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Beyond Diathesis Stress: Differential Susceptibility to Environmental Influences

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Evolutionary-biological reasoning suggests that individuals should be differentially susceptible to environmental influences, with some people being not just more vulnerable than others to the negative effects of adversity, as the prevailing diathesis-stress view of psychopathology (and of many environmental influences) maintains, but also disproportionately susceptible to the beneficial effects of supportive and enriching experiences (or just the absence of adversity). Evidence consistent with the proposition that individuals differ in plasticity is reviewed. The authors document multiple instances in which (a) phenotypic temperamental characteristics, (b) endophenotypic attributes, and (c) specific genes function less like "vulnerability factors" and more like "plasticity factors," thereby rendering some individuals more malleable or susceptible than others to both negative and positive environmental influences. Discussion focuses upon limits of the evidence, statistical criteria for distinguishing differential susceptibility from diathesis stress, potential mechanisms of influence, and unknowns in the differential-susceptibility equation.

Keywords: parenting, differential susceptibility, diathesis stress, GXE, psychopathology

Students of human development appreciate that individuals vary in whether and/or the degree to which they are affected, over the shorter and longer term, by environmental experiences, including child-rearing ones. Perhaps the most striking evidence that person characteristics condition or moderate environmental effects is to be found in developmental research on Temperament × Parenting interaction (Rothbart & Bates, 2006) and psychiatric research on Gene × Environment interaction (GXE; Burmeister, McInnis, & Zollner, 2008).

Work in both these areas of inquiry is guided primarily, even if not exclusively, by what developmentalists regard as the transactional/dual-risk model (Sameroff, 1983) and what psychiatrists and others studying and treating psychopathology regard as the diathesis-stress model (Monroe & Simons, 1991; Zuckerman, 1999). Central to both these frameworks is the view that some individuals, due to a "vulnerability" in their make-up—which may be behavioral/temperamental in character (e.g., difficult temperament), physiological or endophenotypic in nature (e.g., highly physiologically reactive), or genetic in origin (e.g., *5-HTTLPR* short alleles)—are disproportionately or even exclusively likely to be affected adversely by an environmental stressor. That stressor may be child maltreatment, insensitive parenting, or negative life events, to name but three that are well studied and figure prominently in this paper, which advances an alternative to the diathesis-stress/dual-risk model of environmental influences and human development.

According to prevailing views, it is the child with a "difficult" (or negatively emotional) temperament, for example, or individuals carrying certain "vulnerability genes" or "risk alleles" who are most likely to develop or function poorly, such as by manifesting a psychopathological condition (e.g., depression), when exposed to a stressor of interest. The dual-risk designation derives from the synergistic effect of a risk (or diathesis) inherent in the individual interacting with one operative in the environment. The point of this paper is not so much to challenge the view that diathesis-stress phenomena exist or that processes related to them operate. That seems incontestable. Nor is its intent to suggest that diathesis-stress thinking and research have proven unproductive, either theoretically or empirically. That, too, seems indisputable.

Rather, the goal in this effort is to assert—and demonstrate empirically—that in many cases where dual-risk/diathesis-stress processes appear to characterize human functioning and development, something of equal or perhaps even greater significance is going on. Indeed, it is our contention that this "something else" is often missed as a result of expectations derived from the prevailing conceptual perspective that guides both inquiry and interpretation of findings. In fact, it is a central claim here that the disproportionate attention paid to the negative effects of contextual adversity, broadly defined and varied in its operationalization, on problematic functioning and disturbances in development and mental

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health may actually lead scholars to mischaracterize some environmental influences, as well as human development processes and phenomena. In essence, then, this essay embraces the perspective of positive psychology (Diener & Biswas-Diener, 2008; Seligman, 2003; Seligman, Parks, & Steen, 2004) and applies it to the study of environmental influences on behavior and development, especially the moderating role of individual attributes.

The central thesis in this paper, as stipulated by the differential-susceptibility hypothesis (Belsky, 1997a, 2005; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009), as well Boyce and Ellis's (2005) biological-sensitivity-to-context thesis, is that those putatively "vulnerable" individuals most adversely affected by many kinds of stressors may be the very same ones who reap the most benefit from environmental support and enrichment, including the absence of adversity. Thus, we should expect individual differences in developmental plasticity and, more generally, susceptibility to environmental influences, with some individuals being far more affected than others by both negative and positive contextual conditions. In the body of the paper we provide extensive, yet still just illustrative evidence to this effect, most of it very recent and much of which has gone unnoticed, even at times by the very investigators generating it (but see Taylor et al., 2006; Uher & McGuffin, 2008).

