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Children's differential susceptibility to effects of parenting

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The investigation and identification of factors shaping children's development have long been central to the field of developmental psychology; and parenting has long been considered one of the most important sources of influence. A vast body of empirical evidence highlights the contribution of parenting to a wide range of cognitive, socio-emotional, and behavioral developmental outcomes. Long appreciated, too, is that parenting effects are often moderated by characteristics of the child, most notably, perhaps, early temperament. Indeed, most such work has been guided by conceptions of vulnerability stemming from negative or difficult temperament that interacts with insensitive, harsh or otherwise unsupportive parenting to undermine child well-being. Belsky's differential-susceptibility framework challenges such diathesis-stress thinking, highlighting the fact that the very individuals who seem most susceptible to environmental adversity, including negatively emotional infants, may also benefit the most from developmentally supportive rearing. Evidence consistent with this view – that some children are more affected than others, for better *and* for worse, depending on the rearing environment – is reviewed, including new research on gene-X-environment interaction. Finally, unknowns of the differential-susceptibility hypothesis are considered.

Keywords: parenting; differential susceptibility; diathesis-stress; GXE; infant temperament

Whether, how, and to what extent parenting affects child development has been of longstanding interest to developmental psychologists and family scholars. Consequently, a vast diversity of empirical work has been conducted over the last decades, with different strands of research in human development providing strong evidence for links between parental rearing practices and child outcome. Consider in this regard Baumrind's (1967) early research on different parenting styles and her findings showing that the so-called authoritative parenting style – marked by both a warm, responsive parent–child relationship and the consistent and firm enforcement of rules by use of rational explanations – predicts greater cooperation, less delinquency, and higher social and cognitive competence in comparison to other less supportive parenting styles (e.g., see Steinberg, Lamborn, Darling, Mounts, & Dornbusch, 1994). Needless to say, contemporary work still in this tradition gets carried out today. Consider, for example, the large-scale longitudinal NICHD Study of Early Child Care and Youth Development in which observer-rated parenting quality – assessed repeatedly across the first 4.5 years of childhood on the basis of videotaped parent–child interactions – was found to predict children's cognitive and social competencies at 10–11 years of age (Belsky, Vandell et al., 2007).

Despite the fact that much empirical work is consistent with the notion that parenting affects children's development, concerns have been voiced about the confidence that can be placed in many findings, especially with regard to the fact that genetic confounds have not been sufficiently – if at all – taken into account (Harris, 1998; Rowe, 1994). Thus, in much research, correlated genetic influences on parenting and on child functioning could masquerade as effects of parenting on child development. Behavior-genetic research that has been designed to address this issue strongly indicates that the environment shared by all children in a family plays a smaller role in child development than generally assumed and that most environmental influence is of the non-shared variety, including that stemming from parenting (Plomin, Asbury, & Dunn, 2001).

While virtually all of the non-genetically informed correlational research on the effects of parenting – even that derived from longitudinal studies – is open to question regarding cause and effect, experimental work does clearly document causal influences of parenting quality. For example, controlled experimental studies informed by attachment theory demonstrate that sensitive mothering causally influences the development of attachment security in the infant and young child (for reviews, see Bakermans-Kranenburg & van IJzendoorn, 2010; Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2003).

Nevertheless, the question as to why the shared environment in the form of parenting often fails to account for substantial variance in developmental outcomes remains. Maccoby (2000) addressed this concern by pointing out

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that variance explained by the shared environment includes only those aspects of the shared environment that make siblings more similar to each other. As soon as similar experiences affect different children in different ways, including some not at all, influences of parenting will be assigned to the non-shared environment component in behavior-genetic research and thus lead to the disputable conclusion that shared environment contributes little to child development (see also Collins, Maccoby, Steinberg, Hetherington, & Bornstein, 2000).

The notion that different children may respond differently to similar experiences – and therefore limit the variance accounted for by shared-environment in genetically informed studies – is certainly consistent with research on the interaction of temperament and parenting in predicting child development, including work indicating that children with certain temperamental traits are more adversely affected by negative environmental conditions than are others (Belsky, Hsieh, & Crnic, 1998). Indeed, this form of temperament-X-parenting interaction is usually interpreted in terms of a diathesis-stress model of psychopathology (Monroe & Simons, 1991; Zuckerman, 1999) or dual-risk model of development (Sameroff, 1983). Both frameworks are based on the view that negative consequences of adverse experiences disproportionately if not exclusively characterize children who are temperamentally "vulnerable" (diathesis = difficult temperament), with children who fail to succumb to the same adversity regarded as "resilient" (Zubin & Spring, 1977). Diathesis-stress/dual-risk models imply also that under conditions of environmental support, including supportive parenting, "vulnerable" and "resilient" individuals will not differ in their functioning. In other words, it is only under conditions of adversity that their differential susceptibility to environmental influence is operative; Figure 1a, an adaptation of Bakermans-Kranenburg and van IJzendoorn's (2007) Figure 1, graphically depicts this characterization.

