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# Gene-Environment Interaction of the Dopamine D4 Receptor (DRD4) and Observed Maternal Insensitivity Predicting Externalizing Behavior in Preschoolers

**ABSTRACT:** Previous studies have related aggression and other externalizing problems in children to either dopamine D4 receptor polymorphisms or harsh and insensitive parenting. In this study it was determined whether the combination of the DRD4 7-repeat polymorphism and maternal insensitivity predicted significantly more externalizing behavior in preschoolers. The results pointed to a gene–environment interaction effect: maternal insensitivity was associated with externalizing (oppositional, aggressive) behaviors, 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 to children without these combined risks was sixfold. The data indicate that children are differentially susceptible to insensitive parenting dependent on the presence of the 7-repeat DRD4 allele. © 2006 Wiley Periodicals, Inc. *Dev Psychobiol* 48: 406–409, 2006.

**Keywords:** DRD4; externalizing behavior; sensitivity; gene-environment interaction; dopamine; parenting

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## INTRODUCTION

A growing number of longitudinal studies have documented that already in preschoolers externalizing problems such as oppositional and aggressive behaviors exist, and that they increase the risk for future maladaptation (Campbell, 2002). In recent years, the dopaminergic system—in particular the 7-repeat DRD4 polymorphism, which is associated with lower reception effectiveness—has been related to several forms of (mal-) adjustment in both childhood and adulthood, such as aggression and

other externalizing problems in children (Benjamin, Ebstein, & Belmaker, 2002; Schmidt, Fox, & Rubin, 2002) and to novelty seeking and substance abuse in adults (Ebstein, Benjamin, & Belmaker, 2002). Behavioral genetic studies in preschool twins demonstrated that externalizing problems are explained by genetic as well as shared and unique environmental factors (Van den Oord, Verhulst, & Boomsma, 1996). The role of harsh and insensitive parenting in the development of children's aggressive and antisocial behaviors has been amply documented (see Campbell, 2002). Children may however differ in their susceptibility to parenting influences (Belsky, 1997; Belsky, Hsieh, & Crnic, 1998), with some children being less responsive and others being more responsive to parental influence—for better (when receiving emotionally supportive care) or for worse (when receiving less supportive care).

It is here that the domains of developmental psychology and clinical behavior genetics partially overlap.

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Studies examining the influence of gene by environment ( $G \times E$ ) interactions illuminate how inheritance contributes to both the dynamics and the outcome of development (Michel & Moore, 1995; Moffitt, 2005; Moffitt, Caspi, & Rutter, 2005; Rutter, 2006). The identification of gene-environment interaction requires however valid measures of environmental differences. The current study is the first in which the interplay between DRD4 and observed parental insensitivity for externalizing problem behaviors was tested. Based on previous studies (see Benjamin et al., 2002; Schmidt et al., 2002), we expected the effects to be specific for externalizing rather than internalizing behaviors.

## METHODS

We observed 47 infants (23 males) at home at 10 months of age. All infants were sampled through the Netherlands Twin Register (Boomsma, Orlebeke, & Van Baal, 1992) and had a twin sibling who through random assignment was not included in the main analyses. The families were predominantly middle-class. On a scale for maternal educational level, ranging from 1 to 7, the mean level was 4.7 ( $SD = 1.6$ ), implying 6 years of secondary education. The mean age of the mothers was 32.1 years ( $SD = 3.4$ ). Mothers and infants were filmed during normal unstructured activities around the home and during two structured activities: feeding and free play. The visits were scheduled at a time that the mother expected the babies to be lively and when a feeding could be observed. Moreover, mothers were asked to complete a questionnaire as a demand that competed with attention to the children (Pederson & Moran, 1996). Maternal sensitivity for each of the twin siblings was independently rated from 1.5 hr of videotaped observations with Ainsworth's 9-point rating scale (Ainsworth, Bell, & Stayton, 1974), comprising four aspects: (1) mother's awareness of her

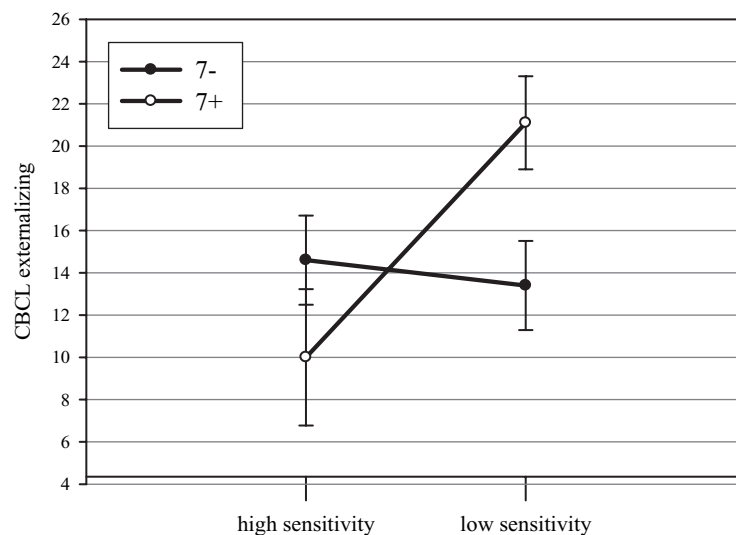
baby's signals; (2) accurate interpretation of them; (3) appropriateness; and (4) promptness of response. The final score represents the extent to which all four of these components of sensitivity were evident during the observations for a specific mother-infant dyad. Interrater reliability was .85 (intraclass correlation). A median split was used to distinguish more sensitive mothers from less sensitive mothers.

