Journal of Child Psychology and Psychiatry 48:12 (2007), pp 1160–1173 doi:10.1111/j.1469-7610.2007.01801.x

Research Review: Genetic vulnerability or differential susceptibility in child development: the case of attachment

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Gene–environment interactions interpreted in terms of differential susceptibility may play a large part in the explanation of individual differences in human development. Reviewing studies on the behavioral and molecular genetics of attachment, we present evidence for interactions between genetic and environmental factors explaining individual differences in attachment security and disorganization. In particular, the DRD4 7-repeat polymorphism seems associated with an increased risk for disorganized attachment, but only when combined with environmental risk. Gene–environment ($G \times E$) interactions may be interpreted as genetic vulnerability *or* differential susceptibility. We found support for the differential susceptibility hypothesis predicting not only more *negative* outcomes for susceptible children in unfavorable environments, but also *positive* outcomes for susceptible children in *favorable* environments. **Keywords:** Attachment, gene–environment interaction, differential susceptibility, disorganized attachment, dopamine, behavior problems, genetics.

Attachment theory is an important theoretical framework for studying infant–parent relationships and individual differences in emotion regulation. Attachment is the evolutionary-based, innate predisposition of a child to seek proximity to and contact with a specific figure, notably when the child is frightened, tired or ill (Bowlby, 1969/1982). In the current review we take the development of attachment as an example to demonstrate the crucial role of gene–environment interactions in explaining individual developmental differences. We argue that gene–environment interactions should not be restricted to negative environmental influences, emphasizing genetic vulnerabilities, but should be interpreted in terms of differential susceptibility of children to environmental influences, 'for better or for worse' (Belsky, 1997, 2005).

The idea that the environment plays a major part in explaining individual differences in quality of the infant–parent attachment relationship is central to attachment theory (Ainsworth, Blehar, Waters, & Wall, 1978; Main, 1990). Parental sensitivity is generally regarded as the single most important determinant of infant attachment security, particularly for the three organized attachment strategies: insecure-avoidant, secure, and insecure-ambivalent attachment (Ainsworth et al., 1978; Bretherton, 1990; Pederson & Moran, 1995). Moreover, meta-analytic results (Van IJzendoorn, 1995) demonstrated that parents' sensitivity to their children's attachment signals is partly determined by parents' own secure or insecure mental representation of attachment as assessed with the Adult Attachment Interview (AAI; Main, Kaplan, & Cassidy, 1985; Hesse, 1999). Maternal sensitivity, however, accounts for only a third of the association between parental attachment representation and infant attachment security, leaving a transmission gap of unexplained variance in infant attachment security (Van IJzendoorn, 1995; Belsky, 2005). Genetic factors affecting both security of attachment in the parent and in the offspring might bridge this gap.

Whereas secure as well as insecure avoidant or insecure ambivalent attachment relationships can be considered organized strategies, adaptive to the child's environment (Main, 1990) and speculated to enhance the child's reproductive fitness (Belsky, 1999), some attachment relationships are characterized by the (momentary) absence or breakdown of an otherwise organized strategy, hence defined as *disorganized* (Main & Solomon, 1990; Hesse & Main, 2006). Indices of disorganized attachment behavior are sequential or simultaneous display of contradictory behaviors, such as distress and avoidance, undirected or misdirected movements and expressions, stereotypical and anomalous movements or postures, freezing or stilling behaviors, or expressions of fear or apprehension regarding the parent (Main & Solomon, 1990), which are unrelated to neurocognitive impairments in the child (Pipp-Siegel, Siegel, & Dean, 1999).

The prevalence of attachment disorganization ranges from about 15% in normal, non-clinical samples to 80% in maltreated samples (Carlson, Cicchetti, Barnett, & Braunwald, 1989). Disorganized attachment and sensitivity have been found to be only weakly associated, with a combined meta-analytic effect size of $r = .10$ (Van IJzendoorn, Schuengel, & Bakermans-Kranenburg, 1999). But associations between specific environmental risk

Conflict of interest statement: No conflicts declared.

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

factors, including parental unresolved loss or trauma, and later infant disorganization have been established in a number of studies (for a narrative review, see Lyons-Ruth & Jacobvitz, 1999; for a meta-analysis, see Van IJzendoorn et al., 1999). Main and Hesse's (1990) hypothesis of a link between frightening or frightened parental behavior and disorganized attachment has been tested and demonstrated (Abrams, Rifkin, & Hesse, 2006; Grienenberger, Kelly, & Slade, 2005; Jacobvitz, Leon, & Hazen, 2006; Schuengel, Bakermans-Kranenburg, & Van IJzendoorn, 1999; True, Pisani, & Oumar, 2001). Lyons-Ruth, Bronfman, and Parsons (1999) added extremely insensitive or disruptive parental behaviors as potentially eliciting disorganization (see also Goldberg, Benoit, Blokland, & Madigan, 2003; Madigan, Moran, & Pederson, 2006b).

In a recent meta-analysis on the determinants of infant attachment disorganization, Madigan et al. (2006a) found robust and moderate associations between maternal unresolved loss or trauma, maternal frightening or anomalous behavior, and disorganized attachment in 12 studies including more than 800 families in total. However, less than half of the association between unresolved loss/trauma and disorganized attachment was explained by mediation of frightening parental behavior, and a second transmission gap has become apparent, pointing to the need for further exploration of infant, parental, ecological, and genetic moderating and mediating factors explaining disorganized attachment. Genes seem plausible candidates for bridging the transmission gap because parents and infants share 50% of their genes, and intergenerational transmission of (disorganized) attachment may (partly) be based on transmission of genes from one generation to the next.