Providing a fundamentally different perspective on temperament-X-parenting interaction, is Belsky's (1997b, 1997a, 2005) differential-susceptibility hypothesis, which stipulates that individuals do not so much vary in the degree to which they are vulnerable to the negative effects of adverse experiences, but more generally so in their *developmental plasticity*: More "plastic" or malleable individuals will be more susceptible to both the adverse developmental sequelae associated with negative environments *and* the positive developmental consequences of supportive environments; less susceptible individuals – so-called "fixed" ones – will be far less or not at all affected by the same environmental conditions (see Figure 1b, an adaptation of Bakermans-Kranenburg and van IJzendoorn's (2007) Figure 1). Boyce and Ellis (2005) recently advanced a perspective somewhat similar to differential susceptibility which focused exclusively on the role of the stress-response system in moderating environmental effects (i.e., "biological sensitivity to context"). In what follows, we first delineate the theoretical foundation of Belsky's (1997b, 2005) differential-susceptibility hypothesis and then provide a review of recent evidence consistent with it. In a concluding section, we highlight some, as of yet, unknowns of the differential susceptibility hypothesis.

Theoretical foundation of differential susceptibility

The view that children should vary in their susceptibility to rearing is founded on evolutionary logic which regards the dispersion of genes in future generations as the ultimate biological imperative and thus goal of all living beings. Indeed, from the perspective of modern evolutionary biology, natural selection does not just shape living things to survive, but to reproduce. Importantly, such reproduction can be direct, as when one produces immediate descendants (i.e., children, grandchildren), but also indirect, as when one's kin – such as brother, sister, niece, or nephew – reproduce and, in so doing, pass on genes that they share, in varying proportions, with the individual in question. "Reproductive fitness" refers to the dispersion of one's genes in future generations and "inclusive fitness" calls attention to the fact that one's genetic material is distributed both directly and indirectly. With this foundation established, we turn to the theoretical argument.

Because the future is and always has been inherently uncertain, ancestral parents, just like parents today, could not have known (consciously or unconsciously) what childrearing practices would prove most successful in promoting the reproductive fitness of offspring – and thus their own inclusive fitness. As a result, and as a fitness optimizing strategy involving the hedging of bets, natural selection would have shaped parents to bear children varying in developmental plasticity, with some children being more affected by the parenting they experience than others (Belsky, 2005). This way, if an effect of parenting proved counterproductive in fitness terms, those children less – or not at all – affected by parenting would not have incurred the cost of developing in ways that ultimately proved "misguided" when it came to passing on genes to future generations. Importantly, in light of inclusive fitness considerations, these less malleable children's "resistance" to parental influence would not only have benefited themselves directly, but their more malleable siblings as well – but indirectly, given that siblings, like parents and children, have 50% of their genes in common. By the same token, had parenting influenced children in ways that enhanced fitness, then not only would more plastic or malleable offspring have benefited directly by virtue of parental influence, but so, too, would their parents and even their less malleable siblings who did not benefit from the parenting they received, again for inclusive fitness reasons (i.e., shared genes). This line of evolutionary argument leads directly to the expectation that children should vary

in their plasticity and thus susceptibility to parental rearing and perhaps to environmental influences more generally. It might also lead to the prediction that variation in malleability should have differential fitness payoffs today, just like it is presumed to have had in ancestral times. To date, no such empirical tests of reproductive fitness have been conducted. Moreover, even if they were, it remains possible that fitness would no longer be related to individual differences in plasticity due to how much the modern world differs from the one in which humans evolved and have even lived until recently.

Beyond the extensive research to be considered in the next section highlighting individual differences in plasticity, of note is that cross-species evidence indicates that plasticity is heritable (Bashey, 2006; Pigliucci, 2007) and may function as a selectable character in and of itself (Sinn, Gosling, & Moltschaniwskyj, 2007). One wild bird population shows evidence that selection favoring individuals who are highly plastic with regard to the timing of reproduction has intensified over the past three decades, perhaps in response to climate change causing a mismatch between the breeding times of the birds and their caterpillar prey (Nussey, Postma, Gienapp, & Visser, 2005). Moreover, a recent simulation study seeking to determine whether plasticity could evolve, with some individuals being more responsive to environmental conditions than others, has yielded evidence in favor of this possibility (Wolf, van Doorn, & Weissing, 2008). Also noteworthy is Suomi's (2006) observation that a single genetic difference distinguishes the two species of primates that fill multiple niches around the world from all others that inhabit singular and rather narrow ones, the presence of the 5-HTTLPR short allele, leading him to regard humans and macaques as "weed species," able to adjust to and flourish in many different environments just like weeds. Given evidence to be reviewed below that this serotonin-transporter gene does not just increase vulnerability to contextual risk but also is associated with disproportionate positive response to supportive rearing conditions, one cannot but wonder whether this allele is better conceptualized as a "plasticity gene" (Belsky et al., 2009; Belsky & Pluess, 2009) rather than, as has routinely been the case in studies of psychopathology based on diathesis-stress/dual-risk thinking, a "vulnerability gene" (Burmeister, McInnis, & Zollner, 2008; Rutter, 2006).

Evidence of differential susceptibility

It is one thing to assert that some children may be more affected by early experiences than others – for better *and* for worse – and yet another to chronicle empirically such a fact. In this section we present selected evidence of differential susceptibility to parenting behavior. First we consider research that addresses behavioral or phenotypic characteristics of children found to moderate effects of parenting followed by gene-by-environment interaction (GXE) evidence showing that genotype moderates such environmental effects. Before doing so, however, we consider empirical criteria for distinguishing findings consistent with diathesis-stress/dual-risk models from a differential-susceptibility one.

