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Attachment, Parenting, and Genetics

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Contents

ATTACHMENT

Without doubt, forming attachments, as defined by Bowlby (1982), is a genetic characteristic of human beings. The most general definition of attachment is one that considers it to be an inborn bias of human infants to seek proximity to a protective caregiver in times of stress, distress, illness, and other physical or psychological discomfort. Human offspring would not be able to survive without the care of a stronger or more experienced conspecific who is able to regulate body temperature, food intake, and stress levels, because young infants cannot take care of these basic physiological and psychological needs by themselves. The early environment of evolutionary adaptedness among humans required the basic ability to become emotionally attached in order to survive and enhance inclusive fitness (Bowlby, 1982).

Attachment, however, is also strongly dependent on the environment. Although all infants are born with the ability to become attached to a protective caregiver, they differ in the way in which this competence is expressed. Infants differ rather drastically in the quality of their attachment relationships, and attachment theory hypothesizes that this “attachment performance” is largely, albeit not exclusively, environmentally determined. Differences in attachment behaviors and relationships emerge in the course of the first few years of life as a consequence of childrearing experiences with parents and other caregivers. Infants may develop secure or insecure attachments in response to a more or less sensitive or predictable social environment. The parallel to language development is useful here. Every child is born with the capacity to learn a language, but the specific language environment determines the kind of language to be learnt.

Paradoxically, the search for the genetic foundation of attachment seems to be inspired by two contrasting goals. On the one hand, cross-cultural researchers who study attachment wish to document the balance between universal and culture-specific influences on attachment *competence*, in order to test the core hypothesis that every human infant is born with a bias to become attached (see xx & yy, chapter xx, this volume). On the other hand, the behavioral and molecular genetics studies of attachment are aimed at elucidating the genetic versus environmental determination of attachment *performance*, with the assumption (on the part of attachment researchers) that attachment differences are mainly rooted in variations in the environment in which an infant grows up. Here we focus on the genetics of individual differences in attachment behavior and relationship quality.

Behavioral Genetics of Attachment

Twins have been a great source of information about human development. The comparison of monozygotic (MZ, or identical) twins, whose structural DNA is exactly the same, with dizygotic (DZ, or fraternal) twins, who share on average half of their DNA, is an experiment-by-nature. If children within an MZ twin pair are more similar to each other in terms of attachment (or any other trait) than children within a DZ twin pair, one might conclude that genetic similarity matters. In the case of strong similarity of attachment between MZ twins and much smaller similarity between DZ twins, attachment would be considered highly heritable. This conclusion is warranted of course only when we assume that parents do not treat MZ and DZ twins differently. The equal-environments assumption has been examined and found to be valid for a variety of phenotypes (Cronk et al., 2002), but for parenting relevant to attachment development this information is not available.

Only a few, rather small twin studies of infants' and preschoolers' attachments have been reported (Bakermans-Kranenburg, Van IJzendoorn, Bokhorst, & Schuengel, 2004; Bokhorst et al., 2003; Finkel, Wille, & Matheny, 1998; O'Connor & Croft, 2001; Ricciuti, 1992; Roisman & Fraley, 2008), and the majority of these studies did not find differences in attachment similarity between MZ and DZ twin pairs. In general about 50% of the variance in attachment security could be attributed to the shared environment (parenting influences that make children within the same family similar), and about 50% of the variation could be explained by unique influences (that make children within a family more dissimilar) and measurement error. There seemed to be no room for genetic influences. Interestingly, the shared environmental variance in attachment security showed substantial overlap with the shared environmental variance in observed maternal sensitivity, suggesting that parental sensitivity is indeed an important part of the (shared) environment shaping children's attachment patterns (Fearon et al., 2006).

The only exception to the rule that young children's attachment security is not heritable was the study by Finkel et al. (1998) that found considerable heritability for attachment, but unfortunately used an attachment measure that was originally meant to assess temperament. In the study by Bokhorst et al. (2003), temperamental reactivity was estimated to be highly heritable whereas attachment security was mainly environmentally based. In a study of infant-father attachment using the Attachment Q-Sort (AQS; Vaughn & Waters, 1990), high heritability of temperament went together with low heritability of attachment security to the father -- using the same measure and the same sample as Bakermans-Kranenburg et al. (2004). It is important to note that the developmental roots of attachment and temperament seem to be radically different, which underlines their conceptual and functional differences

(Van IJzendoorn & Bakermans-Kranenburg, 2012; see Vaughn & Bost, chapter xx, this volume).

Disorganized attachment has rarely been studied with a twin design. Disorganized attachment is observed in children who are maltreated or otherwise frightened by parental behavior, for example because their parents struggle with unresolved loss or other potentially traumatic experiences (Cyr et al., 2010; Schuengel et al., 1999; see Lyons-Ruth & Jacobvitz, chapter xx, this volume). Disorganized attachment behaviors include, among others, frightened facial expressions, freezing or stilling of behavior, or avoidance in distress when a parent returns following a brief separation in the Strange Situation (Main & Solomon, 1990). Heritability estimates of disorganized attachment approach zero, and in remarkable contrast to attachment security, no trace of shared environmental influence can be found (Bokhorst et al., 2003). Variance in disorganized attachment seems to be almost exclusively explained by a unique environment. This suggests that unique experiences with the parents trigger children's disorganized attachment. It may also imply a large error component in the assessment of disorganized attachment, which indeed is by far the most difficult part of the attachment coding system to master. Of course, low statistical power should be taken into account when considering the absence of heritability; the modest sample size and skewed distribution of disorganized attachment result in large confidence intervals around the estimates.

In several cases the influence of genetics on traits or characteristics such as cognitive development has been shown to increase with age. The influence of the environment seems to decrease as children grow older, undergo a variety of influences outside the family, and are more able to shape their own environments. Indeed genetic studies of individual differences in mental development and temperament confirm this

view (e.g., Plomin, 1994; but see Haworth, Dale, and Plomin, 2009, for contrasting effects). In the largest twin study on attachment to date, Fearon and colleagues (2014) used the semi-structured Child Attachment Interview (CAI; Shmueli-Goetz, Target, Fonagy, & Datta, 2008) in a sample of 551 twin pairs aged 15 years. The CAI is modeled after the Adult Attachment Interview (see Hesse, Chapter xx, this volume), assessing attachment security in terms of coherence of discourse when discussing childhood attachment experiences. Surprisingly, the authors found correlations between attachment security in MZ twins that were about twice as strong as correlations in DZ twins, and they concluded that attachment in this sample of young adolescents was about 40% heritable, whereas the influence of the shared environment was negligible (Fearon et al., 2014).

Of course, this finding might point at a genuine developmental phenomenon of increasing genetic influence with growing age. It should be noted, however, that adolescence is a somewhat difficult age period to measure attachment, because many adolescents are in the middle of a potentially confusing struggle for independence from their parents. This might be the reason that in this and other studies, dismissing attachments seem to be temporarily overrepresented (Bakermans-Kranenburg & Van IJzendoorn, 2009). Fearon and colleagues found insecure-preoccupied attachments in only 5% of the cases, and unresolved attachments in only 3% of their subjects, so any conclusion about heritability of adolescent attachment is limited to the specific security-dismissing dimension (see also Van IJzendoorn & Bakermans-Kranenburg, 2014). Clearly more longitudinal studies going beyond adolescence are needed to test whether heritability of attachment indeed increases with age, and well into adulthood. One relevant study included adopted sibling pairs from the Iowa Adoption Studies who were on average 39 years old when the AAI was administered (Caspers et al.,

2007). Concordance rates showed substantial similarity of attachment representations between the siblings, although they were genetically unrelated – they only grew up in the same family. These findings do not support the idea of increased heritability with age, but point to an important role for shared environmental influences. Thus, the findings reported by Fearon et al. (2014) may be specific to adolescence.

Molecular Genetics of Attachment

Behavioral genetic studies of the kinds discussed so far involve inferring heritability from phenotypic (dis-)similarities between mono- and dizygotic twins, but the genetic makeup of the study participants' itself is not assessed. This indirect method of inferring heritability has several drawbacks, including dependence on the specific population distribution of relevant environmental and genetic features. In an environment with sufficient food for everyone, physical growth would appear to be much more heritable than in an environment with large variation in food supply. In contrast, in molecular genetic studies structural DNA patterns are assessed directly, often with great precision, and variation in the environment does not play a critical role in estimating heritability, except when the environment influences the expression of genes. (This issue – the study of epigenetics - will be discussed later on in this chapter.)