Behavioral genetics

Behavioral geneticists have stressed two major points: First, traditional research designs with one child per family, focusing on between-family comparisons, may confound genetic similarities between parents and children with supposedly shared environmental influences (Rowe, 1994; Plomin, 1994). Second, talking about the influence of 'the environment' on child development confounds shared and unique environment. Indeed, behavioral genetic research on twins, siblings, and unrelated (adoptive or step-)children have changed our views on child development drastically, and it has been argued that we have overestimated the role of parents in child development (Harris, 1998; but see Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000; Rose, 1995).

Much of the behavioral genetic research involves large samples but meager measurements; paper-and-pencil methods have been amazingly popular. The statistical need for relatively large samples has probably hampered the application of behavioral genetic methodologies in the field of attachment where detailed, labor-intensive observational assessments prevail. Only a few studies on attachment using genetically informative designs have been conducted. Nevertheless, behavior genetic methodologies can be viewed as useful natural experiments (Rutter, 2003) to test developmental theories.

Behavioral genetics of attachment

Attachment of siblings and unrelated pairs. Genetically informative studies include pairs of children with divergent degrees of relatedness growing up in the same environment (or identical twins growing up in different families). Attachment theory would suggest that children growing up in the same family are likely to relate in similar ways to their parents, at least when parental attachment representations and interactive styles remain stable across time. A study with biological siblings ($N = 138$ pairs) who were observed with their mother in the Strange Situation Procedure (SSP) when each sibling was between 12 and 14 months of age indeed showed significant concordance of attachment (62%; 68% for siblings of the same gender; Van IJzendoorn et al., 2000). Maternal insensitivity to both siblings (shared environment) was associated with concordance of sibling non-security.

In adoptive and step-families biologically unrelated siblings share the same caregiver, and any concordance in attachment quality is thus accounted for by shared environmental influences. Unfortunately, no data on attachment for such families has become available yet. However, Sagi et al. (1995) reported on attachment of biologically unrelated 'siblings' in Israeli kibbutzim, where children typically spend much of their days with six infants and two (biologically unrelated) caregivers in an 'infant house' from their third month onwards. The classifications assigned to each pair of children observed with the same caregiver showed a concordance of 70% ($n = 27$ pairs of children), suggesting that a substantial shared environmental component accounted for the variance in attachment security.

The designs of these kibbutz and sibling studies did not allow for distinguishing the role of (shared and non-shared) environment from the role of genes, because of the absence of contrast groups with varying degrees of genetic relatedness. The question of heritability of (disorganized) attachment could thus not be addressed.

Attachment of twins. The first study of attachment of twins goes back to the early seventies (Brooks & Lewis, 1974). Attachment behavior of 17 pairs of

opposite-sex twins was observed during 15 min of free play of each of the twins with their mother. Proximity seeking, looking, touching, and pleasant vocalizations directed toward the mother were scored. Because the study focused on differences in attachment behaviors between boys and girls no associations between pairs were reported. Moreover, since only dizygotic (DZ) twins were included, any twin concordance in attachment behavior could not be compared to pairs with other degrees of relatedness.

In general, however, twin studies (including both MZ and DZ twins) provide a unique opportunity to test the similarity of siblings' attachment relationships under conditions of similar age and child-rearing contexts. Several studies on MZ and DZ twins' attachment have been conducted, usually involving relatively small samples. Ricciuti (1992) combined three small sample studies of twins (Goldberg, Perrotta, Minde, & Corter, 1986, see also Minde, Corter, Goldberg, & Jeffers, 1990; Goldsmith & Campos, 1990; Vandell, Owen, Wilson, & Henderson, 1988). In this combined sample of 27 DZ twin pairs Ricciuti (1992) found 78% concordance of attachment security; concordance in the 29 MZ twin pairs was 66%, and she therefore concluded that attachment security did not show genetic influence.

Finkel, Wille, and Matheny (1998) found 67% concordance of security in 34 MZ twins but only 38% concordance in 26 DZ twins, indicating only 'modest rearing environment effects' (Finkel et al., 1998, p. 7). It should be noted that the percentage of DZ twin concordance is below chance (see Van IJzendoorn et al., 2000). Finkel and Matheny (2000) reported on the complete Louisville Twin Study of attachment (including the 60 twin pairs from the previous report). In 108 DZ twin pairs they found only 48% concordance of attachment security, whereas in 99 MZ twin pairs 66% concordance was found. Finkel and her colleagues (1998, 2000) estimated the heritability of attachment at 25%; the remaining variance was attributable to non-shared environmental influences, without any role for shared environmental influences. Finkel et al. (1998, 2000), however, used a separation–reunion procedure originally designed for assessing temperament, and it should be noted that this adapted attachment measure was only moderately associated with the Strange Situation procedure.

O'Connor and Croft (2001) observed 110 MZ and DZ twin pairs at 43 months in the Strange Situation procedure. Attachment was coded using the preschool coding manual developed by Cassidy and Marvin in cooperation with the MacArthur Working Group on Attachment (1992). Their findings suggested a modest role for genetic influence (14%) and substantial influences of shared (32%) and non-shared (53%) environment. They did not find a mediating role for temperamental differences in explaining similarities or dissimilarities in attachment between the siblings.