Criteria for differential susceptibility

Belsky, Bakermans-Kranenburg, and van IJzendoorn (2007) recently offered empirical criteria for evaluating the prediction that some individuals will be more affected by environmental conditions than others – in a for-better-*and*-for-worse manner. Whereas diathesis-stress/dual-risk phenomenon are evident when the most vulnerable (i.e., diathesis/risk #1) are disproportionately affected in an adverse manner by a negative environment (i.e., stress/risk #2), differential susceptibility is evident when a cross-over interaction characterizes the data, with some (susceptible/plastic/malleable) individuals disproportionately, if not exclusively, affected by both *negative and positive* experiences and others not affected at all or far less so (see Figure 1).

A further criterion that needs to be fulfilled to distinguish differential susceptibility from diathesis-stress/dual-risk evidence is the independence of the outcome measure from the susceptibility factor: if the susceptibility factor and the outcome are related, dual risk is suggested rather than differential susceptibility. Finally, predictor variable and susceptibility factor must also be unrelated to exclude the alternative explanation that susceptibility merely represents a function of the environment (i.e., gene–environment correlation).

Temperament as a phenotypic marker of differential susceptibility

Some of the earliest and most suggestive evidence of differential susceptibility to environmental influences emerged in research on temperament-X-parenting interaction (Belsky, 1997a), a long-standing focus of developmental inquiry (Rothbart & Bates, 2006). Belsky's (2005) review of relevant research revealed that predictive links between rearing experience and a variety of behavioral outcomes often were consistently greater for a subgroup of children characterized by a temperamental propensity for high negative affectivity, whether operationalized in terms of difficult temperament, irritability, fearfulness, or inhibition. But even though most of the work considered revealed that *greater variance* in a variety of developmental outcomes could be explained by rearing experiences in the case of more negatively emotional children, statistical analyses in the studies in question often did not afford determination of whether this result was itself a function of a for-better-*and*-for-worse parenting effect. Fortunately, the situation is

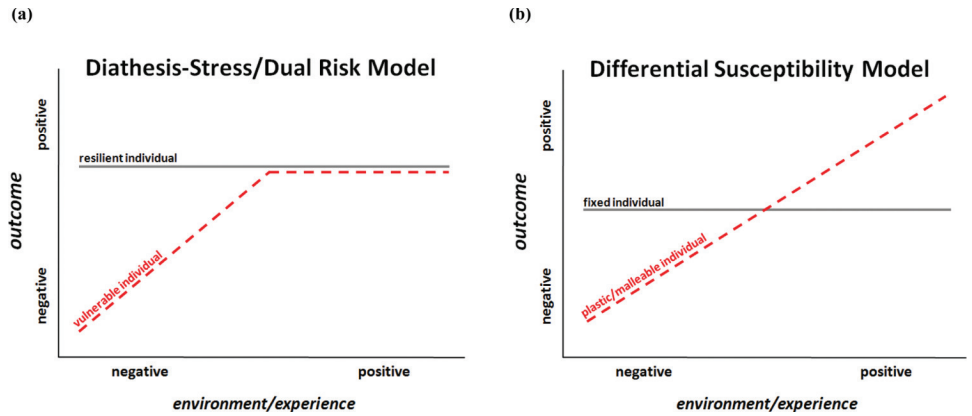

Figure 1. Graphical display of differences between the diathesis-stress/dual-risk and the differential-susceptibility model (an adaptation of Bakermans-Kranenburg and van IJzendoorn's (2007) Figure 1). The X-axis indicates quality of the environment/experiences from negative to positive. The Y-axis indicates the developmental outcome from negative to positive. The lines depict two categorical groups that differ in their responsiveness to the environment. Model (a) represents diathesis-stress/dual risk: the "vulnerable" group shows a negative outcome when exposed to a negative environment, while the "resilient" group is not affected by it. No differences between the two groups emerge in a positive environment. Model (b) represents differential susceptibility: the "plastic" group is disproportionately more affected by both negative and positive environments. Plastic individuals have a more negative outcome in response to negative environments (i.e., negative slope) but also a more positive outcome in response to positive environments (i.e., positive slope) compared to the "fixed" individuals.

different today, with many new studies chronicling such individual differences in developmental plasticity.

Consider, for example, van Aken, Junger, Verhoeven, van Aken, and Deković's (2007) evidence that 16–19-month-old boys with difficult temperament (i.e., susceptibility factor) manifest the smallest increase 6 months later in externalizing problems scores when reared by highly sensitive mothers who only infrequently used negative control, but the largest increase when highly insensitive mothers relied heavily on negative control. These striking parenting effects simply did not obtain in the case of other children. Consider next work by Kochanska, Aksan, and Joy (2007) focused on father's reliance on power assertion (15 months), children's fearfulness (i.e., susceptibility factor) at 7 and 15 months and their rule compatible conduct (38 months). Whereas high versus low power assertiveness made no apparent difference for children scoring low in fearfulness (at 7 and 15 months), children who had been highly fearful infants proved less obedient than all others when fathers' power assertion was high, yet more obedient than all others when fathers' power assertion was low.