What follows should not be regarded as an exhaustive review of the literature, nor should it be seen to demonstrate, much less imply, that evidence of differential susceptibility outweighs evidence of diathesis stress, either in the literature as a whole or in each and every study cited for illustrative purposes. To make the case, as we exclusively seek to, that differential susceptibility appears operative in human development and functioning but that individual differences in plasticity have been largely even if not entirely overlooked in favor of prevailing views that some individuals are simply more vulnerable to adversity than others, we contend that an admittedly selective compilation of a multiplicity of illustrative findings is exactly what is appropriate at the present time. This would seem especially so in light of the fact that much of the available research, most particularly that investigating GXE interaction, focuses on both a restricted range of environments, typically emphasizing the negative end of the spectrum and failing to measure at all the positive (except for the absence of adversity), and a restricted range of psychological and behavioral outcomes, also typically emphasizing the negative, and thereby fails to assess competent functioning (except for the absence of dysfunction). Of course there are exceptions (e.g., Kaufman et al., 2004, 2006; Wilhelm et al., 2006).

Nevertheless, as a result of the design characteristics of so many investigations, it remains unclear whether extensive evidence consistent with a diathesis-stress model and seemingly inconsistent with a differential-susceptibility framework is an accurate reflection of how human psychological and behavioral functioning operates or, instead, an artifact of study design. Quite conceivably, simply treating the absence of adversity as the "good" end of the environmental-exposure spectrum and/or the absence of a disorder as the "good" end of the psychological-functioning continuum, as so many studies do, may lead to the underdetection of differential-susceptibility findings and an overrepresentation of vulnerability ones. It is for these reasons that we consider it appropriate at the present time to provide extensive illustrative evidence of apparent differential-susceptibility effects rather than to undertake a formal meta-analysis of all findings involving person characteristics moderating environmental effects in hopes of determining which model fits the data better.

Before extensive evidence is presented consistent with the claim that the very same individuals who may be most adversely affected by many kinds of stressors may simultaneously reap the most benefit from environmental support and enrichment (including the absence of adversity), the evolutionary-biological bases of differential susceptibility are presented, followed by evidentiary criteria used in this review to define differential susceptibility. Thereafter, research highlighting phenotypic, endophenotypic, and genetic susceptibility factors—or moderators of environmental effects—is reviewed in three separate subsections, with an exclusive focus on studies and findings that point toward differential susceptibility. In other words, this effort is not intended to be a general review of Temperament × Parenting or GXE interaction research (or any other). In a concluding section, ways of advancing the study of differential susceptibility are proposed, with a focus upon (a) statistical criteria for evaluating differential susceptibility, (b) potential mediating mechanisms responsible for it, and (c) still-to-be-illuminated unknowns in the differential-susceptibility equation.

Theoretical Foundations

Two distinct, though by no means mutually exclusive, evolutionary-inspired theoretical arguments advance the claim that individuals should vary in their developmental plasticity and susceptibility to environmental influence, Belsky's (1997a; 1997b; 2005) differential-susceptibility hypothesis and Boyce and Ellis's (2005; Ellis, Essex, & Boyce, 2005; Ellis, Jackson, & Boyce, 2006) biological-sensitivity-to-context thesis. Whereas the former has emphasized the role of nature in shaping individual differences in plasticity, without excluding a role for nurture, the latter has emphasized nurture, without excluding nature. Additionally, whereas the theoretical argument for differential susceptibility leads to no specific hypotheses about susceptibility factors or mediating mechanisms and regards these as essentially empirical questions, such concerns are central to the biological-sensitivity-to-context thesis. Both models nevertheless predict that some children and perhaps adults will be more susceptible than others to both the adverse and beneficial effects of, respectively, unsupportive and supportive contextual conditions.

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 things. Indeed, from the perspective of modern evolutionary biology, natural selection shapes living things not just to survive but to reproduce. 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. This evolutionary-biological foundation forms the basis for the differential-susceptibility hypothesis.

Because the future is and always has been inherently uncertain, ancestral parents, just like parents today, could not have known (consciously or unconsciously) what child-rearing practices would prove most effective 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 (Belsky, 2005). This way, if an effect of parenting proved counterproductive in fitness terms, those children not 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. In light of inclusive-fitness considerations, the reduced susceptibility of these less malleable children to parental influence would not only have benefited themselves directly but their more malleable sibs as well—but indirectly, given that sibs, like parents and children, share 50% of their specific alleles. By the same token, had parenting influenced children in ways that enhanced fitness, 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 sibs who did not benefit from the parenting they themselves had received, again for inclusive-fitness reasons (i.e., shared genes).

Such evolutionary reasoning leads directly to the proposition that children should vary in their plasticity and thus susceptibility to parental rearing and perhaps to environmental influences more generally. To be clear, though, this is not in any way a group-selectionist argument but one that regards the individual as the unit of selection. After all, on the basis of the preceding analysis, it is considered adaptive for an individual child to be more *or* less malleable and to have siblings with contrasting susceptibilities, thereby accruing potentially direct and/or indirect benefits, and for an individual parent to bear children of both kinds, thereby benefiting directly (i.e., immediate offspring) and indirectly (e.g., grandchildren).