Participants from two sites, London (United Kingdom, 62 twin pairs) and Leiden (The Netherlands, 76 twin pairs), were combined in Bokhorst et al.'s (2003) study on attachment in twins. The two studies used similar designs and measures. For secure versus non-secure attachment as observed in the Strange Situation procedure 52% of the variance in attachment security was explained by shared environment, and 48% of the variance was explained by unique environmental factors and measurement error. The role of genetic factors was negligible. In the same study, genetic factors did explain 77% of the variance in temperamental reactivity (and non-shared environmental factors and measurement error 23%), but differences in temperamental reactivity were not associated with attachment concordance. Similar results were shown for infant–father attachment and temperamental dependency, both assessed with the Attachment Q-Sort (Vaughn & Waters, 1990; Waters, 1995) in the Leiden part of this sample (Bakermans-Kranenburg, Van IJzendoorn, Bokhorst, & Schuengel, 2004). Attachment security was largely explained by shared environmental (59%) and unique environmental (41%) factors. For temperamental dependency, genetic factors explained 66% of the variance, and non-shared environmental factors 34%.

Interestingly, disorganized attachment appears to behave differently when subjected to behavior-genetic analysis. So far only one study (Bokhorst et al., 2003) has applied behavioral genetics to disorganized attachment. Genetic modeling pointed to only unique environmental factors explaining the variance in disorganization.

It should be noted that twin studies of *adult* attachment representations and parental sensitivity are lacking. Whether environmental influences are evident in measures of attachment in later childhood and adulthood remains an important question to be addressed in future research. So far, genetic studies have only covered self-reported adult attachment styles (Brussoni, Jang, Livesley, & MacBeth, 2000; Neyer, 2002) or self-reported parenting (Spinath & O'Connor, 2003) – with diverse (and sometimes mixed) findings. Recently, the first study with AAIs conducted on twins has been reported (Constantino et al., 2006), but genetic analyses were impossible since the design included only MZ twins (with and without conduct problems) reared together. Interestingly, in a sample of genetically unrelated (adopted) sibling pairs (mean age 39 years), 61% concordance of AAI attachment security was found, suggesting that shared environment influences sibling similarities in attachment in adulthood (Caspers, Yucuis, Troutman, Arndt, & Langbehn, in press).

The internal working models view of attachment would predict that continuity over time in patterns of attachment would be driven by shared environmental factors (Fraley, 2002) – a prediction that

could be tested in longitudinal genetic studies of attachment. Several behavior geneticists have suggested that shared environmental factors are likely to be more significant in infancy and early childhood than later in life, and indeed genetic studies of individual differences in mental development and temperament confirm this view (e.g., Plomin, 1994; Plomin & Daniels, 1987). Longitudinal genetic research would allow for the estimation of genetic and environmental influences at different developmental stages and of their influence on age-to-age changes in attachment security.

Shared and non-shared environment in attachment

What are these shared and non-shared environmental factors affecting infant attachment security, and what does the prominent role for unique environment in the case of disorganized attachment mean? For attachment security the importance of shared environmental factors confirms one of the basic notions of attachment theory, and it may point to the vital importance of parental sensitivity. The question is whether parental sensitivity is shared or non-shared across twins or siblings and, critically, whether sensitivity is associated with the shared or non-shared aspects of attachment security. An important weakness of univariate behavioral genetic studies such as described above is that they quantify only the *cumulative* effects of a potentially large number of unspecified processes (genetic or environmental). Since proposed mechanisms or established correlates are not measured, it is difficult to evaluate how behavior-genetic findings fit with empirical data on associations, and whether causal interpretations of one kind or another are plausible. The quantification of variance components is not informative about what specific factors actually play a part (Deater-Deckard, 2000). In recent years there has been increasing recognition of the limitations of univariate methods and the benefits of multivariate designs (e.g., Rutter, 2003).

Using multivariate genetic analyses, Fearon et al. (2006) included both maternal sensitivity and infant attachment of the Bokhorst et al. (2003) twin sample, and examined the extent to which genetic and environmental aspects of maternal sensitivity accounted for the pattern of similarity and dissimilarity in twins' attachments to their mother. In theory, three factors might be responsible for the association between sensitivity and attachment. First, the association between sensitivity and attachment may be attributed to shared environmental factors. If maternal sensitivity is influenced by her attachment representation and this in turn causes variations in attachment security (Van IJzendoorn, 1995), then consistencies in parenting behavior between twins lead to consistencies in their attachment classifications (regardless of their zygosity). In that case the attachment classification of each twin is equally well predicted from the sensitivity shown towards either twin, regardless of genetic similarity. In contrast, when genetic factors underlie the association between maternal sensitivity and attachment (sensitivity as experienced by the child and attachment influenced by the same genes), sensitivity expressed to one twin is a better predictor of the other twin's attachment classification in MZ twins than in DZ twins. Finally, non-shared environmental factors are present when a parent's sensitivity to one twin does not predict the other twin's attachment security; in such cases strong within-twin correlations between sensitivity and attachment are found but low cross-twin correlations. Bivariate behavior genetic models use the differences in within-twin and cross-twin correlations to estimate genetic, shared environmental and non-shared environmental correlations between two measures (Neale & Cardon, 1992; Plomin, DeFries, McClearn, & McGuffin, 2001; Purcell, 2001).