Drawing on data of the large-scale longitudinal NICHD Study of Early Child Care and Youth Development (NICHD Early Child Care Research Network [ECCRN], 2005) and focusing upon maternally reported difficult temperament (i.e., susceptibility factor) at 1 and 6 months (composited), Bradley and Corwyn (2008) also discerned evidence of differential susceptibility when it came to evaluating effects of observed maternal sensitivity, harshness, and productive activity on teacher-reported behavior problems: Children with more difficult temperaments had more behavior problems in first grade than all other children if they experienced low-quality parenting across the infant, toddler, and preschool years, but fewer problems than all other children if they experienced high-quality parenting; the anticipated effect of parenting quality was weaker in the case for children with intermediate levels of difficult temperament and weaker still in the case of children scoring very low on difficult temperament (i.e., easy temperament).

Dopkins-Stright, Cranley-Gallagher, and Kelley (2008) were able to extend findings of differential susceptibility to positive developmental outcomes, also drawing on data from the NICHD Study. Once again an interaction emerged, this time between difficult temperament (at 6 months) and parenting style (composited across 6, 15, 24, 36, and 54 months) in the prediction of teacher-rated academic competence, social skills, teacher–child relationships, and peer-status at first grade. Predictive power proved greater for infants with more difficult temperaments than for infants with less difficult temperaments. Although all interactions were of a cross-over nature and in line with a for-better-*and*-for-worse parenting effect for only some children, not all criteria for differential susceptibility were met; of special significance is that the temperament-susceptibility factor itself predicted the parenting predictor (as well as at least one outcome measured).

Pluess and Belsky (in press) overcame this problem in their longer-term analysis of differential susceptibility using the same NICHD Study data. After finding that parenting quality prior to school entry predicted reading, math, picture vocabulary, social competence and academic work habits in the fifth grade more strongly for children with difficult temperament than for those with easy temperaments – and in a for-better-*and*-for-for worse

manner in the case of reading and social competence – they reran their analysis using an adjusted parenting quality measure discounting discerned evocative effects of the putative susceptibility factor (i.e., temperament) on the environmental predictor (i.e., parenting quality). The differential-susceptibility findings remained virtually unchanged when the parenting measure was statistically adjusted to control for the effect of 6-month, mother-reported difficult temperament.

Although the Pluess and Belsky (in press) work indicates that differential-susceptibility effects pertaining to early parenting and involving temperament-based susceptibility factors extend beyond the early childhood years, the question arises as to whether rearing and related experiences *in later childhood* operate in a similar manner. Some suggestive evidence that they do comes from Lengua's (2008) temperament-X-parenting interaction study which sought to explain change in externalizing problems using a community sample of 8–12-year-olds. Children's reports of their mothers' parenting style (i.e., rejection/acceptance, inconsistent discipline) predicted change over a 1-year period in mother-reported internalizing and externalizing problems, but differentially as a function of temperament. Children highly prone to frustration increased in externalizing problems over time when mothers were rejecting, but decreased when mothers manifest little rejection, with no such apparent effects of rejection evident in the case of children scoring low on frustration.

Intriguingly, there is also suggestive evidence of the legacy and even operation of differential susceptibility in early adulthood. Of importance in this regard is work testing hypothesized interactions between sensory-processing sensitivity, a personality characteristic measureable by means of the Highly Sensitive Person scale (Aron & Aron, 1997), and various environmental factors in predicting adult shyness and negative affectivity (Aron, Aron, & Davies, 2005). According to Aron and Aron (1997), about 20% of the population are characterized by a high-sensitive personality which encompasses a sensitive nervous system, awareness of subtleties in surroundings, and a tendency to be more easily overwhelmed when in a highly stimulating environment. The study with perhaps the most relevant results showed that a problematic (and retrospectively reported) childrearing history predicted high levels of (self-reported) shyness and negative affectivity in a sample of undergraduate students, whereas its absence predicted low levels of these same outcomes, but principally in the case of those students scoring high on sensory-processing sensitivity.

The repeatedly discerned moderational effect of negative emotionality/difficult temperament, including perhaps that of sensory-processing sensitivity, in the case of parenting and other environmental experiences raises the question of why this should be the case. This would seem especially important to address in view of the fact that even though Belsky (1997a, 2005) theorized that children should vary in their susceptibility to environmental influences (i.e., plasticity), his differential-susceptibility hypothesis did not stipulate that more negatively emotional children or those with difficult temperament (or with high sensory-processing sensitivity) would prove especially malleable; this was an empirical observation (Belsky, 2005). As it turns out, several non-mutually exclusive explanations have been advanced with regard to the issue at hand. Kochanska (1993) drew explicitly on Dienstbier's (1985) thinking on anxiety to account for her results, arguing that more negatively emotional/fearful/inhibited infants have lower thresholds for anxiety, thereby making them more easily aroused by discipline and thus responsive to it. Not unrelatedly, Belsky (2005) contended that a negatively emotional/difficult temperament reflects a highly sensitive nervous system on which experience – of both the positive and negative variety – registers especially strongly (see also Aron & Aron, 1997).