The first molecular genetic study of attachment was published by the Hungarian team of Gervai (Lakatos et al., 2000). It was conducted on a rather small low-risk Hungarian sample (N = 95 infants) and is an example of the candidate-gene approach (i.e., focusing on a particular gene of interest). It revealed a strong association between the dopamine receptor D4 gene (DRD4) and infant disorganized attachment. Child carriers of the DRD4 7-repeat allele appeared to run a fourfold

elevated risk of disorganized attachment. The T-variant of the -521 C/T single nucleotide polymorphism (SNP) in the regulatory region of the DRD4 gene increased the risk for disorganization even further (Lakatos et al., 2002). DRD4 had already acquired a bad reputation as a "risk" genotype for impulsivity, addiction, and attentional problems, and the neurotransmitter dopamine had been found to be involved in motivational and reward mechanisms (Robbins & Everitt, 1999). But did this DRD4 genotype also deserve a bad reputation in relation to attachment?

Although the link between DRD4 and attentional and motivational issues seemed to make the association with disorganization somewhat plausible, the findings were surprising against the background of the behavior genetic study of disorganization by the Leiden team (Bokhorst et al., 2003), which did not find any evidence for genetic influences on disorganized attachment. DNA was therefore collected in the Leiden twin sample to replicate the Hungarian findings but without success (Bakermans-Kranenburg & Van IJzendoorn, 2004). Several other replication attempts followed, but the picture did not change: Across a series of studies (total N = 542) the combined effect size of the association between DRD4 and disorganization was close to zero (Bakermans-Kranenburg & Van IJzendoorn, 2007). Compared to the combined effect size across studies of the association between parental frightening or anomalous behavior and disorganized attachment (Cohen's d = 0.72, total N = 644; Madigan et al., 2006) this was a disappointing outcome for advocates of genetic influences on attachment.

More molecular genetic studies involving candidate genes have been conducted in recent years. Some of the studies indicated a potential role for candidate genes. For example, Spangler et al. (Spangler, Johann, Ronai, & Zimmermann, 2009) reported an association between attachment disorganization and the short

polymorphism of the serotonin transporter-linked polymorphic region (5-HTTLPR), qualified by an interaction with maternal responsiveness (see below). This genotype is one of the usual suspects in the study of psychiatric genetics, and is considered to be a "risk" factor for depression and anxiety. Fearon and colleagues (Frigerio et al., 2009) studied the associations between several gene polymorphisms implicated in the serotonin and dopamine systems (5-HTT, COMT, GABRA6, DRD4, DRD4/-521) and attachment security as well as attachment disorganization in an Italian sample of 100 infants, but no association survived stringent statistical tests.

The largest candidate-gene study on attachment to date is the combination of the Generation R study, a large cohort study in Rotterdam, the Netherlands, and the NICHD Study of Early Child Care and Youth Development (SECCYD), the two including more than 1,000 infants in all (Luijk et al., 2011a). It was the first study to replicate key findings across two relatively large samples. Associations of candidate genes involved in the dopamine, serotonin, and oxytocin systems (DRD4, DRD2, COMT, 5-HTT, OXTR) with attachment security and disorganization were examined. The only replicable significant finding was the association between COMT and attachment disorganization. Children with the Val/Met genotype received higher disorganization scores (combined effect size $d = 0.22$). This co-dominant risk model for COMT Val158Met was consistent across both samples but difficult to explain. Perhaps the broader range of plasticity in heterozygotes (the Val/Met carriers) increased susceptibility to environmental influences or, in case of a frightening environment, to dysregulation of emotional arousal (Luijk et al., 2011a).

With increasing age, the heritability of traits might become more pronounced, as discussed above. In a German sample of 167 adults the associations of adult attachment representations (using the AAI) and two candidate genes, 5-HTTLPR and

DRD4, were examined (Reiner & Spangler, 2010). Carriers of DRD4 7-repeat alleles were significantly more often securely attached and received higher coherence scores compared to carriers of the other alleles. The authors suggested that this main effect was qualified by an interaction with recollections of a loving caregiver, but because this "loving" scale was part of the AAI coding system for attachment representations, the variable cannot be considered an independent assessment of past child rearing environments. 5-HTTLPR was not significantly associated with adult attachment, with or without taking reported experiences into account. The absence of molecular genetic evidence for heritability diverges from the Fearon et al. (2014) behavior genetic findings but converges with the Caspers et al. (2007) results in adoptive families.

Failure to find replicable main effects of candidate genes is not unique for attachment security or disorganization. Publication bias may account for the lack of replicable genetic findings, because initially positive results may be selectively published whereas numerous negative results may remain unpublished. This is the so-called winner's curse (see Bakermans-Kranenburg & Van IJzendoorn, 2013, for an example). Candidate genes are the proverbial needles in a haystack, and cannot be solely or largely responsible for complex behaviors or traits such as attachment security. Candidate genes might serve as important and valid indices for broader underlying genetic pathways that modulate the production, transport, and reuptake of neurotransmitters involved in attachment–related behaviors and emotions. When isolated from the environment, however, it seems overly optimistic to expect them to explain more than a small amount of variance in the attachment phenotype.

Genome Wide Analysis Study (GWAS) and Genome Wide Complex Trait Analysis (GCTA)

At least two ways to try to solve the complex puzzle of genetic determination of variance in attachment security and disorganization remain to be explored. The first is to expand the number of genes involved in the hunt for attachment genes using the method of Genome Wide Analysis Study (GWAS; Plomin, 2013) and related approaches such as genetic pathway analysis (Plomin & Simpson, 2013) and Genome Wide Complex Trait Analysis (GCTA; Benjamin et al., 2012). The second approach is broadening the focus to include the interaction between genes and environment (GxE) instead of limiting the search to main effects. Here we briefly discuss the GWAS, genetic pathways, and GCTA approaches; in the next section we will discuss GxE studies of attachment.

Genome Wide Analysis Studies (GWAS) differ from the candidate-gene approach in associating a large part of the genome with a complex phenotype such as attachment, in a hypothesis-free manner. Instead of including the usual genetic suspects with known biological functions, the GWAS approach covers the one million or so independent single nucleotide polymorphisms (SNPs) that are markers of the most common genotypic variation in humans. Using linkage disequilibrium to prune the number of markers, one million SNPs efficiently represent the 16 million SNPs of the human genome. In GWAS, associations of these SNPs with the targeted phenotype are tested, of course with massive correction for multiple testing by an increase of the significance threshold to $p < .00000005$ to avoid chance results.

Although GWAS was successfully used in the detection of the genetic basis of some diseases (e.g., macular degeneration) and led to new treatments, application to

behavioral phenotypes and complex psychological traits has so far been disappointing. Plomin (2013) summarized GWAS results on reading, mathematics, and general cognitive ability and showed that less than 0.5% of the variance could be explained by a small number of GWAS hits. The amazingly large gap between GWAS based estimates of heritability and heritability found in twin studies is called the *missing heritability problem* (Manolio et al., 2009; Plomin & Simpson, 2013; Van IJzendoorn et al., 2011). The gap made Plomin (2013) sigh: "Gene hunters are still recovering from the shock of finding that the largest associations account for so little variance in the population" (p. 109).

In an exploratory effort to apply GWAS to attachment security and disorganization in the Generation R sample (N = 641) no significant hit was found, and the suggestive hits ($p < .00005$) did not replicate in an independent sample of similar size. Of course, the sample size was way too small for the small effects to be expected on the basis of previous GWAS (Plomin & Simpson, 2013). But it is difficult to imagine how samples 100 times larger might ever be assembled, given the time-consuming gold-standard attachment assessments at our disposal, let alone the usefulness of finding genes accounting for less than 1% of the variance in attachment.

Alternative approaches that may require fewer subjects are genetic pathways and GCTA, which might be more powerful in discovering the genetic basis of complex traits (Plomin et al., 2014). Genetic pathways are functionally related genotypes potentially consisting of hundreds of SNPs that are associated with the phenotype as one block, thus requiring less correction for multiple testing. GCTA pairs every individual in a sample with every other genetically unrelated individual and correlates any similarity in genotype with the phenotypic similarity within each pair (Yang, Lee, Goddard, & Visscher, 2011). When genotypic similarities go

together with stronger similarity in a trait, the genetic component of the trait can be estimated. Both approaches have been used in Generation R (Jaddoe et al., 2013), the largest ethnically homogeneous (Caucasian) attachment sample to date, but these efforts have again failed to yield significant effects (Pappa et al., in preparation; Szekely et al., in preparation).

GxE

Overall, main-effects studies of the genetics of attachment have not yielded impressive effects. Given Bronfenbrenner's (1979) idea that *main effects are in the interactions*, it seemed sensible to examine gene-by-environment (GxE) effects on attachment. Certain genotypes may act as a "risk factor" that makes it more likely that insensitive or frightening and anomalous parenting will result in disorganized infant attachment. Alternatively, genes may act as "susceptibility factors" that increase the effects of both sensitive and insensitive parenting on children's positive or negative outcomes (Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2007; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011).

