene–environment interactions in psychiatry: Joining forces with neuroscience. *Nature Reviews Neuroscience, 7,* 583–590.

Crockenberg, S. C., & Leerkes, E. M. (2005). Infant temperament moderates associations between childcare type and quantity and externalizing and internalizing behaviors at 2 1/2 years. *Infant Behavior and Development, 28,* 20–35.

Ding, Y., Chi, H., Grady, D. L., Morishima, A., Kidd, J. R., Kidd, K. K., et al. (2002). Evidence of positive selection acting at the human dopamine receptor D4 gene locus. *PNAS, 99,* 309–314.

Ebstein, R. P., Benjamin, J., & Belmaker, R. H. (2002). Behavioral genetics, genomics, and personality. In J. Benjamin, R. P. Ebstein, & R. H. Belmaker (Eds.), *Molecular genetics and the human personality* (pp. 365–388). Washington, DC: American Psychiatric Publishing.

Evans, M. G. (1985). A Monte Carlo study of the effects of correlated method variance in moderated multiple regression analysis. *Organizational Behavior and Human Decision Processes, 36,* 305–323.

Falzone, T. L., Gelman, D. M., Young, J. I., Grandy, D. K., Low, M. J., & Rubinstein, M. (2002). Absence of dopamine D4 receptors results in enhanced reactivity to unconditioned, but not conditioned, fear. *European Journal of Neuroscience, 15,* 158–164.

Fox, N. A., Nichols, K. E., Henderson, H. A., Rubin, K., Schmidt, L., Hamer, D., et al. (2005). Evidence for a gene–environment interaction in predicting behavioral inhibition in middle childhood. *Psychological Science, 16,* 921–926.

Greenberg, M. T. (1999). Attachment and psychopathology in childhood. In J. Cassidy & P. R. Shaver (Eds.), *Handbook of attachment: Theory, research, and clinical applications* (pp. 469–496). New York: Guilford Press.

Haberstick, B. C., Schmitz, S., Young, S. E., & Hewitt, J. K. (2005). Contributions of genes and environments to stability and change in externalizing and internalizing problems during elementary and middle school. *Behavior Genetics, 35,* 381–396.

Hoffman, M. L. (1984). Empathy, its limitations, and its role in a comprehensive moral theory. In J. L. Gewirtz & W. Kurtines (Eds.), *Morality, moral development, and moral behavior* (pp. 283–302). New York: Wiley.

Imumorin, I. G., Dong, Y. B., Zhu, H. D., Poole, J. C., Harshfield, G. A., Treiber, F. A., et al. (2005). A gene–environment interaction model of stress-induced hypertension. *Cardiovascular Toxicology, 5,* 109–132.

Ioannidis, I. (2003). Genetic associations: True or false? *Trends in Molecular Medicine, 9,* 135–138.

Juffer, F., Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2005). The importance of parenting in the development of disorganized attachment: Evidence from a preventive intervention study in adoptive families. *Journal of Child Psychology and Psychiatry, 46,* 263–274.

Juffer, F., Bakermans-Kranenburg, M. J., & Van IJzendoorn, M. H. (2007). *Promoting positive parenting: An attachment-based intervention.* Mahwah, NJ: Lawrence Erlbaum.

Keenan, K., Shaw, D., Delliquadri, E., Giovannelli, J., & Walsh, B. (1998). Evidence for the continuity of early problem behaviors: Application of a developmental model. *Journal of Abnormal Child Psychology, 26,* 441–452.

Kieling, C., Roman, T., Doyle, A. E., Hutz, M. H., & Rohde, L. A. (2006). Association between DRD4 gene and performance of children with ADHD in a test of sustained attention. *Biological Psychiatry, 60,* 1163–1165.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., Moffitt, T. E. (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry, 11,* 903–913.

Klein Velderman, M., Bakermans-Kranenburg, M. J., Juffer, F., & Van IJzendoorn, M. H. (2006). Effects of attachment-based interventions on maternal sensitivity and infant attachment: Differential susceptibility of highly reactive infants. *Journal of Family Psychology, 20,* 266–274.