Whatever the mechanisms involved in making more negatively emotional children seemingly more malleable – in an often for-better-*and*-for-worse manner – it would be mistaken to conclude that this is the most important phenotypic marker of plasticity. Even though this could turn out to be the case, it could also be an artifact of the disproportionate attention that investigators guided by the diathesis-stress perspective pay to so-called "risk factors" that interact with contextual adversity in producing problematic functioning (Belsky & Pluess, 2009). If this is so, then it certainly behooves us to consider other potential behavioral markers of plasticity/malleability rather than reify a single one. At this point, however, the only empirically supported behavioral-susceptibility markers besides negative emotionality and difficult temperament are sensory-processing sensitivity (Aron & Aron, 1997; Aron et al., 2005), impulsivity (Lengua, Wolchik, Sandler, & West, 2000), and anger proneness (Smeekens, Riksen-Walraven, & van Bakel, 2007). Certainly there might be other susceptibility factors and, indeed, identification of them remains a wide-open theoretical, as well as empirical, issue.

Genetic markers of differential susceptibility

Whereas almost all the evidence cited through this point derives from studies of children, GXE interaction findings consistent with the differential-susceptibility hypothesis often derive from research with adults; this is especially true of psychiatric research focused upon pathological outcomes (e.g., depression, antisocial behavior). Whereas most attempts to identify reliable associations between single genes and psychological disorders failed to reveal replicable links (Burmeister et al., 2008), a growing

number of studies suggest that some individuals with specific variants of the same gene are indeed more likely to develop disorders, but only in combination with exposure to adverse experiences (e.g., stressful life events). Variations of a single gene – so-called polymorphisms – are frequent across the human population and are generally characterized by the existence of two or more different versions of the same gene. Because every individual has two complete sets of chromosomes, the existence of a two-allelic polymorphism of a specific gene means that an individual can have one out of three different combinations of gene variants: (1) both chromosomes carry the gene variant A; or (2) both chromosomes carry the gene variant B; or (3) one of the chromosome sets carries gene variant A and the other one variant B.

Whereas most research on GXE interaction is guided by diathesis-stress thinking, thus seeking to identify allelic combinations that in concert with adverse environments predict the negative outcomes, especially psychiatric disorders, many findings from this literature suggest that such putatively vulnerable genotypes are actually differentially susceptible because they often also show a disproportionately positive outcome under beneficial or at least less adverse circumstances.

In this section, we call attention to GXE findings involving three well-known and widely investigated polymorphisms of genes coding for: (1) monoamino oxidase A (MAOA), an enzyme which deactivates specific neurotransmitters, (2) the serotonin transporter (5-HTTLPR), a protein which is involved in the reuptake of serotonin from the synaptic cleft into the neuron, and (3) the dopamine receptor D4 (DRD4), a protein which is transmitting dopamine signals from one neuron to another.

Monoamino oxidase A (MAOA)

The neurotransmitter-metabolizing enzyme monoamino oxidase A or *MAOA* gene is located on the X chromosome. It encodes the *MAOA* enzyme, which metabolizes neurotransmitters such as norepinephrine, serotonin, and dopamine, rendering them inactive. Two sets of evidence, one linking the low-activity MAOA allele to antisocial behavior, and another linking abuse and neglect in childhood to the same developmental outcome, led Caspi et al. (2002) to hypothesize that inconsistency in findings in both literatures could be a result of the fact that maltreatment effects are moderated by genotype; and this is exactly what they discovered in their groundbreaking and widely cited GXE research carried out on a New Zealand birth cohort followed into young adulthood. More specifically, it was principally young men – females were not studied – with one form of the gene, that associated with low *MAOA* activity, who proved more violence prone when they had been subject to maltreatment in childhood. For those children with the high-MAOA-activity allele, a substantially smaller effect of child maltreatment emerged.

Although most have interpreted these findings, not unreasonably, in diathesis-stress terms, few have noticed that those most vulnerable to the adverse effects of maltreatment actually scored lowest in antisocial behavior when not exposed to maltreatment, suggesting perhaps greater plasticity – for better *and* for worse – rather than just greater vulnerability to adversity in the case of those with the low-activity MAOA allele. This interpretation is buttressed by results from a significant number of efforts to replicate the Caspi et al. (2002) findings. For example, Kim-Cohen et al. (2006) studied a large number of boys to determine whether the MAOA polymorphism moderated effects of mother-reported physical abuse in early childhood on later mental health problems. At age 7 years boys with the low-MAOA-activity variant were rated by mothers and teachers as having more mental health problems – and specifically ADHD symptoms – if they had been victims of abuse, but fewer problems if they had not, compared to boys with the high-MAOA-activity genotype. In another longitudinal study, involving adolescent twin boys aged 8–17 years, Foley et al. (2004) found that childhood adversity – based on parent and child report – predicted 3-month history of conduct disorder (DSM-III) differently for children with the low- and high-activity MAOA allele. Once again, boys with the low-MAOA-activity allele were more likely to be diagnosed with conduct disorder if exposed to higher levels of childhood adversity and less likely if exposed to lower levels of adversity, compared to boys with the high-MAOA-activity allele. Similar results emerged in Nilsson et al.'s (2006) cross-sectional investigation of 81 adolescent boys when the predictor was psychosocial risk, operationalized in terms of maltreatment experience and living arrangement. Only boys with the low-MAOA-activity allele were affected by such risk, such that those with a history of adversity engaged in more criminal behavior (composite of vandalism, violence, stealing) and those lacking this history engaged in less, compared to boys with the high-MAOA-activity allele.