Although some have argued that the search for GxE effects is warranted only when genetic main effects have been established (Munafò et al., 2009; Risch et al., 2009), this point of view is not correct, as evident from the following example: Imagine that for a specific gene, environmental effects are absent for one gene variant, but present for the other gene variant. Imagine further that for this second gene variant, good outcomes are observed under favorable conditions and bad outcomes under unfavorable conditions. This pattern of effects *for better and for worse* in a specific subgroup, as proposed by the differential susceptibility model, has been

documented in many studies (for reviews and meta-analytic evidence see Bakermans-Kranenburg & Van IJzendoorn, 2011; Belsky and Pluess, 2009; Van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). In that case GxE effects are found in the absence of a genetic main effect (the two directions *within* one genotype cancel each other out; Bakermans-Kranenburg & Van IJzendoorn, 2015).

Two types of GxE studies of attachment can be distinguished, depending on the role of attachment quality as an environmental factor or as an outcome. In both types of studies, the genetic factor is the moderator. In the first scenario, attachment security is used as an index of a supportive environment, for example with emotion regulation or cortisol reactivity to a stressor as outcomes. The pertinent question in these studies is whether genotypes moderate the association between attachment quality (predictor) and these outcomes. In the second scenario, the moderating role of genotype in the association between caregiving quality (predictor) and attachment quality (outcome) is examined. We will first review studies with attachment quality as the observed environmental predictor, and then studies with attachment as outcome.

Attachment as Environment

Attachment security was used as an indirect index of a supportive caregiving environment in a GxE study of child self-regulation (Kochanska, Philibert, & Barry, 2009). Infant-mother attachment was assessed at 15 months, and children's ability to self-regulate was assessed at 25, 38, and 52 months. Among children who carried a short 5-HTTLPR allele, those who were insecurely attached developed poor regulatory capacities, whereas those who were securely attached developed as good regulatory capacities as children without the short allele. For children with two long alleles, attachment security did not predict self-regulation.

In a study of 7-year-old Dutch children, emotion regulation was observed during a stressful public speaking task, the Trier Social Stress Test for Children (TSST-C). 5-HTTLPR moderated the association between attachment security as assessed with the Attachment Story Completion Task (Bretherton et al., 1990; Cassidy, 1988) and electrodermal reactivity during the TSST-C. There was a fan-shaped interaction pattern: Children with a secure attachment representation as well as two long alleles were less stressed during the TSST-C than all other children (Gilissen, Bakermans-Kranenburg, Van IJzendoorn, & Linting, 2008). Children who had the "double protection" of both the ll genotype and secure attachment were the only ones who experienced low levels of stress, perhaps indicating how much support is needed for being unconcerned about giving a public speech.

In a study with 4- to 6-year old Norwegian children, the COMT gene polymorphism moderated the effect of disorganized attachment (assessed at age 4 with the doll play story completion task) on social development. Children homozygous for the COMT*val* allele who were highly disorganized at age 4 became more aggressive over time and showed reduced social competence compared to highly disorganized children with one or two *met* alleles (Hygen et al., 2014).

Lastly, Luijk and colleagues (2010) related attachment security to cortisol reactivity levels during the SSP, and tested the moderating role of HPA-axis related SNPs (BclI, rs41423247; TthIIII, rs10052957; GR-9b, rs6198; N363S, rs6195; ER22/23EK, rs6189 and 6190; and FKBP5, rs1360780) in more than 300 14-month-old infants. FKBP5 rs1360780 was related to cortisol reactivity and a double-risk for heightened cortisol reactivity was found in infants with one or two T-alleles of the FKBP5 SNP and an insecure-resistant attachment relationship with their mother.

Attachment as Outcome

Based on data from the Minnesota Longitudinal study, Raby et al. (2012) found no moderating effect of the 5-HTTLPR genotype on the association between maternal sensitivity and attachment security. This study thus failed to replicate the GxE findings of Barry, Kochanska, and Philibert (2008), who observed mothers' sensitivity at 7 months during lengthy naturalistic interactions combining Ainsworth's (1978) scales with time-sampled, event-triggered ratings of mother's response to each child signal. Infant attachment was assessed at 15 months. Infants with the short 5-HTTLPR allele and insensitive mothers were more likely to be insecure as compared to infants whose mothers were sensitive, but infants with the ll genotype scored high on attachment security independent of the variation in maternal responsiveness.

Surprisingly, similar results emerged in conditions of severe deprivation. Institutional care has been shown to lead to insecure and disorganized attachment (Van IJzendoorn et al., 2011). This is no wonder, since institutional care has so many characteristics of structural neglect (minimal physical resources, unfavorable staffing patterns, and socially-emotionally inadequate caregiver-child interactions) that they fail to respond to children's basic need for stable and positive personal relationships as well as for adequate care and stimulation. In these conditions environmental effects may be expected to overrule any genetic or GxE effect. However, some children appear to be surprisingly resilient to the adverse environment, and in a small hypothesis-generating study the potentially moderating role of 5-HTTLPR was explored (Bakermans-Kranenburg, Dobrova-Krol, & Van IJzendoorn, 2011). The study involved Ukrainian preschoolers reared in institutional settings or with their biological families. 5-HTTLPR moderated the association between caregiving environment and attachment disorganization. Children with a short allele showed

more attachment disorganization and less attachment security when they grew up in an institution compared to children who lived in a family, but when children had the ll genotype they were not more disorganized when they grew up in an institution than children growing up in their biological families.

This seems to suggest that the protective role of the 5-HTTLPR ll genotype is not limited to moderately adverse environments (as shown by, e.g., Barry et al., 2008, and Gilissen et al., 2008) but also in extremely untoward circumstances. Notably, the findings are in line with the outcomes of adoptees in the English and Romanian Adoptee Study (Kumsta et al., 2010), where adoptees with the ll genotype showed the lowest levels of emotional problems during adolescence even when they experienced severe early institutional deprivation, and with results of the Bucharest Early Intervention Project, where children with the ll genotype showed low levels of indiscriminate social behavior irrespective of their living arrangement (institutionalized care or high quality foster care; Drury et al., 2012).

For disorganized attachment, Spangler and colleagues found an interaction between maternal responsiveness and child 5-HTTLPR: Children with the short allele were more often disorganized when maternal responsiveness was low. Maternal responsiveness was observed during a 30-minute session, in which the mother was asked to complete a questionnaire but to respond to the infant as she usually would. Responsiveness was indexed with an aggregated score that combined the number and promptness of maternal responses to infant signals, irrespective of the (emotional) quality of the response. The proportion of disorganized infants increased with the number of short alleles, but only in the low responsiveness group (Spangler et al., 2009).

Van IJzendoorn and Bakermans-Kranenburg (2006) examined whether infants with the DRD4 7-repeat allele were more susceptible to parental unresolved loss and anomalous parenting behavior than infants without this allele. This turned out to be the case: Maternal unresolved loss or trauma was associated with infant disorganization in the presence of the DRD4 7-repeat allele, whereas children without this allele did not have higher scores for disorganized attachment when their mothers were unresolved. However, children with the DRD4 7-repeat allele who had mothers without unresolved loss showed the *lowest* levels of attachment disorganization. These findings support the notion that the DRD4 7-repeat allele constitutes not a genetic risk but a genetic marker of differential susceptibility (Ellis et al., 2011). The differential susceptibility model is described more extensively in the section on intervention (see below).

Gervai and colleagues (2007), combining a low-risk Hungarian and a high-risk US sample, found that maternal affective communication was related to disorganized attachment in children *without* the DRD4 7-repeat allele and not in carriers of the DRD4 7-repeat allele. In light of the meta-analytic results (Bakermans-Kranenburg & Van IJzendoorn, 2011, 2015), the latter outcome is not convergent with the general finding of higher susceptibility of carriers of the 7-repeat allele, and this may have to do with the ethnically heterogeneous US sample in the Gervai et al. (2007) study.

The moderating role of DRD4 was also found for the adult equivalent of disorganized attachment, unresolved loss or trauma as assessed with the AAI. Participants were adopted adults from the Iowa Adoption Studies, interviewed with the AAI when they were on average 39 years old (Bakermans-Kranenburg, Van IJzendoorn, Caspers, & Philibert, 2011). Participants with the DRD4 7-repeat allele with independently reported parental problems in their adoptive families had the

highest scores for unresolved loss or trauma, whereas participants with the DRD4 7-repeat allele who did not experience parental problems showed the lowest ratings. Among participants without the DRD4 7-repeat allele, parental problems during childhood did not make a difference for unresolved loss or trauma, again pointing to heightened susceptibility to environmental influences for carriers of the DRD4 7-repeat allele.

In the Generation R study, two genes involved in the regulation of stress responses were examined: those for the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) (Luijk et al., 2011b). In more than 500 infant-parent dyads, maternal sensitivity was observed during a psychophysiological assessment using Ainsworth's rating scales for sensitivity (Ainsworth et al., 1978). Moreover, maternal extreme insensitivity was observed, including withdrawal and neglect, and intrusive, negative, aggressive, or otherwise harsh parental behaviors (Out et al., 2009). There were no main effects of MR or GR on infant attachment. However, infants with the minor MR allele (G) were more securely attached if their mothers were more sensitive and less securely attached if their mothers showed more extremely insensitive behaviors, whereas these associations were not present in children without the G allele. No main or interaction effects were found for attachment disorganization.