Fearon et al. (2006) found no evidence for a contribution of genetic factors (residing in the infants) to differences in maternal sensitivity. The correlations for sensitivity as rated from 1.5 hours of home observations by independent coders for twin 1 and twin 2 were high in both MZ and DZ twins (between .64 and .69). Genetic modeling indicated that shared environmental factors explained 66% of the variance in sensitivity as experienced by the child, and non-shared environmental factors 34%. Using bivariate behavior-genetic analyses it was then tested whether shared environmental and/or non-shared environmental processes were responsible for the link between sensitivity and attachment (since there was no genetic contribution to maternal sensitivity). Shared environmental effects on sensitivity correlated with shared environmental effects on attachment ($r_C = .58$), indicating that shared environmental effects underlie the association between maternal sensitivity and attachment security, and that the shared environmental component of maternal sensitivity accounted for approximately 33% of the correlation between twins in attachment security.

Non-shared environmental effects created an inverse relationship between sensitivity and attachment. This negative non-shared effect was small in size, accounting for only 2% of the non-shared variance in attachment. What this implies is that non-shared environmental effects had the effect of suppressing the phenotypic association resulting from the shared environmental pathway between sensitivity and attachment. Greater sensitivity to one twin that was not expressed towards the other was associated with lower likelihood of security in the first twin. Or, alternatively, sensitivity towards twin 2 (that was *not* shown to twin 1) impacted *positively* on the twin 1's attachment security. In short, shared variance in maternal sensitivity accounted for part of

the similarity between twins in attachment security, but weak non-shared associations between sensitivity and attachment suppressed the magnitude of the correlation between attachment and sensitivity in twin children. The attachment security of one twin appears to depend on the relationship the parent has with the other twin. These findings underscore the importance of effects of relationships on relationships within a family system (Hinde & Stevenson-Hinde, 1988). The identification of such non-shared influences is essential for the understanding of attachment processes.

For disorganized attachment, at least three factors may contribute to the large effect of non-shared environment. First, in behavioral genetic modeling non-shared environment cannot be distinguished from measurement error. The coding of attachment disorganization might be liable to intercoder differences and low reliability. It seems, however, unlikely that measurement error can account for a large part of the non-shared environmental factor, since the intercoder reliabilities in the pertinent studies were adequate, and both statistically and theoretically significant associations have been reported across a substantial number of studies concerning the determinants and sequelae of disorganized attachment (Van IJzendoorn et al., 1999).

Second, unique characteristics of the children that are not shared by their (twin) siblings might be responsible for the effect of non-shared environment. These unique child characteristics might either make the children differentially susceptible to parenting influences (Belsky, 1997, 2005), or they may evoke differential parenting. Bokhorst et al. (2003) reported that differences in observed fearfulness, parent-reported temperament, and peri-natal conditions and experiences between the twins were not associated with differences in attachment disorganization. Nevertheless, aspects of parenting that are experienced by one but not the other twin may have consequences for each of the twins' attachment as was shown in the Fearon et al. (2006) study. In a similar vein, attachment disorganization of one twin may depend on the parenting behavior shown towards the other twin. Bivariate genetic studies of anomalous parenting and disorganized attachment would be highly informative in this regard.

Third, attachment disorganization may have various determinants, some of which may reside in the unique environment (e.g., one twin sibling but not the other may have a near resemblance with a deceased relative, with unique consequences for parental caregiving), others in the shared environment (e.g., maternal depression, conflicts in the marital relationship) or in genetic factors (see below). A large non-shared environmental effect may reflect heterogeneity of the mechanisms leading to disorganized attachment, and maybe also heterogeneity in the phenotype of disorganization.

Taken together, the influence of non-shared environment is evident in organized and particularly in disorganized attachment behavior. New ways of conceptualizing and investigating these non-shared influences are essential for the understanding of attachment processes. Their identification requires valid measures of environmental factors, together with designs that can separate genetic from environmental influences. For disorganized attachment, the absence of any genetic effect might be somewhat surprising given the molecular genetic findings of a Hungarian research group (see below), and given the idea that dissociation might be the underlying mechanism of disorganization (Hesse & Main, 2006). For dissociation some studies have reported a role for genetic factors (Becker-Blease et al., 2004; Jang et al., 1998), although others did not (Waller & Ross, 1997; see also Harari, Van IJzendoorn, & Bakermans-Kranenburg, 2007).

It should be noted that behavioral genetic studies of attachment used small samples and the confidence boundaries of the reported values for both genetic and environmental factors are broad; in the case of disorganized attachment they are even based on only one study. Furthermore, findings of behavioral genetic studies do not provide information about the relation between actual genes and behavior. Gene expression is not a straightforward process, and may be more dependent on environmental influences than once thought (e.g., Meaney, 2001; Meaney & Szyf, 2005; Rutter, 2006). Molecular genetic studies are a complement – and sometimes an alternative – to behavioral genetics.

Molecular genetics: the dopamine system

DRD4 and -521 C/T. In a first molecular genetic study on attachment Lakatos and colleagues (Lakatos et al., 2000) found an association between the dopamine D4 receptor (DRD4) 7-repeat allele and attachment disorganization. In previous studies the DRD4 gene polymorphism had shown associations with pathological impulsive behavior and substance abuse in adults and attention deficit hyperactivity disorder (ADHD) in children. The dopaminergic system is engaged in attentional, motivational, and reward mechanisms (Robbins & Everitt, 1999), and the 7-repeat allele has been linked to lower dopamine reception efficiency. In Lakatos' (2000) low-risk Hungary sample of 95 infants the estimated relative risk for disorganized attachment among children carrying the 7-repeat allele was 4.15. There was no association between the 7-repeat allele and the three organized attachment classifications.