Serotonin transporter (5-HTTLPR)

Far more investigated than GXE interactions involving MAOA have been those involving 5-HTTLPR. The serotonin-transporter-linked polymorphic region (5-HTTLPR) is a degenerate repeat polymorphic region in SLC6A4, the gene that codes for the serotonin transporter. Much research focuses on two variants – those carrying at least one short allele (s/s, s/l) and those homozygous for the long allele (l/l) – though more variants than these have been identified (Nakamura, Ueno, Sano, & Tanabe, 2000). The short allele has generally been associated with reduced expression of the serotonin-transporter molecule – which is

involved in the reuptake of serotonin from the synaptic cleft – and thus considered to be related to depression, either directly or in the face of adversity.

Again breaking empirical ground in GXE research, Caspi et al. (2003) were the first to show that the 5-HTTLPR moderates effects of stressful life events during early adulthood on depressive symptoms, as well as on probability of suicide ideation/attempts and of major depression episode at age 26 years. Individuals with two short alleles (s/s) proved most adversely affected whereas effects on those with two long alleles (l/l) were weaker or entirely absent. Of special significance given our focus on differential susceptibility, is that those homozygous for the short allele scored best on the outcomes just mentioned when stressful life events were absent, though just as was true among low-MAOA activity individuals in Caspi et al. (2002), not by very much.

Several research groups have attempted to replicate Caspi et al.'s (2003) findings of increased vulnerability to depression in response to stressful life events for individuals with one or more copies of the s allele, with most succeeding. Going unnoticed in most even if not all of this work to be summarized below, however, is that those carrying one or two short alleles (s/l, s/s) did not just function most poorly when exposed to many stressors, but best – showing least problems – when encountering few or none. Consider, for example, Taylor et al.'s (2006) findings (appreciated by the investigators) indicating that young adults homozygous for short alleles (s/s) manifested greater depressive symptomatology than individuals with other allelic variants when exposed to early adversity (i.e., problematic childrearing history), as well as many recent negative life events, consistent with a diathesis-stress framework, yet the fewest symptoms when they experienced a supportive early environment or recent positive experiences, that is, not just the absence of adversity. A similar for-better-*and*-for-worse pattern of environmental effects is evident – and noted – in Eley et al.'s (2004) research on adolescent girls who were and were not exposed to risky family environments. Similarly, retrospectively reported emotional abuse in childhood was more predictive of anxiety sensitivity in the case of individuals with s alleles in a cross-sectional study involving undergraduate students (Stein, Schork, & Gelernter, 2008). The significantly steeper abuse-anxiety slope in the case of students homozygous for short alleles relative to those with one or more long alleles indicated that s/s individuals scored highest in anxiety sensitivity when exposed to abuse and lowest when not exposed.

Considering ADHD (in childhood and adulthood), Retz et al. (2008) focused on the moderated effects of an adverse childhood environment in their study of male delinquents who averaged 34 years of age. Using a retrospective assessment of childhood ADHD, as well as of early adversity, but a clinical interview to assess functioning in adulthood, these investigators detected a cross-over interaction with respect to the persistence of ADHD over time (though interpretively important associations between moderator and predictor were not reported). Compared to l/l genotypes, individuals with s alleles had more and less persistent ADHD, depending on whether or not, respectively, they experienced an adverse early environment.

Dopamine receptor D4 (DRD4)

Moving from the serotonergic to the dopaminergic system, which is engaged in attentional, motivational, and reward mechanisms, a polymorphism of the dopamine receptor D4 (DRD4) gene also has stimulated much GXE research. Variants of the DRD4 differ by the number of 48-base pair tandem repeats in exon III, ranging from 2 to 11. The 7-repeat variant has been identified as a vulnerability factor due to its links to ADHD (Faraone, Doyle, Mick, & Biederman, 2001), high novelty-seeking behavior (Kluger, Siegfried, & Ebstein, 2002), and low dopamine reception efficiency (Robbins & Everitt, 1999), among other correlates.

As it turns out, a number of studies indicate that children carrying this putative risk allele are not only more adversely affected by poorer quality parenting than other children, but also benefit more than others from good-quality rearing. In a longitudinal study of infants, maternal insensitivity observed when children were 10 months predicted externalizing problems reported by mother more than 2 years later, but only for children carrying the 7-repeat DRD4 allele (Bakermans-Kranenburg & van IJzendoorn, 2006). Moreover, although children with the 7-repeat DRD4 allele displayed, consistent with a diathesis-stress model, the most externalizing behavior of all children when mothers were judged insensitive, they also manifested the least externalizing behavior when mothers were highly sensitive.

A cross-sectional study of sensation seeking in 18–21-month-old children generated results in line with those of Bakermans-Kranenburg and van IJzendoorn (2006), with toddlers carrying the 7-repeat allele rated by parents as showing, compared to children without the 7-repeat allele, less sensation-seeking behavior when parenting quality was high and more when parenting quality was low (Sheese, Voelker, Rothbart, & Posner, 2007). Whereas parenting proved significantly associated with sensation seeking in the 7-repeat individuals, it did not in other children. Of importance is that genotype did not predict parenting or sensation seeking, fulfilling important differential-susceptibility criteria.