Based on combining two large cohorts, the Generation R study and the NICHD Study of Early Child Care and Youth Development (SECCYD), the interactions between candidate genes involved in the dopamine, serotonin, and oxytocin systems (DRD4, DRD2, COMT, 5-HTT, OXTR) and maternal sensitivity were examined in more than 1,000 Caucasian infants in total. Gene-by-environment interaction effects were not replicable across the two samples (Luijk et al., 2011a).

Even though in this latter study the combined sample size was substantial, and indeed the largest available to examine the interplay between genetics and parenting predicting attachment with state-of-the-art observational measures, the power to detect GxE effects may have been insufficient. The power of correlational GxE studies is inherently limited by several factors (see Bakermans-Kranenburg & Van IJzendoorn, 2015; Van IJzendoorn & Bakermans-Kranenburg, 2015): The distributions of genotypes and parenting quality tend to be skewed, and genetic and environmental factors may not be independent, because through passive or evocative gene-environment correlation (rGE) parenting may be related to either the parent's or the child's genotype. Unmeasured genotypes eliciting specific parental behaviors may play a role, and last but not least power is reduced by measurement errors. Selective recruitment and attrition, processes that are unavoidable in cohort studies, result in low numbers of participants in the eccentric parts of the distribution, with consequences for the distribution of the interaction term. Duncan and Keller (2011) argued that the primary reason for reduced power to detect interactions in non-experimental studies is that the variance of the product term tends to be low. Thus, replication and meta-analysis to document the replicability of any finding is essential (Cumming, 2014). At the same time, experimental designs constitute a powerful alternative to examine GxE effects (see the section on *Interventions from a GxE Perspective*).

Epigenetics

In the past, behavioral and molecular genetics researchers assumed that the genetic make-up of every individual was invariable, originating from conception and

remaining basically the same across the life-span, except in rare cases of mutations through radiation or other toxic influences. This assumption is valid as far as it pertains to the structural properties of the double helix of DNA. But even MZ twins with identical DNA structures may grow apart in gene expression. They may develop radically different disease patterns because of changes in the epigenome that influences and regulates the expression of genes. Fraga et al. (2005) found, for example, that a 3-year-old MZ twin pair had about 1,000 genes with differential gene expression, whereas a 50-year-old MZ twin pair showed more than 5,000 differently expressed genes. Differences in the epigenome increase with age and with non-shared environmental influences, implying that they are larger when twins have spent more time in separate environments.

One of the most widely studied epigenetic mechanisms is methylation, which is, simply put, the blocking of gene expression through the linking of a methyl (CH3) molecule to one of the bases, cytosine, at a CpG site located in a gene-promotor region. Methylation might be loosely compared to a cork on a bottle of champagne, down-regulating the escape of bubbles (messenger RNA) and thus modulating the level of protein and enzyme production encoded for by the specific gene (Van IJzendoorn, Bakermans-Kranenburg, & Ebstein, 2011). Epigenetic studies on rodents (e.g., Meaney, 2010; Szyf et al., 2005) have made clear that the caregiving environment – for example the amount of licking and grooming and arched-back nursing that parents provide – may radically alter methylation patterns, and consequently gene expression, in the pups, and not only in the pups exposed to sensitive parenting (or deprived thereof) but even in these pups' offspring (Meaney, 2010). In particular altered methylation of the glucocorticoid receptor gene induces

long-term changes in response to stress, affecting the next generation (Weaver et al., 2004; Zhang & Meaney, 2010).

One of the first epigenetic studies on human development relevant for attachment theory was conducted by Meaney's team (McGowan et al., 2009). They examined the brains of deceased young males stored in the Quebec Suicide Brain Bank, matching suicide victims with and without a history of abuse, and comparing these two groups with age- and gender-matched victims of fatal accidents. They found that, through methylation, glucocorticoid receptor gene expression in the hippocampus of the suicide victims was decreased but only when they had experienced child abuse. Hippocampal glucocorticoid receptors play a crucial role in down-regulating the HPA-axis that is responsible for the level of the stress hormone cortisol. In other studies, similar epigenetic alterations have been found as a result of child maltreatment (Perroud et al., 2013) or structural neglect in orphanages (Naumova, Dozier et al., 2012), and in adolescent children whose mothers were exposed to intimate partner violence during pregnancy (Radtke et al., 2011).

The first epigenetic study of adult attachment was conducted with participants in the Iowa Adoption Studies (Van IJzendoorn et al., 2010). The AAI was administered, and participants (N = 143) reported on any loss or other potentially traumatic event during their childhood years in the adoptive family. The AAI scale for Unresolved loss or trauma was not associated with 5-HTTLPR. When the level of methylation was taken into account, genotype predicted Unresolved loss or trauma. Carriers of the long variant of 5-HTTLPR showed more Unresolved loss or trauma but only when more methylation was observed. Thus, the potentially protective effect of the long variant seemed to be mitigated by the effects of methylation suppressing the activity of this variant. The short variant of 5-HTTLPR appeared to be associated

with more Unresolved loss or trauma but only with low levels of methylation. Unexpectedly, high levels of methylation of the short variant led to lower Unresolved loss or trauma, a finding still in search of an explanation (Van IJzendoorn et al., 2010). What this study shows however is that genetic effects on attachment might be hidden behind interactions with epigenetic changes, which in turn might be critically dependent on environmental input such as abusive or neglectful parenting. This first study on methylation and attachment is relatively small and should be considered exploratory.

Jones-Mason (2011) administered the AAI to 101 participants of various ethnic backgrounds (half of them Asian American, another third European American). DNA was genotyped for 5-HTTLPR as well as GR, and methylation analyses were conducted in the upstream regions of these genotypes. GR methylation was not associated with any of the variables. The author suggested that in the Asian American group more methylation in the 5-HTTLPR short allele carriers was associated with less Unresolved loss or trauma, and that methylation seemed to have protected them from the potentially traumatizing effects of low SES. Similarly, in the Iowa Adoption study high methylation in carriers of the short alleles might have blunted their susceptibility to the environment, resulting in low Unresolved scores. Because of ethnic heterogeneity and the lack of power for multivariate analyses, the Jones-Mason (2011) study can only be used as a takeoff point to generate hypotheses to be tested in larger and more homogeneous samples.

At present, the study of the epigenetics of attachment is in an embryonic stage and much more work needs to be done to find out whether epigenetics mediate the influence of (in-)sensitive and abusive parenting on the development of attachment relationships and representations.

PARENTING

The study of intergenerational transmission of attachment involves the assessment of adult attachment representations in the parent and relating these representations to infant-parent attachment quality (see Hesse, Chapter xx, this volume; Van IJzendoorn, 1995). For the study of intergenerational transmission of *parenting*, it would be ideal if we could observe parents interacting with their offspring and then come back two or three decades later and observe the toddlers of the first wave now interacting with their own offspring. This is exactly what has been done by Kovan, Chung, and Sroufe (2009). They videotaped interactions of parents and their offspring at 2 years of age, and did so again several decades later – when the offspring had children of their own who were approximately 2 years of age. Comparing the interactions across the two generations, they found substantial similarity in parenting behaviors (r = .43), even when various confounds were taken into account.

Can genetic factors play a role in the explanation of intergenerational transmission of parenting? Unfortunately, traditional studies of parents and their biological children cannot disentangle the effects of shared genes from those of the environment. As with attachment, genetically informative twin or adoption studies are needed to examine the etiology of parenting.

Behavioral Genetics of Parenting

Two types of behavioral genetic studies of parenting can be found. The first is that of *parent-based twin designs*. Such studies involve adult twin siblings parenting their offspring, and heritability estimates are computed based on a comparison of the

similarity between MZ twins' parenting and DZ twins' parenting. Such studies are scarce. One of the obvious reasons is that twin siblings – notwithstanding the anecdotal and proverbial similarity of their life courses – usually do not have children at the same point in time. The comparability of parenting behaviors in case of divergent timing, numbers, gender, and ages of children is thus hampered. In terms of estimations of variance explained by genetic factors, shared environmental factors, and non-shared environment, parent-based twin designs are directly comparable to twin studies on infant attachment.

The second type of study involves parents of twins, and is called a *child-based twin design*. These studies compare the similarity between parents of MZ twins and parents of DZ twins. The extent to which parenting behavior towards MZ twin siblings is more similar than parenting behavior towards DZ twin siblings indicates genetic influence on parenting, because genetically influenced characteristics of the children (e.g., temperament) apparently elicit these parenting behaviors. Child-based genetic effects on parenting are thus indicative of evocative rGE: The child's genetic makeup evokes certain parenting behaviors, and these are child-driven genetic influences on parenting.