A second study with the same group of infants involved additional analyses including the functional -521 C/T single nucleotide polymorphism (Lakatos et al., 2002). The -521 T variant has been shown to reduce transcriptional efficiency by approximately

40% compared to the -521 C allele (Okuyama, Ishiguro, Toru, & Arinami, 1999), and may thus be relevant for the dopaminergic neurotransmission. Indeed the association between disorganized attachment and the 7-repeat DRD4 allele was stronger in the presence of the -521 T variant. In the presence of both the DRD4 7-repeat and the -521 T allele in the upstream regulatory region of the DRD4 gene the risk for disorganized attachment was suggested to increase tenfold (Lakatos et al., 2002). The -521 C/T genotype itself had no effect on attachment classification.

A third study followed (Gervai et al., 2005). Using genetic data of the parents of the same sample of infants as used in the previous two reports, the focus was now on the haplotype. Whereas in the Lakatos et al. (2002) study the mere presence of both a DRD4 7-repeat allele and a -521 T variant in the child's DNA had been associated with disorganized attachment, parental DNA now provided the possibility to determine whether the presence of the T.7 haplotype (containing both DRD4 7-repeat allele and the -521 T variant) was responsible for attachment disorganization. Using transmission disequilibrium tests, it was tested whether heterozygous parents transmitted the T.7 haplotype at higher-than-chance rate to disorganized infants. The frequencies of the haplotypes of the two polymorphisms (DRD4 7-repeat and -521T) did not differ between parents of disorganized and parents of secure children, and a preferential transmission of the 7-repeat allele from parents to disorganized children was not significant ($p = .07$). Parental genetic data, therefore, did *not* confirm the link between the two polymorphisms and disorganized attachment. However, the absence of the T.7 haplotype was related to secure attachment ($p = .01$).

Need for replication. Since multiple gene effects are based on an increasingly large number of statistical tests, and are thus liable to false positives (Ebstein, Benjamin, & Belmaker, 2002), and the number of participants with particular genotype combinations and the predicted phenotype becomes increasingly small (Van Gestel & Van Broekhoven, 2003), there was a clear need for independent replication of the study. 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). Whereas a modest genetic effect would not be incompatible with an environmental explanation of disorganized attachment (e.g., through differential susceptibility; Belsky, 1997, 2005), a tenfold increase of the risk to become disorganized as the result of two polymorphisms (Lakatos et al., 2002) is stronger than the developmental model of disorganized attachment would suggest.

In the Leiden twin sample (Bokhorst et al., 2003) cheek cells were collected from 132 children at 50 months of age. As described above, they had been observed with their mothers in the SSP at 13 months. The Leiden twins did not show an association of disorganized attachment with the 7-repeat DRD4 allele ($p = .38$), nor with the -521 C/T genotype ($p = .20$). The interaction was not significant either ($p = .12$). In the presence of the -521 T variant, the 7-repeat DRD4 allele did not increase the risk for attachment disorganization. Including one child of each twin pair did not change the outcomes; the Hungarian findings were not replicated.

No parental DNA was available for the Leiden twins, and thus any disequilibrium in the transmission of the T.7 haplotype could not be tested. It was, however, determined which children were carrying a T.7 haplotype and which children certainly had no T.7 haplotype. Contrasting these children ($n = 115$) for attachment security and disorganization no differences were found: secure attachment was evident in 58% of the children with the T.7 haplotype and in 57% of the children without the T.7 haplotype, and disorganized attachment was observed in 23% of the children carrying the T.7 haplotype and in 19% of the children without the T.7 haplotype (Bakermans-Kranenburg & Van IJzendoorn, 2004). A second attempt to replicate Gervai et al.'s (2005) finding of an association between the presence or absence of the T.7 haplotype and either attachment security or disorganization in a different sample also failed (Van IJzendoorn & Bakermans-Kranenburg, 2006).

Further attempts followed. The appealing link between DRD4 7-repeat and disorganized attachment has now been tested in six samples that we are aware of, some of them with unpublished data on this issue (the Hungarian sample, Lakatos et al., 2000, 2002; Gervai et al., 2005; the Leiden and London twin samples, Bakermans-Kranenburg & Van IJzendoorn, 2004; Bokhorst et al., 2003; Fearon et al., 2006; the Bielefeld study, Spangler & Zimmermann, 2007; the Leiden study on intergenerational transmission of disorganized attachment, Schuengel et al., 1999; Van IJzendoorn & Bakermans-Kranenburg, 2006; and the Leiden Longitudinal Study, Van der Mark, Van IJzendoorn, & Bakermans-Kranenburg, 2002). The combined sample size of these studies amounts to 542 infant–mother dyads. Examining the association between the presence of the DRD4 7-repeat allele and disorganized attachment in this combined group shows no significant effect, χ^2 ($df = 1, N = 542$) $= .29$, $p = .66$.

Summarizing, we may say that the pioneering study of the Hungarian group (Gervai et al., 2005; Lakatos et al., 2000, 2002) reported a potentially important role of two polymorphisms related to the dopamine system, but independent replication of the study did not confirm the role of the DRD4 7-repeat allele and the -521 C/T promoter gene in disorganized attachment – although the power to find the tenfold increase in disorganized attachments in the

attempted replication was more than 95% (Bakermans-Kranenburg & Van IJzendoorn, 2004).