Experimental intervention research designed to enhance parenting also documents a moderating effect of the 7-repeat allele on parenting. When Bakermans-Kranenburg, van IJzendorn, Pijlman, Mesman, and Juffer (2008) looked at change over time in parenting – from

before to well after a video-feedback parenting intervention was provided on a random basis to mothers of 1—3-year-olds who scored high on externalizing problems – they not only found that the intervention succeeded in promoting more sensitive parenting and positive discipline, but that experimental effects extended to improvements in child behavior, but only for those children carrying the DRD4 7-repeat allele.

The same team of Dutch investigators also reported that the DRD4 7-repeat allele moderated the effect of maternal unresolved loss or trauma, as measured by means of the Adult Attachment Interview, on early infant development. More specifically, unresolved loss predicted infant attachment disorganization, an early developmental marker of psychological disturbance later in life (Carlson, 1998), but only in the case of infants carrying the 7-repeat allele (van IJzendoorn & Bakermans-Kranenburg, 2006). Indeed, these infants manifest both the most and least disorganized attachment behavior when stressed in the laboratory depending on whether their mothers had or had not experienced unresolved loss or trauma in their own lives.

Conclusion: unknowns of the differential-susceptibility hypothesis

A substantial number of studies, rather diverse in their focus and design, show that some individuals are more susceptible to both negative and positive parenting experiences than others – just as the differential-susceptibility hypothesis would predict. Consequently, parenting behavior seems to exert more influence on some children than on others. In extremis, the same parenting behavior may affect some children substantially yet not affect others at all, depending on their temperament and/or genetic make-up. In contrast to the "vulnerability" concept central to diathesis-stress/dual-risk models, being more or less susceptible to rearing experiences is not exclusively associated with the effects of adversity; this greater susceptibility also operates with respect to supportive rearing environments. What needs to be made clear is that whether or not being highly malleable is considered advantageous or not depends entirely on the environment to which the child is exposed. Whereas more plastic individuals would seem to benefit from responding more positively to supportive parenting, less malleable children would seem to benefit more from not being susceptible to the adverse consequences of problematic parenting.

The observation that children differ in their response to environmental conditions may explain why shared environment generally accounts for so little variance in behavior-genetics studies. Because children, even siblings, differ in their temperament and/or genetic make-up, they are not influenced in the same way even when exposed to the very same parenting. This observation raises the first unknown to be considered in the differential-susceptibility hypothesis, as well as the second: *Do parents have a sense that one or more of their offspring are affected more than others by how they are reared? If so, do they modify their efforts to influence them?*

The findings consistent with differential susceptibility summarized herein suggest that the widely embraced diathesis-stress/dual-risk model of development may seriously misrepresent some developmental processes, especially how developmental plasticity operates: Some children may not be simply more vulnerable to adverse environments but in fact more susceptible to both negative and positive experiences. One reason this possibility has rarely been discussed in the literature is probably a result of psychology's disproportionate focus on the *adverse* effects of *negative* experiences on *problems* in development and, thereby, the identification of individuals, including children, who – for organismic reasons – are particularly "vulnerable" to contextual risks or "protected" from them. What the differential-susceptibility hypothesis postulates, in contrast, is that the very children who are putatively "vulnerable" to adversity vis-à-vis problems in development may be equally and disproportionately susceptible to the developmentally *beneficial* effects of *supportive* rearing environments.

This fundamentally different understanding may actually require the recasting of common concepts like "vulnerability" and "resilience." "Vulnerability" may represent just one side of plasticity – the negative one – and therefore reflect only half of the story. The observation that so-called "vulnerable" children will also benefit disproportionately from positive environments calls for a different, more neutral, term – susceptibility, plasticity, or malleability. "Resilience," generally understood as the advantageous ability to withstand negative effects of adverse environments, may in fact represent a general immunity to environmental influences of all kinds, including positive ones, not just to adversity. To the extent that this is the case, "resilience," typically regarded as an advantage (in adverse environments), would seem to be disadvantageous, too – in supportive environments. In these latter contexts, the malleable will reap developmental benefits whereas the less malleable, including perhaps the resilient, will not or do so to a far less extent.

The research considered herein suggests that parenting effects are moderated in a differential-susceptibility manner not just by a single factor but, rather, by many different ones, some phenotypic (i.e., temperament) and some genotypic (i.e., MAOA, 5-HTTLPR, DRD4). Interestingly, some data suggest that early infant temperament – which has been highlighted above as moderator of environmental influences and thus marker of plasticity – is related to at least two of the genotypes also associated with differences in susceptibility to rearing, the serotonin-transporter promoter polymorphism (5-HTTPLR) and the dopamine DRD4 polymorphism (Auerbach, Faroy,

Ebstein, Kahana, & Levine, 2001). This raises another unknown of the differential-susceptibility hypothesis: *Are putatively different differential-susceptibility factors actually manifestations of the same underlying disposition?*

Another important question that remains unanswered at this point is whether such a disposition for heightened susceptibility is general or domain-specific in nature. In other words: *Does the disposition for susceptibility to environmental influences determine an individual's susceptibility to any or at least many environmental influences or only to certain specific ones?* Whereas the latter conceptualization might make more intuitive sense, of interest is a recent computer modeling effort designed to determine whether individual differences in susceptibility to environmental influences could evolve through natural selection (Wolf et al., 2008). Not only did it show that it could, but it further indicated that it would occur in a more domain-general, across-the-board manner rather than a domain-specific one.