Shared environmental influences on parenting are due to parents' own characteristics (personality or parenting attitudes), or due to similar behaviors of siblings that result from siblings' shared experiences, regardless of their degree of genetic relatedness. These shared environmental influences include factors such as family socioeconomic status and cultural environment – because they increase similarity in the parenting that children receive. Somewhat counterintuitively, this implies that in child-based twin studies effects of parents' genes are included in estimates of the shared environment. Lastly, parents may treat siblings differently for

reasons unrelated to the children's genetically influenced characteristics, such as the specific experiences they have with each of their children, with non-shared environmental effects as a result. As always, measurement errors are included in the non-shared environmental effect estimates. It is important to note that child-based twin designs cannot be informative regarding the impact of the parents' own genes or early experiences on their parenting. Only parent-based twin designs can be used to estimate these genetic and (shared and non-shared) environmental effects.

Parent-Based Twin Designs

A recent meta-analysis of behavioral genetic studies of parenting identified only six unique parent-based studies (Klahr & Burt, 2014). Most studies were based on questionnaires; in only one study (Neiderhiser et al., 2004) were these combined with observations. Heritability estimates in individual studies varied greatly, ranging from 0% for maternal overprotection to 48% for parental authoritarianism. Distinguishing three dimensions of parenting, namely warmth, control, and negativity, combined genetic estimates were moderate for parental warmth and negativity (28%–37%), but zero for parental control. Non-shared environmental influences accounted for the largest proportion of variance (63%–90%). Heritability estimates were similar for father and mothers. The substantial role for non-shared environmental influences points to parents' unique experiences and the specific conditions they find themselves in, including the relationship with their spouses and characteristics of their children.

Child-Based Twin Designs

The same meta-analysis identified 27 studies with child-based twin designs, presenting combined estimates for genetic, shared environmental, and non-shared

environmental influences on parental warmth, control, and negativity (Klahr & Burt, 2014). Estimates were largely similar across these three parenting dimensions, with genetic influences ranging from 23% to 40%, shared environmental influences from 27% to 39%, and non-shared environmental influences ranging from 32% to 44%. Remember that the genetic influences represent child evocative rGE effects on parenting. Evocative genetic influences on parenting were larger for negativity than for warmth and control, whereas shared environmental influences were largest for warmth, and non-shared environmental influences were largest for control.

Shared environmental influences in child-based twin studies may, among other things, reflect genetic influences in parent-based studies; the results for parental warmth may point in that direction, since moderate genetic estimates for warmth were found in parent-based studies. In child-based twin studies maternal control and negativity were explained to a greater extent by genetic influences than paternal control and negativity. Fathering was more influenced by shared environmental factors than mothering. Unfortunately and similar to parent-based twin studies, most child-based twin studies used questionnaire measures of parenting. Notably, observer-rated parenting yielded lower estimates of heritability than child-report or parent-report; for observed parenting, genetic influences on warmth and negativity were not significant.

Evocative Gene-Environment Correlation

In the meta-analysis of parent-based and child-based twin studies, genetic influences on negativity were found in both types of studies. This may indicate a process in which, in addition to potential passive rGE (parents give their genes as well as the environment to their children), children inherit the genetic tendency to negative

behavior from their parents, and then through evocative rGE elicit negative parental behavior in their parents (Klahr & Burt, 2014).

Indeed, in a recent child-based twin study in the UK, Oliver, Trzaskowski, and Plomin (2014) found that the negative side of parenting showed significantly more genetic influence than the positive side. A weakness of the design was, again, that self-reports were used, and that the same parent completed the questionnaire twice, once for each twin sibling, creating non-independent scores with similar response biases. Importantly, a different UK child-based twin study (Jaffee et al., 2004) showed a genetic effect for harsh parenting, but not for physical maltreatment; in other words, the child's behavior may evoke harsh discipline, but risk factors for physical maltreatment are more likely to reside in characteristics of the parent and the environment.

The disadvantages of self-reports were overcome in a multivariate child-based twin study of parental sensitivity as related to attachment, a study that was somehow left out of Klahr and Burt's (2014) meta-analyses. Fearon et al. (2006) examined the extent to which genetic and environmental aspects of maternal sensitivity accounted for the pattern of similarity and dissimilarity of twins' attachments to their mothers (see the section on behavioral genetics of attachment). Bivariate behavior genetic modelling is based on the pattern of within-twin and cross-twin correlations to estimate genetic, shared environmental and non-shared environmental correlations between two measures (Plomin, DeFries, McClearn, & McGuffin, 2001). No genetic factor (residing in the infants) explained differences in maternal sensitivity. The variance in maternal sensitivity was explained by shared environmental (66%) and non-shared environmental (34%) factors. Thus, in line with attachment theory, shared environmental effects were found to underlie the association between maternal

sensitivity and attachment security. The shared environmental component of maternal sensitivity accounted for approximately a third of the twins' similarity in attachment security. Exploring the non-shared environmental effect, it appeared that sensitivity towards twin 2 (that was *not* shown to twin 1) affected twin 1's attachment security *positively*. The attachment security of one child thus depends on the relationship the parent has with the other child, and not just on his or her parenting behavior. These findings underscore the importance of effects of relationships on relationships within a family system (Hinde & Stevenson-Hinde, 1988), and point to the need for studies including more than one child per family.

Molecular Genetics of Parenting

The gene systems that have been examined in relation to parenting behavior converge with the gene systems that have been central to studies of attachment. These are genes related to the neurotransmitters dopamine and serotonin, and to the neuropeptide oxytocin. Here we will first review studies on potential main effects of these genes on human parenting, and then review GxE studies.

Dopamine

What makes dopamine-related gene polymorphisms candidate genes for associations with parenting? Part of the answer lies in the demonstrated implication of dopamine for maternal behavior in rats (Miller & Lonstein, 2005; Stolzenberg et al., 2007). Individual differences in their licking and grooming behavior have been found related to variations in dopamine levels in the nucleus accumbens (Champagne et al., 2004). Another part of the answer can be found in studies of humans. Dopamine is related to motivational and reward mechanisms (Robbins & Everitt, 1999), and infants are

expected to be rewarding to parents, motivating them to respond to their infants and initiate and maintain interaction with them. Variation in dopaminergic system genes may thus be related to variation in parenting.

In a sample of more than 200 mother-child dyads, Lee and colleagues (2010) tested the association between the dopamine transporter (DAT1) gene and three dimensions of observed maternal parenting behavior (positive parenting, negative parenting and total maternal commands). The sample consisted of a group of children with ADHD and demographically matched comparison children without ADHD. The observed interaction included free play as well as tasks that were frustrating for the child (e.g., clean-up, sit and count geometric shapes, play while the mother reads a magazine and takes a telephone call). Maternal DAT1 was significantly associated with negative parenting and commands, also when child disruptive behavior and various other confounders were taken into account. Mothers with the 9/9 genotype showed the least negative parenting: Mothers with the 9/9 and 10/10 genotypes showed less negative parenting than mothers with the 9/10 genotype, and mothers with the 9/9 genotype used fewer commands than mothers with the 9/10 and 10/10 genotypes. DAT1 genotype was not related to positive parenting.

In the Maternal Adversity, Vulnerability, and Neurodevelopment (MAVAN) study, Mileva-Seitz et al. (2012) found an association between genetic variation in several SNPs in the DRD1 and DRD2 genes and maternal orienting away and infant-directed vocalizing during 20 min of free play at 6 months. In three out of five DRD1 SNPs (rs 265981, rs4532, and rs686) the heterozygote group oriented away from the infant less frequently than the two homozygous genotypes, which may be associated with dopamine-related distractibility. Two of the three DRD2 SNPs were associated with infant-directed vocalizing: rs6277 and rs1799732. Although the observations

were also rated with Ainsworth's sensitivity rating scales (Ainsworth et al., 1978), the associations with DRD1 and DRD2 polymorphisms were not found with these more global sensitivity ratings, but only with the frequencies of the discrete maternal behaviors. The absence of an association with global ratings for maternal sensitivity replicated findings of Mills-Koonce et al. (2007), who in a mixed sample of African-American and European-American families found no relation between DRD2 and maternal sensitivity or negativity during free play. The authors suggest that discrete behavioral tendencies may show stronger molecular genetic associations than complex phenotypes such as overall sensitivity (Mileva-Seitz et al., 2012).

Serotonin

The serotonin transporter gene 5-HTTLPR has been studied extensively in relation to depression (e.g., Caspi et al., 2003; Lesch et al., 1996), biased attention for emotional information (Pergamin-Hight, Bakermans-Kranenburg, Van IJzendoorn, & Bar-Haim, 2012), and increased amygdala activation in response to emotional stimuli (Hariri et al., 2002). Usually short and long alleles are distinguished, but strictly speaking, taking into account an adjacent upstream polymorphism, three allelic variants exist: s, l_G (functionally similar to s), and l_A. Short alleles (including l_G) are associated with lower transcription of 5-HTT mRNA, which encodes for a protein involved in serotonin reuptake. Some but not all studies on 5-HTTLPR and parenting take this additional allelic variant into account. Given the increased attention to emotional stimuli found in carriers of the short allele, the expected direction of the association between 5-HTTLPR and parenting quality is not unequivocal: Carriers of the short allele may be more attentive to children's emotional signals, and thus respond more promptly and sensitively than carriers of the long alleles, but they may also be more

easily overwhelmed by negative child signals and prone to depression, with compromised parenting as a result.