Levitan, R. D., Masellis, M., Lam, R. W., Kaplan, A. S., Davis, C., Tharmalingam, S., et al. (2006). A birth-season/DRD4 gene interaction predicts weight gain and obesity in women with seasonal affective disorder: A seasonal thrifty phenotype hypothesis. *Neuropsychopharmacology, 31,* 2498–2503.

Lieberman, A. F. (2004). Child-parent psychotherapy. A relationship-based approach to the treatment of mental health disorders in infancy and early childhood. In A. J. Sameroff, S. C. McDonough, & K. L. Rosenblum (Eds.), *Treating parent–infant relationship problems* (pp. 97–122). New York: Guilford Press.

Patterson, G. R. (1976). The aggressive child: Victim and architect of a coercive system. In E. J. Mash, L. A. Hamerlynck, & L. C. Handy (Eds.), *Behavior modification and families* (pp. 267–316). New York: Brunner/Mazel.

Patterson, G. R. (1982). *Coercive family process: A social learning approach.* Eugene, Oregon: Castalia.

Ramos, M. C., Guérin, D. W., Gottfried, A. W., Bathurst, K., & Oliver, P. H. (2005). Family conflict and children's behavior problems: The moderating role of child temperament. *Structural Equation Modeling, 12,* 278–298.

Robbins, T. W., & Everitt, B. J. (1999). Motivation and reward. In M. J. Zigmond et al. (Eds.), *Fundamental neuroscience* (pp. 1246–1260). San Diego: Academic Press.

Romano, E., Tremblay, R., Boulerice, B., & Swisher, R. (2005). Multilevel correlates of childhood physical aggression and prosocial behavior. *Journal of Abnormal Child Psychology, 33,* 565–578.

Rutter, M. (2006). *Genes and behavior. Nature–nurture interplay explained.* Oxford, England: Blackwell.

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene–environment interplay and psychopathology: Multiple varieties but real effects. *Journal of Child Psychology and Psychiatry, 47,* 226–261.

Schmidt, L. A., Fox, N. A., Rubin, K. H., Hu, S., & Hamer, D. H. (2002). Molecular genetics of shyness and aggression in preschoolers. *Personality and Individual Differences, 33,* 227–238.

Seeger, G., Schloss, P., Schmidt, M. H., Rüter-Jungfleisch, A., & Henn, F. A. (2004). Gene–environment interaction in hyperkinetic conduct disorder (HD + CD) as indicated by season of birth variations in dopamine receptor (DRD4) gene polymorphism. *Neuroscience Letters, 366,* 282–286.

Sheese, B. E., Voelker, P. M., Rothbart, M. K., & Posner, M. I. (2007). Parenting quality interacts with genetic variation in dopamine receptor D4 to influence temperament in early childhood. *Development and Psychopathology, 19,* 1039–1046.

Snyder, J. J. (1995). Coercion: A two-level theory of antisocial behavior. In W. T. O'Donohue & L. Krasner (Eds.), *Theories of behavior therapy: Exploring behavior change* (pp. 313–348). Washington, DC: American Psychological Association.

Stein, A., Woolley, H., Senior, R., Hertzmann, L., Lovel, M., Lee, J. et al. (2006). Treating disturbances in the relationship between mothers with bulimic eating disorders and their infants: A randomized, controlled trial of video feedback. *The American Journal of Psychiatry, 163,* 899–906.

Thomas, A., Chess, S., & Birch, H. G. (1968). *Temperament and behavior disorders in children.* New York: New York University Press.

Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., & Juffer, F. (2005). Why less is more: From the dodo bird verdict to evidence-based interventions on sensitivity and early attachments. In L. J. Berlin, Y. Ziv, L. Amaya-Jackson, & M. T. Greenberg, (Eds.), *Enhancing early attachments: Theory, research, intervention, and policy.* (pp. 297–312). New York: Guilford Press.

Van Zeijl, J., Mesman, J., Stolk, M. N., Alink, L. R. A., Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., et al. (2006). Terrible ones? Assessment of externalizing behaviors in infancy with the Child Behavior Checklist. *Journal of Child Psychology and Psychiatry, 47,* 801–810.

Van Zeijl, J., Mesman, J., Van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Juffer, F., Stolk, M. N., et al. (2006). Attachment-based intervention for enhancing sensitive discipline in mothers of 1- to 3-year-old children at risk for externalizing behavior problems: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 74,* 994–1005.

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