The combined effect size for the association between DRD4 and disorganized attachment is $d = .05$. It should be noted that this is much smaller than the combined effect size for the association between anomalous parenting and disorganized attachment (Madigan et al., 2006b), which is $d = .72$ ($N = 644$). In previous studies the dopamine system has been associated with attention, state regulation, and orienting responses in children, but also with alcohol and drug addiction in adults (Benjamin, Ebstein, & Belmaker, 2002; Ebstein et al., 2002). Its influence on human functioning seems to be broad-band and rather non-specific. State regulation and orientation to stimuli in the outside world may concern cognitive processes involved in the emergence of attachments – as well as in other aspects of socio-emotional development. If further research were to confirm that the dopamine system is important for state regulation in infants, infants with less adequate state regulatory abilities may have more problems with processing potentially inconsistent and paradoxical communication from parents suffering from unresolved loss. However, the scarce behavioural and genetic data are not unequivocal. Spangler et al. (Spangler, Fremmer-Bombik & Grossmann, 1996; Spangler & Grossmann, 1999) reported an association between attachment disorganization and lower newborn orienting ability and regulation. Somewhat paradoxically, Ebstein et al. (1998) found the DRD4 7-repeat allele to be associated with *better* infant orientation and state regulation. The latter results do not seem to support the idea that infants with the 7-repeat DRD4 polymorphism were overrepresented in Spangler et al.'s low-oriented newborns who were later classified as disorganized. Now that genetic data of Spangler et al.'s (1996) sample are available (Spangler & Zimmermann, 2007), it appears that the DRD4 7-repeat allele indeed did not play a role in explaining disorganized attachment in this sample.

Gene–environment interaction

In view of the behavioral genetic and molecular studies on attachment, it must be concluded that the empirical evidence to date falls short in explaining the presence or absence of secure and disorganized attachment behavior on the basis of mere genetic factors. An alternative or complementary explanation including genetic contributions to disorganized attachment pertains to the possibility of gene–environment interaction, the interplay between 'nature' and 'nurture' deriving from genetic effects on liability to risk exposure and susceptibility to environmental risks (e.g., Bennett et al., 2002; Caspi et al., 2002, 2003; Fox et al., 2005; Kaufman et al., 2004). As demonstrated by Suomi (1999) for primates and by Caspi et al. (2002, 2003) for humans, an individual's response to environmental influences may be moderated by his or her genetic make-up (gene–environment interaction). Studies examining the influence of (measured) gene by (measured) environment (G × 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; Rutter, Moffitt, & Caspi, 2006). A failure to include G × E interaction may lead to an overestimation of the genetic component in the case of an interaction between genes and shared environment (Rutter, Pickles, Murray, & Eaves, 2001), and to an overestimation of the non-shared environmental effects when actual interaction effects between genes and non-shared environment are not taken into account (Eaves, Silberg, & Erkanli, 2003). The finding that in the only genetically informative study of attachment disorganization (Bokhorst et al., 2003) all variance was attributed to the non-shared environmental component might reflect this omission of potential G × E effects.

For disorganized attachment, the crucial question may be whether infants with the 7-repeat DRD4 allele are more susceptible to parental unresolved loss and anomalous parenting behavior than infants without this allele. Recently, the first study combining molecular genetics with measurement of the pertinent environmental influences on disorganized attachment has been conducted (Van IJzendoorn & Bakermans-Kranenburg, 2006). Unresolved loss or trauma as a distal index of a risk environment and frightening maternal behavior as a proximal risk factor in the emergence of attachment disorganization were included. In a sample of 63 mothers who experienced at least one important loss (Schuengel et al., 1999), unresolved loss was assessed with the AAI. In the AAI (George, Kaplan, & Main, 1985; Main et al., 1985) the interviewee is asked about childhood experiences and the influence of these experiences, but also about any loss of loved ones and other traumatic experiences. Independent from secure or insecure mental representation of attachment, an unresolved classification is assigned if lapses in the monitoring of reasoning or discourse appear in the discussion of loss or trauma experiences or if the participant describes extreme behavioral reactions in connection with these experiences (Main & Goldwyn, 1984/1998). Frightening/frightened behavior (Main & Hesse, 1992/1995) of the mothers was coded on the basis of 3 to 4 hours of home observations when the infants were 10 to 11 months old. The Strange Situation procedure (Ainsworth et al., 1978) was administered between 14 and 15 months.

A moderating role of the DRD4 gene was found: Maternal unresolved loss or trauma was associated with infant disorganization, but only in the presence of the DRD4 7-repeat allele in the child. Children

with the short DRD4 allele did not show higher scores for disorganized attachment when their mother was unresolved. The increase in risk for disorganization in children with the 7-repeat allele exposed to maternal unresolved loss/trauma compared to children without these combined risks was 18.8 fold. The T.7 haplotype showed a similar interaction effect: an elevated risk for infant disorganization in the case of maternal unresolved loss (odds ratio 3.24). However, because children with long DRD4 combined with -521 CC were absent in the sample the effects of the haplotype containing both the long DRD4 and the -521 T alleles could not be distinguished from the effects of DRD4 alone. For maternal frightening behaviour no moderating effects were found.