In MAVAN study mentioned before, Mileva-Seitz et al. (2011) found support for the former hypothesis: At 6 months postpartum, mothers with the short allele were more sensitive during their interactions with their infants, and they less often oriented away from their infants.

Pener-Tessler et al. (2013) found that in families with twins, maternal positive parenting was related to 5-HTTLPR in different ways for mothers of boys and mothers of girls: In mothers of boys positive parenting significantly decreased with the number of maternal short alleles, whereas in mothers of girls positive parenting non-significantly increased with the number of short alleles. Three-way interactions, however, are notoriously difficult to replicate.

In a Dutch study, maternal sensitivity was observed in a community sample of 159 Caucasian, middle-class mothers with their 2-year-old toddlers at risk for externalizing behavior problems. The dyads were asked to solve puzzles that were too difficult for the child, and mothers were instructed to help their child in the way they usually did. Mothers' supportive presence, intrusiveness and clarity of instruction were rated on 7-point scales drawn from Egeland et al. (1990). These observation scales extend Ainsworth et al. 's (1978) original scales with an age-appropriate concept of sensitivity that includes the developmental domain of coping with cognitive challenges. The short allele was related to lower levels of maternal sensitive responsiveness (Van IJzendoorn, Bakermans-Kranenburg & Mesman, 2008).

Oxytocin

Given the important role of oxytocin in parturition, breastfeeding, and parenting (for a review see Galbally, Lewis, Van IJzendoorn, & Permezel, 2011), it is only natural that research on parenting has examined associations between various aspects of maternal behavior and oxytocin-related genes. Moreover, oxytocin receptor levels were found to be related to maternal behavior in various types of mammals (Carter, 2014; Dwyer, 2008; Insel & Shapiro, 1992). With regard to studies of human mothers, a few have focused on single nucleotide polymorphisms (SNPs) in the OXT peptide gene, and somewhat more studies have included SNPs in the OXTR receptor gene.

Although the functionality of these polymorphisms have not yet been demonstrated, two SNPs in the third intron of OXTR have been suggested as particularly promising candidates to explain differences in oxytocinergic functioning: rs53576 and rs2254298 (Meyer-Lindenberg et al., 2011). For both SNPs, the A alleles are hypothesized to confer risk in comparison to the G alleles. It should be noted, however, that a meta-analysis covering 82 studies, 48 (N= 17,559) for OXTR rs53576 and 34 (N= 13,547) for OXTR rs2254298, with five domains of outcomes (biology, personality, social behavior, psychopathology, and autism), did not yield significant combined effect sizes for any of the domains, nor for all domains combined (Bakermans-Kranenburg & Van IJzendoorn, 2013).

Notably, only one study on parenting was included in the meta-analysis (Bakermans-Kranenburg & Van IJzendoorn, 2008). That specific study tested the association between OXTR rs53576 and sensitive parenting of mothers in interaction with their 2-year-old toddlers at risk for externalizing behavior problems. Controlling for differences in maternal education, depression, and marital discord, parents with the A allele showed lower levels of sensitive responsiveness to their toddlers.

Since then, a number of additional studies on oxytocin-related genes and parenting have been conducted. Replication of the effect found in the first study was provided by the Twin Study of Behavioral and Emotional Development in Children (TBED-C), including 500 families with twins aged 6-10 years old (Klahr, Klump, & Burt, in press). Three dimensions of parenting were observed, warmth, negativity, and control, for both fathers and mothers. Parents as well as children were genotyped for OXTR rs53576. Child OXTR genotype did not predict the type of parenting received, and father's genotype was also not associated with his parenting behavior. But mothers' genotype was related to maternal warmth; mothers with the AA genotype showed less warmth in interaction with their children than mothers with the GG or AG genotypes. Importantly, the association between maternal OXTR genotype and warmth was unchanged when controlling for child OXTR genotype, age, and gender – that is, controlling for child-driven evocative effects.

In a longitudinal study of children with ADHD and matched controls, 40 mothers were selected based on their extreme scores on positive or negative parenting of their 4–6 year old children to maximize variation in parenting (Michalska et al., 2014). Parenting was observed during free play and a series of tasks, for about twenty minutes in total, and 15 years later mothers were exposed to pictures of their own and other children in an fMRI session. OXTR rs53576 and rs1042778 were both associated with quality of parenting, although only rs53576 survived correction for multiple testing. In contrast with studies reviewed above, not the G allele but the A allele was associated with higher levels of positive parenting. Note, however, that an interaction with ethnicity suggested that the association with parenting might be different for African-American mothers (almost half of the sample) and European-American mothers. Looking at pictures of their own child vs. an unknown child, A-

allele carriers showed greater activation in the orbitofrontal cortex (OFC, involved in orienting toward, monitoring, and evaluating infant cues and emotional stimuli in general) and the anterior cingulate cortex (ACC, involved in regulating emotional responses). Finally, when exposed to pictures of their own child's inappropriate vs. appropriate behavior, A-allele carriers showed more right hippocampus activation. As the activation of OT receptors in the hippocampus is related to inhibited behavioral reaction to stress in rats (Cohen et al., 2010), this may suggest that increased hippocampal activation helps to inhibit a strong negative behavioral reaction to child transgressing behavior.

In another small study, adult females without children of their own were exposed to bouts of infant crying. Cries produce autonomic arousal in adults, which in turn facilitates a quick response to the infant in order to terminate the cry (Del Vecchio et al., 2009). Almost half of the variance in adults' cardiac reactivity to an experimental paradigm with bouts of infant crying of varying pitch (Crowe & Zeskind, 1992) was shown to be explained by genetic factors in a behavioral genetic study with adult twins (Out et al., 2010), and this cry paradigm was thus used to test whether OXTR rs53576 would be related to variation in reactivity to cry sounds. Women with the GG genotype had greater heart rate responses to infant cries, but only among women with low depression scores (Riem et al., 2011). The participants were female twins and the results were replicated in their twin sisters.

In an Israeli study, three SNPs were investigated: OXTRrs2254298 and rs1042778, and CD38 rs3796863 (Feldman et al., 2012). CD38 is a regulator of OT release and has been found related to autism spectrum disorders (Munusue et al., 2010). In mice without CD38, reduced oxytocin levels and marked deficits in social and maternal behavior were observed (Jin et al., 2007). During the observation,

infants sat on an infant seat, parents sat next to them, and parents were asked to play with their infants as they would typically do. Gaze synchrony and parental touch were coded. Parents with the CD38 CC genotype touched their infants less frequently than those carrying the A allele, and parents with the OXTR rs1042778 TT genotype touched their infant less than parents carrying the G allele. For gaze synchrony no genetic effects were found.

In the MAVAN study mentioned above, two polymorphisms in the oxytocin peptide gene (OXT rs2740210, rs4813627) and one polymorphism in the oxytocin receptor gene (OXTR rs237885) were genotyped and related to mother-infant interaction (Mileva-Seitz et al., 2013). At 6 months, the two OXT SNPs were related to infant-directed vocalizing, though not to maternal sensitivity as assessed with Ainsworth's maternal sensitivity scales (Ainsworth et al., 1978). A allele carriers showed less infant-directed vocalizing. Because the two SNPs were in high linkage disequilibrium (that is, specific allelic combinations were found more often than would be expected based on the allele frequencies in the sample), they cannot be considered independent effects, and the effect may also be due to some other SNP in linkage disequilibrium with these two SNPs. OXT rs2740210 was also related to breastfeeding duration, with replication in an independent sample (Jonas et al., 2013). The OXTR (rs237885) genotype was not related to either vocalizing or maternal sensitivity or breastfeeding.

Although the role of oxytocin in parenting is undisputed, variations in the OXT peptide gene and in the OXTR receptor gene have not yet produced a convincing picture of associations between particular polymorphisms and sensitive parenting. The link between particularly OXTR genotypes and parenting has been

suggested as an important direction for research into parenting (Taylor, 2008), but so far the results are at best promising and not as consistent as might be expected on the basis of animal research. The possibility to have much more control over environmental variation in animal studies may allow for stronger genetic effects in studies of parenting in rats compared to studies on human parenting.

In a similar vein, findings regarding associations between maternal dopamine- and serotonin-related genotypes and observed parenting are inconclusive. All studies published so far have been based on relatively small samples. The lack of convergence in the results points to the risk of chance results, and replication in larger samples is badly needed. Unfortunately, in the two large studies with child genotype and attachment data reviewed above (Generation R and NICHD SECCYD), measures of parenting quality are available but maternal DNA has not (yet) been genotyped.