The next in our current list of unknowns of the differential-susceptibility hypothesis is whether susceptibility is a function of nurture – consequently modifiable – or whether it represents an innate and therefore unchangeable trait, a function of nature: *Is differential susceptibility born or made?* The GXE work certainly suggests that susceptibility is a function of genetics. However, according to Boyce and Ellis (2005) physiological stress reactivity which also has been found to moderate effects of the environment (Boyce et al., 1995) is likely to be a function, at least in part, of experience. Also, difficult infant temperament has been associated with stressful prenatal and postnatal experiences as we point out below. Therefore, as depicted in Figure 2, susceptibility to environmental influences is probably best understood as a function of both nature and nurture.

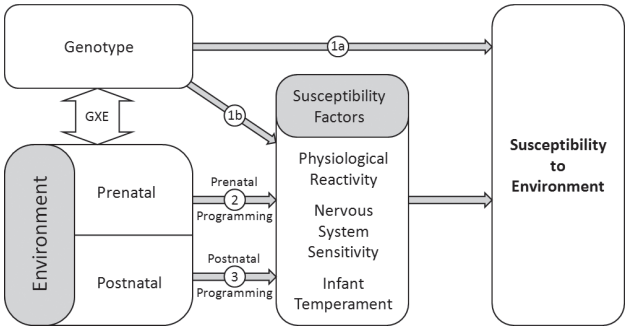

Figure 2. Nature, nurture, and differential susceptibility: A process model. 1a = direct genetic contribution to general susceptibility (nature); 1b = genetic contribution mediated by susceptibility factors (nature); 2 = prenatal environment shapes susceptibility factors (nurture); 3 = postnatal environment shapes susceptibility factors (nurture). In addition, genotype interacts with both prenatal and postnatal environment to shape susceptibility factors.

The review of GXE findings certainly suggests a direct genetic contribution to individual susceptibility. Moreover, significant associations between the gene variants considered and phenotypical susceptibility factors (e.g., infant fearfulness and s/s genotype of the 5-HTTLPR, see Auerbach et al., 2001) and also endophenotypical ones (e.g., physiological stress reactivity and 5-HTTLPR, see Gotlib, Joormann, Minor, & Hallmayer, 2008) suggest that the genetic contribution – or at least some of it – is mediated by such behavioral/physiological susceptibility factors.

Evidence that susceptibility may also be a function of nurture stems from research showing that early experiences – both prenatal and postnatal – predict several of the established susceptibility factors. Consider in this regard research showing (1) that maternal stress during pregnancy predicts difficult temperament at 3 months of age (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002); (2) that maternal prenatal anxiety predicts awakening cortisol in 10-year-olds (O'Connor et al., 2005); (3) that maternal sensitivity predicts emotional responsivity in 4-month-old infants (Kaplan, Evans, & Monk, 2008); and (4) that early postnatal adversity (childhood abuse) predicts increased physiological stress reactivity in adult women (Heim et al., 2000). Before concluding on the basis of such findings that there may be prenatal and postnatal programming of plasticity (nurture), we raise another unknown of the differential-susceptibility hypothesis: *May it be that for genetic reasons some individuals are more likely to be affected by prenatal (and postnatal) experiences than others?* GXE research certainly suggests that GXE interaction may also characterize these programming processes. Prenatally programmed susceptibility may even increase the potential for postnatal programming of susceptibility, perhaps thereby affecting susceptibility to environmental influences in middle childhood or even later in life.

Finally, in light of the fact that the differential-susceptibility hypothesis derived from an evolutionary analysis of rearing influences (Belsky, 1997b, 1997a, 2005; see also Boyce & Ellis, 2005), it seems appropriate to wonder *whether susceptibility is itself truly adaptive* in terms of enhancing fitness, especially in the modern world today. While research on the effects of prenatal social stress on offspring in guinea pigs suggests that behavioral effects of the (prenatal) environment are not necessarily nonadaptive consequences of adverse social conditions, but rather adaptive adjustments to the specific characteristics of the environment with the ultimate goal of optimizing reproductive success (Kaiser & Sachser, 2009), as noted at the outset, there are no studies of humans addressing this issue.

In conclusion, differential susceptibility represents a fundamentally new and different theoretical approach regarding how environmental influences operate, based as

it is on the theoretical premise that individuals differ in their developmental plasticity. Differential-susceptibility reasoning extends diathesis-stress claims that some individuals are more likely than others to be adversely affected by negative developmental experiences by calling attention to the fact that these same putatively "vulnerable" individuals are simultaneously more susceptible to positive environmental influences. As already noted, this raises questions about the use of the terms "vulnerability" and "resilient" to describe individuals.

Reconceptualizing so-called "vulnerable" children as children highly susceptible to the benefits of supportive rearing environments as well as the costs of poor ones could prove useful to practitioners when dealing with parents and their "difficult" children. Viewing such children as having substantial developmental plasticity instead of simply being "difficult" may create hope for many parents who often feel overwhelmed when dealing with such infants and toddlers. Knowing that the return on a heavy investment in sensitive, authoritative parenting may be substantial on the upside could provide the motivation to work hard to do so when exhaustion and irritation rise to the surface.

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