What do these findings imply? First, all participating mothers experienced the loss of a relative. The absence of an association between DRD4 7-repeat and infant disorganization in this group of mothers means that the environmental risk of being exposed to a parent who suffered an important loss is insufficient for the child to become disorganized. As attachment theory would predict (Ainsworth & Eichberg, 1991; Hesse, 1999; Hesse & Main, 2006), only parents who show signs of unresolved loss or trauma in their cognitive representation of past experiences might unwillingly stimulate their infants to become disorganized. Second, frightening parental behavior showed no moderating effect on infant disorganized attachment. The distal risk factor 'unresolved loss' must be transmitted to the child through some kind of parental behavior, but frightening behavior might be just one of the possible pathways (and thus one of the relevant proximal risk factors), with others being important as well. Although the specific parental behavior that constitutes the active ingredient of the environmental component has yet to be revealed, the findings nicely illustrate gene–environment interaction; they support the idea that genetic effects may be contingent upon gene–environment co-action (Rutter, 2006).

Research into gene–environment interactions, complementary to the traditional environment-focused explanations of attachment, may be a fruitful approach to the understanding of the developmental pathways to (in-)secure and disorganized attachment. Extension of studies combining molecular genetics with careful measurement of environmental factors may provide the pathways to unraveling the interplay between genes and environment in the development of attachment relationships.

Towards a model for gene × environment interaction as differential susceptibility

The search for gene–environment interactions may be inspired by the hypothesis of 'differential susceptibility' (Belsky, 1997, 2005; Boyce & Ellis, 2005), or by the idea of 'genetic vulnerability' (Paris, 2000; Rutter, 2006). The former idea implies that some individuals, perhaps for genetic reasons, are more susceptible than others to positive *as well as* negative rearing experiences that influence both positive and negative outcomes, whereas the latter model views some children as having a (genetic) susceptibility exclusively to a negative rearing experience resulting in a negative outcome (see Figure 1). These two models are of course not mutually exclusive, but the differential susceptibility hypothesis predicts that not only will children who are more susceptible to environmental influences show more negative outcomes in unfavorable environments, but also that these children will show more positive outcomes when they grow up in favorable environments. Although much of the biological processes involved in these models are still unknown, changes in gene expression, known as environmental programming, may play a role (Meaney, 2001; Meaney & Szyf, 2005).

Applied to the study of parental unresolved loss and infant disorganized attachment, the differential susceptibility hypothesis would predict higher levels of disorganized attachment for infants with the long DRD4 variants when their mothers struggle with unresolved loss or other trauma, and *lower* levels of disorganization in children with the same genotype when their mothers do *not* show evidence of unresolved loss. We tested this hypothesis empirically by contrasting children with the long DRD4 variant of mothers without unresolved loss with the three other groups. The contrast was significant; t (20.76, unequal variances) = 4.70 ($p < .01$). Children with long DRD4 who had mothers without unresolved loss showed significantly *less* attachment disorganization than children with the short DRD4 variant (regardless of their mothers' unresolved loss status) or children with long DRD4 and mothers with unresolved loss. The contrast with the latter subgroup was also significant t (4.37, unequal variances) = 4.53 ($p < .01$), as was the contrast with the group of children with short DRD4 (regardless of their mothers' unresolved loss status), t (26.34,

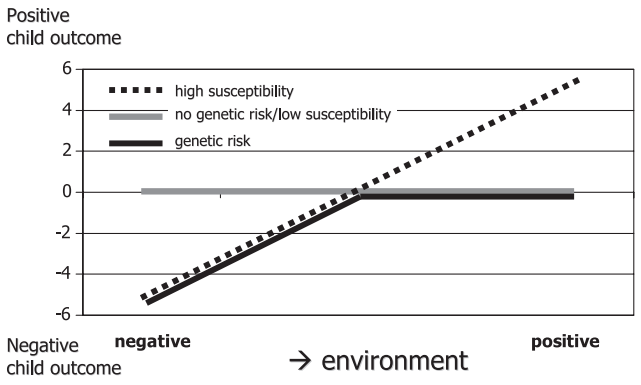

Figure 1 Genetic vulnerability and differential susceptibility: a model

unequal variances) = 3.19 ($p < .01$). These findings support the notion that the DRD4 7-repeat allele constitutes not only a genetic risk but may be a genetic basis for differential susceptibility over the whole range, with most positive outcomes for children with the long DRD4 variant *without* the negative environmental factor.

Studies examining a negative outcome (disorganized attachment) and negative rearing environments (i.e., unresolved loss, frightening behavior) may be considered only partially testing the differential susceptibility hypothesis, because the absence of a negative outcome and a negative rearing environment is not necessary equal to the presence of a positive rearing environment and positive developmental outcomes. In this respect a crucial question that remains to be addressed is whether the genotype that appears to make a child vulnerable to unresolved loss vis-à-vis disorganization also makes the organism more susceptible to certain positive rearing experiences (e.g., high quality of sensitive parenting) when it comes to a positive outcome (e.g., higher levels of attachment security).

In that regard one other study on differential susceptibility and the role of DRD4 polymorphisms may be of interest. The study addressed not attachment security or disorganization, but externalizing problem behaviors (Bakermans-Kranenburg & Van IJzendoorn, 2006). The 7-repeat DRD4 allele has been associated with several forms of (mal-)adjustment in both childhood and adulthood, such as aggression and other externalizing problems in children (Benjamin et al., 2002; Schmidt, Fox, Rubin, Hu, & Hamer, 2002). The role of harsh and insensitive parenting in the development of children's aggressive and antisocial behaviors has also been amply documented (see Campbell, 2002), but findings were not always convergent. The interplay between DRD4 and observed parental insensitivity for externalizing problem behaviors (Child Behavior Checklist (CBCL); Achenbach, 1992) was tested in a sample of 47 twins, with a random selection of one child per twin pair included in the analyses (Bakermans-Kranenburg & Van IJzendoorn, 2006). A gene–environment interaction effect was found: Children with the 7-repeat DRD4 allele and insensitive mothers displayed significantly more externalizing behaviors than children without the DRD4 7-repeat allele (irrespective of maternal sensitivity). 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 six fold. The results were replicated in the second half of the twin pair sample, with similar results (Bakermans-Kranenburg & Van IJzendoorn, 2006). It should be noted that DRD4 was not related to maternal sensitivity, excluding active gene–environment correlation as an alternative explanation for the findings (see Kim-Cohen et al., 2006).