Of course, genes may play additive or interactive roles that so far have not been taken into account. Dopamine and oxytocin work together to regulate behavioral responses to social stimuli. In rats, there is a direct effect of oxytocin on dopamine release within the mesocorticolimbic dopamine system (Shahrokh et al., 2010). In a similar way, genetic variants in dopamine- and oxytocin-related genes may interact to affect parenting in humans. This may be an important future step for studies on parenting, along with the examination of genetic pathways and genome-wide association studies (see above, section on GWAS and GCTA).

GxE

Gene-by-environment interactions may explain why some parents are more and others less affected by disadvantageous childhoods or concurrent daily stresses in responding sensitively to their offspring's signals. For example, in the MAVAN study mentioned

before, OXT rs2740210 moderated the effect of early life experiences on breastfeeding through depression. In women with the CC genotype, childhood abuse experiences were related to lower maternal mood at 6 months postpartum, which in turn was associated with reduced breastfeeding duration across the first year (Jonas et al., 2013). Parents may also be differentially susceptible to environmental influences *for better and for worse*. In an Israeli study with mothers of twins, mothers with the DRD4 7-repeat allele who experienced more stress around child birth (e.g., low gestational age, low birth weight, and prolonged stay at the neonatal intensive care unit) were less sensitive when interacting with their children at age 3.5 than other mothers, whereas mothers with the DRD4 7-repeat allele whose children had few complications around birth showed the highest levels of sensitivity (Fortuna et al., 2011).

Including not only DRD4, but also COMT gene polymorphisms, mothers and toddlers were observed in a series of problem-solving tasks, and parents reported on their daily hassles (Van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008). The two dopamine-related genes moderated the negative influence of daily hassles on sensitive parenting behavior to their offspring. In parents with the combination of genes leading to the least efficient dopaminergic system functioning (COMT*val* allele, DRD4 7-repeat allele), more daily hassles were associated with less sensitive parenting, but in this group lower levels of daily hassles were associated with more sensitive parenting. The other combinations of COMT and DRD4 polymorphisms did not show significant associations between daily hassles and maternal sensitivity.

The latter two studies (Fortuna et al., 2011; Van IJzendoorn et al., 2008) yielded interaction effects that are reminiscent of the GxE effect found for infant disorganization (Van IJzendoorn and Bakermans-Kranenburg, 2006). Remember that

in that study, infants with the DRD4 7-repeat allele were more susceptible to parental unresolved loss than infants without this allele. Infants with the DRD4 7-repeat allele and mothers with unresolved loss had relatively high levels of infant disorganization, but infants with the DRD4 7-repeat allele and mothers without unresolved loss showed the lowest levels of attachment disorganization. In children without this allele maternal unresolved loss was not related to disorganized attachment.

Here similar patterns of results emerge: Parents with the DRD4 7-repeat allele (and, in one study, an additional COMT*val* allele) were more affected by stress than parents without this specific genotype. Under conditions of stress, they were among the least sensitive parents, but lower levels of stress were accompanied by an increase in caregiving sensitivity, much stronger so than for parents without this genotype. The role of DRD4 as a susceptibility marker may thus not be limited to children, but extend to adults. Support for this idea is also provided by the Iowa Adoption Studies, showing that adults with the DRD4 7-repeat allele were most susceptible to the absence or presence of parental problems in their adoptive families (Bakermans-Kranenburg et al., 2011). Differential susceptibility has important implications for interventions. Susceptible individuals, whether parents or children, may profit more from interventions that systematically improve the environment.

GENETICALLY MODERATED INTERVENTION EFFICACY

Interventions with the aim of enhancing parenting sensitivity or reducing attachment insecurity are manifold (see Berlin, Lieberman, & Zeanah, Chapter xx, this volume). They vary in scope and intensity from brief and focused to covering a broad range of topics and approaches over a period of several years. What the vast majority of these

interventions have in common is that their impact is only modest, with intervention effects that are disappointing in relation to the large investments in terms of time and money. In this section we will delineate the role of genetics in explaining differences in susceptibility to intervention that may mask the efficacy of interventions in specific groups (Bakermans-Kranenburg & Van IJzendoorn, 2015).

Differential susceptibility

The differential susceptibility model is of particular importance to intervention research. If environmental effects are more pronounced for specific groups compared to others, the effect of interventions will also be stronger for some than for others. As a consequence, the average intervention effect would be an underestimate of the effectiveness/efficacy in the most susceptible groups. This is a completely different perspective on intervention, and for that reason we will dig somewhat deeper into differential susceptibility in general and genetic differential susceptibility in particular.

The first three decades of GxE research were characterized by approaches such as the transactional/dual-risk (Sameroff, 1983), cumulative risk (Rutter, 2010), and diathesis-stress model (Monroe & Simons, 1991). These approaches share a focus on psychopathology: Children with a vulnerable constitution ("risk" genes) and poor developmental experiences (e.g., insensitive parenting, low quality child care, stressful life experiences) are expected to be at increased risk for bad outcomes. A typical example would be that children with the 5-HTTLPR short allele were more often disorganized when maternal responsiveness was low (Spangler et al., 2009), or that infants with the minor MR allele (G) were less securely attached if their mothers showed extremely insensitive behaviors, whereas these associations were not present in children without the G allele (Luijk et al., 2011b). The G-allele might easily be

indicated as the "risk allele". In the latter study, however, infants with the G allele were more securely attached if their mothers were more sensitive. Genetic variation in MR thus modulated infants' sensitivity to care, for better (increased susceptibility to maternal sensitive behavior) and for worse (increased vulnerability to maternal extreme insensitivity), and it would be mistaken to consider the G allele a risk allele when it also enhances the chance of developing secure attachments with sensitive caregivers.

In short, the same genotype that makes individuals vulnerable to adversity may also make them disproportionately likely to benefit from contextual support (Belsky, Bakermans-Kranenburg & Van IJzendoorn, 2007). The differential susceptibility hypothesis proposes that in positive environments "vulnerable" children may flourish even more than their peers who are less susceptible to both supportive and unsupportive environments (Bakermans-Kranenburg & Van IJzendoorn, 2007; Belsky et al., 2007; Ellis et al., 2011). The differential susceptibility model is not so much complementary to the diathesis-stress model; it is fundamentally different from it. Its evolutionary foundation implies that certain genotypes must be called "susceptibility" genes instead of "risk" genes (Bakermans-Kranenburg & Van IJzendoorn, 2015).

Evidence for genetic moderation of environmental effects according to the differential susceptibility model has been specifically tested for serotonin and dopamine-related gene polymorphisms, although other genotypes have been identified as potential markers of susceptibility as well (e.g., MAOA, BDNF, MR). The first GxE differential susceptibility study showed that children with the DRD4 7-repeat allele displayed the most externalizing behavior at 39 months when their mothers were observed to be insensitive during home observations at 10 months of age but the

least externalizing behavior when their mothers were highly sensitive (Bakermans-Kranenburg & Van IJzendoorn, 2006). The findings of this pioneering small study were confirmed in a meta-analysis on dopamine-system related genotypes (15 studies, *N*= 1,232). The combined effect sizes for the association between adverse rearing influences and behavioral disturbance amounted to *r* = .37 for carriers of the "risk alleles", and only *r* = .10 for the comparisons without the risk alleles. But the combined effect sizes for association between support and better adaptation were *r* = .31 for carriers of the putatively risk alleles, and *r* = -.03 for those without the risk alleles (Bakermans-Kranenburg & Van IJzendoorn, 2011). Thus, genotypes that in adverse contexts put children at risk for behavior problems allowed them to benefit more from support.

For 5-HTTLPR as a genetic susceptibility marker, quite similar meta-analytic results were found, but with a difference depending on the inclusion of samples with mostly non-Caucasian and mixed ethnicities (Van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). In the total set of studies (77 studies, *N* = 9,361) children with short alleles were more negatively affected by adverse contexts than carriers of two long alleles with regard to negative outcomes, but they did not benefit significantly more from positive environments. The pattern of results was thus convergent with the diathesis-stress model; with short alleles as "risk alleles" rendering individuals more vulnerable to environmental adversity but not more open to supportive contexts. In studies with predominantly (>80%) Caucasian participants (52 studies, *N* = 6,626), carriers of short alleles were more sensitive to negative (*r* = .18) as well as positive (*r* = .17) environmental influences than individuals with two long alleles (*r* = .04 for negative environments and *r* = .05 for positive environments), in accordance with the

differential susceptibility model. These differences point to ethnicity as an important moderator in GxE studies, including genetic differential susceptibility studies.

Most of these first studies that formed the basis for the two meta-analyses were correlational. More often than not the studies did not specifically aim at testing the "bright side" of better outcomes in carriers of "risk alleles" in positive environments. In a way this is an advantage, because it implies that those results that were derived as part of the meta-analytical process were not the focus of the specific study, which counters the risk of publication bias. The crucial test of the differential susceptibility model is, however, whether in randomized controlled trials (RCT) individuals with the susceptible genotypes profit more from interventions – that is, from experimental improvement of the environment.