Mothers completed the Child Behavior Check List (CBCL/2-3 years; Achenbach, 1992) at 39 months. It contains six syndrome scales: Oppositional, Aggressive, and Overactive ( $r$  ranging from .48 to .60, factor: Externalizing Behavior), Anxious/Depressed, and Withdrawn, ( $r = .62$ , factor: Internalizing Behavior), and Sleep Problems.

Cheek cells were collected at 50 months of age. For amplification primers 5'-GCGACTACGTGGTCTACTCG-3' and 5'-AGGACCTCATGGCCTTG-3' were used. The exon 3 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 3 PCR products on a 2% agarose gel. The main genotypes in the sample (4/4, 4/7) were in Hardy-Weinberg equilibrium ( $\chi^2 = 1.42$ ,  $df = 1$ ,  $p = .49$ ).

## RESULTS

A significant interaction of DRD4 and maternal sensitivity was found for externalizing behavior,  $F(1, 43) = 6.24$ ,  $p = .02$ . Children with the 7-repeat DRD4 and insensitive mothers displayed significantly more externalizing behaviors than children with the 7-repeat with sensitive mothers and than children without the DRD4 7-repeat, irrespective of maternal sensitivity (Fig. 1). The contrast between the group with 7-repeat DRD4 and insensitive mothers and the other groups was significant,  $t(43) = 3.18$ ,



**FIGURE 1** Externalizing scores ( $M$ ,  $SE$ ) of preschoolers with and without the DRD4 exon III 7-repeat allele experiencing sensitive or insensitive parenting.

$p < .01$  (Odds ratio 5.81). Moreover, for children with the 7-repeat the contrast between sensitive and insensitive mothers was significant,  $t(43) = 2.84, p < .01$ , whereas for children without the 7-repeat it was not,  $t(43) = 0.41, p = .69$ . Maternal insensitivity was associated with externalizing behavior, but only in the presence of the DRD4 7-repeat polymorphism.

Concerning the separate syndrome scales, significant interaction effects were found for oppositional behavior,  $F(1, 43) = 6.46, p = .02$ , and aggression,  $F(1, 43) = 5.52, p = .02$ . Only in children with the 7-repeat polymorphism did maternal insensitivity lead to more oppositional and aggressive behavior. For overactive behavior, the interaction was not significant,  $F(1, 43) = 0.52, p = .52$ . There were no significant main effects for either DRD4 or maternal sensitivity.

For internalizing behavior there was no significant interaction effect,  $F(1, 43) = 2.43, p = .13$ , nor any main effect of DRD4 or maternal sensitivity. Child gender was unrelated to DRD4 polymorphisms, to maternal sensitivity, and to CBCL scores. DRD4 was unrelated to maternal sensitivity.

Results were replicated in the second half of the twin-pair sample. Again, the interaction effect of DRD4 and (independently rated) maternal sensitivity was significant for externalizing behavior,  $F(1, 43) = 4.29, p = .04$ . The interaction was also significant for oppositional behavior,  $F(1, 43) = 4.40, p = .04$ , but not for aggression,  $F(1, 43) = 1.33, p = .26$ . Other results replicated those in the first set of children. No significant effects for overactive or internalizing behaviors were found, and there were no main effects of either DRD4 or maternal sensitivity. Only in children with the 7-repeat polymorphism did maternal insensitivity lead to more externalizing (in particular oppositional) behavior.

## DISCUSSION

Our results suggest that children are differentially susceptible to insensitive parenting dependent on the presence of the 7-repeat DRD4 allele. There was a sixfold increase in externalizing behaviors in children with the 7-repeat allele exposed to insensitive care compared to children without this combination of risk factors. Our findings support the idea that genetic effects may be contingent upon gene-environment coaction (Rutter, 2006). Indeed, after genetic studies that made the now well-established case for the importance of genetic influences on psychological traits and mental disorders (Plomin, DeFries, McClearn, & McGuffin, 2001), the current generation of studies is directed at the interplay between nature and nurture (e.g., Bennett et al., 2002; Caspi et al., 2002, 2003; Fox et al., 2005; Jaffee et al.,

2005; Kaufman et al., 2004). Better measurement of the environment is likely to be crucial to discover this interplay even in samples of modest size (Rutter, 2003; Wong, Day, Luan, Chan, & Wareham, 2003).

In a groundbreaking study, Caspi et al. (2002) found a measured gene (*MAO-A*) by measured environment interaction for antisocial behaviors in adult males. The current study on a mixed male and female sample demonstrates the role of DRD4 and observed maternal insensitivity in the development of externalizing problem behaviors. In children with the 7-repeat allele exposed to insensitive care we found a sixfold increase in externalizing behaviors compared to children without this combination of risk factors, indicating that children are differentially susceptible to insensitive parenting dependent on the presence of the 7-repeat DRD4 allele. Further research is needed to detail the developmental processes through which DRD4 interacts with other biological constituents and with the environment in shaping children's externalizing behaviors.

## NOTES

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