In order to test the 'favorable side' of the differential susceptibility hypothesis, we now contrasted children with the long DRD4 polymorphism and sensitive mothers with the other groups. Indeed, children with the DRD4 7-repeat polymorphism and sensitive mothers tended to show the *lowest* levels of externalizing problem behavior, $t(43) = 1.84$, $p = .07$. A similar tendency was found for oppositional behavior, $t(43) = 1.82$, $p = .07$; for aggressive behavior the contrast was significant, $t(9.99$, unequal variances) $= 2.31$, $p = .04$, see Figure 2. Thus, children were differentially susceptible to both sensitive *and* insensitive parenting dependent on the presence of the 7-repeat DRD4 allele.

The next step in this line of research is testing whether children with the DRD4 7-repeat allele are differentially susceptible to experimental manipulation of the environment. The findings of the first *experimental* tests of (measured) gene by (observed) environment interaction in human development indicate that children are indeed differentially susceptible to intervention effects depending on genetic differences. Children with the DRD4 7-repeat allele were more susceptible to experimentally induced changes in maternal discipline with respect to externalizing behavior outcomes (Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, in press) and they showed lower levels of daily cortisol (Bakermans-Kranenburg, Van IJzendoorn, Mesman, Alink, & Juffer, in press) after an intervention aimed at enhancing maternal sensitivity and positive discipline strategies (Van Zeijl et al., 2006).

These first studies testing the applicability of the differential susceptibility hypothesis for positive environmental effects on the more susceptible groups involve relatively small samples and certainly

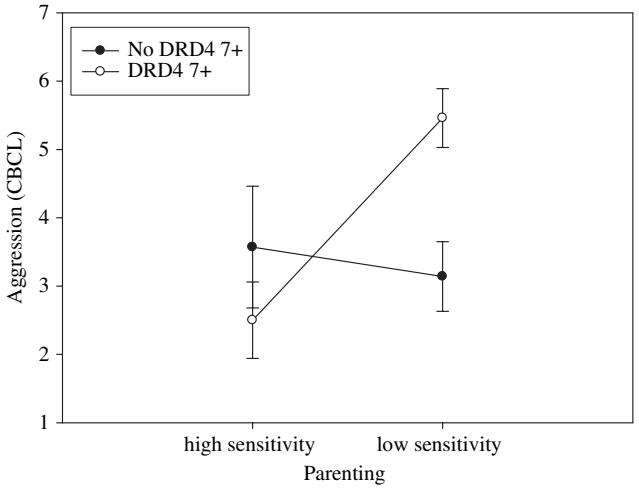

Figure 2 Aggression (*M,SE*) of children with and without the DRD4 7-repeat allele experiencing sensitive or insensitive parenting

need replication. Furthermore, future research may address the question whether such differential susceptibility to favorable and unfavorable environmental influences is also applicable to adult attachment and parenting behaviors. Parents with a DRD4 7-repeat allele may, for example, be more vulnerable to unresolved loss when they suffer the loss of a loved one or experience other traumatic events, or their parenting may be more affected by the presence or absence of, e.g., a supportive partner relationship.

When these questions are addressed, it should be realized that genes steering the dopamine production are only one set of candidates to be investigated. As an example of a polymorphism that affects the serotonin rather than the dopamine system, Caspi et al. (2003) found that negative life events predicted depression among carriers of a short variant of the 5-HTTLPR serotonin transporter, whereas no direct association between the 5-HTT gene and depression was observed. Exploratory investigations of adult attachment suggest that attachment representations of adult adoptees and the biological offspring of adoptive parents with a short 5-HTT allele are less often secure when assessed with the AAI than their counterparts with the L-L variant (Riggins-Caspers, Cadoret, & Philibert, 2003).

Both serotonin and dopamine systems are highly relevant for attachment-related studies of the interplay of genes and environment, because various investigations have documented the significance of these systems for psychological functioning (e.g., Bennett et al., 2002; Caspi et al., 2002, 2003; Fox et al., 2005; Jaffee et al., 2005; Kaufman et al., 2004). In a similar vein, genes affecting the oxytocin and vasopressin neuropeptide systems may play a part in the establishment of social bonds and the regulation of emotions (Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005).

We therefore propose a model (see Figure 1) in which genes steering these systems are included as genotypes indicating genetic vulnerability or differential susceptibility (with the DRD4 receptor polymorphism and the 5-HTTLPR serotonin transporter as examples that have proven to be useful in past research). The selection of risk environments in order to examine gene–environment interaction (Moffitt, 2005; Moffitt et al., 2005) may be optimal to uncover genetic vulnerabilities, but the additional inclusion of more positive environments may be necessary to examine the bright side that is implied in the differential susceptibility hypothesis.

Acknowledgements

The authors were supported by research grants from the Netherlands Organization for Scientific Research (MJBK: VIDI grant no. 452-04-306; MHvIJ: NWO SPINOZA prize).

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Manuscript accepted 30 May 2007