Interventions from a GxE perspective

GxE experiments (or G*x*E, G x *experimental* E) are randomized controlled trials (RCTs) with random assignment of participants to intervention and control groups. GxE experiments have at least three advantages compared to correlational GxE studies (see Van IJzendoorn & Bakermans-Kranenburg, 2015).

First, G and E are uncorrelated. Correlational GxE studies may test for gene-environment correlation (rGE) and set it aside when the genetic marker is not correlated with the environmental factor, but this provides no definite proof of the absence of gene-environment correlation, because unmeasured genes may be related to the environmental factor under study. In RCTs, the environment is manipulated in standard ways, and randomization breaks any possible gene-environment correlation. Only random assignment to experimental and control conditions can disentangle genetic and environmental factors (Van IJzendoorn et al., 2011).

Second, GxE experiments decrease the risk of unequal measurement errors in the GxE equation. If genetic assessments are done in a careful way but broad or "quick-and-dirty" measures are used for the environment (e.g., self-reported retrospective childhood experiences), the error components are smaller for G than for E, creating risks for Type 1 and Type 2 errors. Experiments with well-defined, standardized manipulations of specific dimensions of the environment reduce measurement error in E. Of course, ineffective interventions do not contribute to a reduction of measurement error in E. Assessing the change in the environment is important to check the impact of the manipulation and to examine dose-response relations between environmental change and outcome in the experimental condition. As an example, in a study on the efficacy of the VIPP-SD parenting intervention in the reduction of child externalizing behavior, the way in which parental discipline strategies were affected by the intervention was measured, and the change in parental strategies was related to decreased externalizing behavior in children with the DRD4 7-repeat allele (Bakermans-Kranenburg et al., 2008).

Third, GxE experiments have more statistical power compared to correlational GxE studies. Experimental studies make participants in the experimental condition maximally different from participants in the control condition, and this creates more variance in the product term. Correlational studies tend to contain few observations at the extremes of the distribution and many observations close to the center of the distribution. Selective recruitment and attrition, especially in the tails of the distribution, are responsible for this effect, and they can hardly be avoided. Experimental GxE studies lead to better distributed variables, and as a result the power can be more than ten times larger compared to correlational studies (McLelland

& Judd, 1993). This is not a trivial issue, because lack of power has been identified as one of the major problems in GxE research.

Randomized controlled intervention studies thus offer great opportunities to examine gene-environment interaction effects. Randomized controlled intervention studies can also provide insight in variation in intervention effectiveness among different groups. This is an important step in uncovering which intervention works best for whom. Lastly, they enable testing whether the dopamine-related and serotonin-related genotypes that emerged as "susceptibility" factors from correlational GxE studies are indeed related to larger intervention effects.

Meta-analysis of Genetic Differential Susceptibility Experiments

In the past decades, a number of genetic differential susceptibility experiments have been conducted. These are RCTs addressing the question whether intervention effects are moderated by a genetic susceptibility marker. In a meta-analysis of these experiments, we tested whether genotypes that were once considered risk factors and that were later suggested to be susceptibility (or "plasticity") factors were related to larger intervention effects.

Twenty-two RCTs could be identified (Van IJzendoorn & Bakermans-Kranenburg, 2015), some of which had attachment as the outcome – for example the intervention study of maltreating families conducted by Cicchetti, Rogosch, and Toth (2011), and the Bucharest Early Intervention Project (Brett et al. 2014, Nelson, Fox, & Zeanah, 2014). The 22 RCTs included 3,257 participants in total, 38% of whom were carriers of susceptibility genes. The combined effect size of the interventions for carriers of the susceptible genotypes amounted to r = .33, which is a large effect even

in terms of Cohen's (1988) conventional criteria. In contrast, the hypothesized non-susceptible group was less affected by the interventions; the combined size of the intervention effects in this group was not significant, r = .08. Intervention effects were much stronger in the *a priori* hypothesized susceptible group.

In the 14 studies with predominantly (>80%) Caucasian participants (N = 2,060), the findings were replicated, with significantly larger intervention effects for the susceptible genotypes (r = .26) than for the non-susceptible genotypes (r = .12). Considering the genetic marker of susceptibility, dopamine-related genes were indeed markers of susceptibility. The eleven studies with dopamine-related genotypes as moderators showed larger intervention effects in susceptible genotype groups (r = .35) than in non-susceptible genotypes (r = -.00). Seven studies with 5-HTTLPR as moderator showed significant combined effects in the susceptible genotype group (r = .30) but also in the non-susceptible genotype group (r = .16); the difference between these two effect sizes is in the expected direction but not statistically significant (p = .15).

As an important final step, the difference between the effect sizes for the susceptible and non-susceptible groups within each study was computed. The combined effect size for the difference between susceptible and non-susceptible genotypes within studies was significant, with a medium effect size. We tested this combined effect size for publication bias, and did not find any, which indicates that the combined effect size was not based on selective publication of studies that reported significant moderation of intervention effects by genotype at the expense of studies that did not find such moderation.

CONCLUSION

The study of the role of genetics in explaining differences in attachment security began only around the year 2000, so it is a relatively young branch of the growing attachment tree. On the one hand this is remarkable because attachment theory might be considered the first application of evolutionary theory to human development – after Charles Darwin but before so-called evolutionary psychology emerged. From evolutionary theory John Bowlby (1982) derived one of the core hypotheses of current attachment theory, the idea that every human infant is born with an innate bias to become attached to a protective conspecific. The genetic basis of this species-wide bias and related behavior in the various stages of attachment development has not yet received any attention.

On the other hand, attachment theory has always emphasized environmental influences, more specifically effects of parenting, on the development of individual differences in attachment relationships and representations. Central to attachment theory is the idea that attachment starts as a dyadic construct, shaped mostly by parents, to be gradually internalized by the child and to become a defining feature of the growing individual. Behavior genetic studies seem to confirm this idea because most twin and adoption studies document the large role of the environment in explaining variance of attachment security and disorganization at a young age.

For three reasons one should be careful deriving strong conclusions from behavior genetics. First, twin studies partition variation in attachment within a specific population and environment, and results are therefore sample-specific and dependent on variation in the environment. In more homogeneous environments higher estimations for heritability are found. Second, results pertain to the group level, and should not be taken to indicate individual genetics. Third, the influence of genetics

might grow with age, and twin studies on attachment beyond adolescence are lacking. As a relatively new development, GCTA extends behavior genetics in that it is not dependent on twin studies. Similar to behavioral genetics, GCTA leads to estimates of heritability without pointing at specific genes or gene pathways that play a role in the phenotype.

Molecular genetics has been used as a tool in search for specific genotypes related to parenting and to attachment security and disorganization. However, few if any clues for finding "attachment genes" have emerged. Considering the complex phenotypic signature of attachment and the necessarily limited sample sizes involved in studies of infant or adult attachment this should not come as a surprise. In fact, the search for main effects in genetics of human behaviors and disorders has been generally disappointing even to the most influential and optimistic gene hunters (Plomin, 2013). Ever larger samples account for ever smaller variance in traits on the level of singular genotypes. Gene pathways, mirroring more closely complex neurobiological endophenotypes of attachment such as the dopamine system, may characterize the next generation of molecular genetic studies.

It seems safe to conclude that the intergenerational transmission gap between parental and child attachments (Van IJzendoorn, 1995) cannot be bridged by genes alone or by separate accounts of genetic and environmental input. Gene-by-environment interactions may be better suited for this challenge. Correlational studies have documented the important role of GxE in explaining human development, and experimental studies showed even more conclusive evidence of the importance of the interplay between genes and environments. In particular the concept of genetic differential susceptibility generates evidence for the hypothesis derived from Belsky's (1997) notion that children might differ in their openness to parenting influences in a

for better and for worse manner. Although conclusive evidence is still missing, particularly in the area of attachment, genetic make-up might make some children vulnerable to develop insecure attachments in less supportive environments, whereas the same genetic endowment enables children to profit more from supportive environments, i.e. sensitive parenting. This is a new perspective on the old issue of the transmission gap, to be explored more carefully in the next decade of attachment studies. In a clinical and practical sense the implication is that the efficacy of attachment-based interventions may have been over- and underestimated depending on the proportions of susceptible parents or children.

In his revised edition of the trilogy *Attachment*, Bowlby (1982) already argued that the antithesis of innate versus acquired behavioral traits is unreal and unproductive: "Just as area is a product of length multiplied by width so every biological character …. is a product of the interaction of genetic endowment with environment" (p. 38). Meaney (2001) attributes this wonderful rectangle metaphor to Donald Hebb and dates it back to the sixties of the last century. Meaney adds that it is impossible to explain to the general public that one ever could make sense of a rectangle by studying only length isolated from width, or the other way around. Nevertheless, this is exactly what has happened in the study of human development, including attachment. Genetic differential susceptibility, incorporating epigenetics, may offer a viable window to study the interplay between genes and environment in attachment.

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