As noted already, without denying the possibility of environmental influences on malleability, Belsky (1997a, 1997b, 2005) presumed that individuals varied for genetic reasons in their developmental plasticity. Not inconsistent with this view is extensive cross-species evidence that plasticity is heritable (Bashey, 2006; Pigliucci, 2007) and may function as a selectable character in and of itself (Sinn, Gosling, & Moltschaniwskyj, 2007). Indeed, one wild bird population shows evidence that selection favoring individuals that are highly plastic with regard to the timing of reproduction has intensified over the past 3 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). Also noteworthy is Suomi's (2006) observation that a single genetic difference distinguishes the two primate species that fill multiple niches around the world from all others that inhabit singular and rather narrow ones, that being the presence (in some individuals) of the *5-HTTLPR* short allele. This leads him to regard humans and macaques as "weed species."

Biological Sensitivity to Context

Boyce and Ellis (2005) argued that for adaptive reasons, children in both especially supportive and especially unsupportive developmental contexts should develop or maintain high levels of physiological stress reactivity, which they regard as a susceptibility factor and thus plasticity mechanism (i.e., the endophenotypic instantiation of susceptibility to environmental influence). Thus, they expect a curvilinear, *U*-shaped relation between levels of supportiveness versus stressfulness in early childhood environments and the development of stress-reactive profiles, with high reactivity disproportionately emerging in both highly stressful and highly protected social environments.

For children fortunate enough to grow up in particularly supportive contexts, Boyce and Ellis (2005) contended, it would be adaptive to be maximally influenced by the developmental environment. Indeed, the physical, behavioral, and psychological embodiment of the rich resource base provided by the family and the broader ecology would enhance the social competitiveness of the individual through the development of a broad range of competencies, thereby increasing his or her mate value and eventual reproductive fitness. In contrast, those growing up under harsh and dangerous conditions would increase their chances of survival and eventual reproduction if they developed heightened vigilance to threat and proved highly prepared to actively combat risks that they might face. For them, too, heightened physiological reactivity is presumed to be the vehicle for getting this developmental job done. Thus, it is Boyce and Ellis's thesis that the stress-response system operates as a conditional adaptation, selected to enable individuals to fit environments that, starting early in life, would enhance their fitness prospects: "Natural selection has favored developmental mechanisms (conditional adaptations) that function to adjust levels of BSC [biological sensitivity to context] to match familial and ecological conditions encountered early in life" (2005, p. 292).

Irrespective of whether plasticity is considered to be principally a function of nature or of nurture—or their interaction—the claim that individual differences in plasticity have evolved is central to both evolutionary arguments under consideration. Of importance, therefore, are the results of a recent simulation study that sought to determine whether plasticity could evolve and clearly showed this to be the case, with some individuals being more responsive than others to environmental conditions (Wolf, van Doorn, & Weissing, 2008).

Both arguments also define individual differences in developmental plasticity to mean that some children and even adults will be more susceptible than others to both the adverse and beneficial effects of, respectively, unsupportive and supportive contextual conditions. This view contrasts markedly with traditional dual-risk/diathesis-stress frameworks, which regard certain putatively "vulnerable" individuals as more likely than others to be adversely affected by unsupportive contextual conditions but stipulate nothing about differential responsiveness to supportive conditions. Just as important, diathesis-stress thinking does not propose, as differential-sensitivity and biological-sensitivity-to-context theorizing does, that the very individual attributes that make some individuals disproportionately susceptible to adversity simultaneously make them disproportionately likely to benefit from supportive ones. Notably, and as is documented more extensively in

this paper, Uher and McGuffin (2008) recently observed that some GXE findings fit a pattern whereby individuals carrying certain alleles prove more susceptible to both adverse and supportive environmental conditions; that is, they are affected in a "for-better-*and*-for-worse" manner (Belsky et al., 2007).

Evidentiary Criteria for Establishing Differential Susceptibility

A series of empirical requirements—or steps—for establishing evidence of differential susceptibility to environmental influence, that is, individual differences in plasticity, has recently been delineated (Belsky et al., 2007). Some of these steps guide the selective review of evidence presented herein. The first concerns the application of conventional statistical criteria for evaluating genuine moderation of a putative environmental influence by an organismic plasticity or susceptibility factor (Dearing & Hamilton, 2006), with some emphasis placed on excluding interactions with regression lines that do not cross (sometimes referred to as removable interactions). The next steps distinguish differential susceptibility from person–environment correlations that may reflect evocative effects of person characteristics on environmental experiences and from diathesis-stress/dual-risk models. If the susceptibility factor and the outcome are related, dual risk (or gain, when positive factors are involved) is suggested. For example, early negativity would itself lead to externalizing behavior but even more so when combined with negative parenting. The specificity of the differential-susceptibility effect is demonstrated if the model is not replicated when other susceptibility factors (i.e., moderators) and outcomes are used (Caspi & Moffitt, 2006; Rutter, 2006). Differential susceptibility is thus demonstrated when the moderation reflects a crossover interaction that covers both the negative and the positive aspects of the environment. The slope for the susceptible subgroup should be significantly different from zero and at the same time significantly steeper than the slope for the non- (or less) susceptible subgroup.

Throughout the next three sections, we present extensive evidence of differential susceptibility to environmental influence that is consistent with the view that individuals differ in their plasticity, with some being more affected than others by experiential influences in a for-better-and-for-worse manner. We begin by considering research that addresses behavioral or phenotypic characteristics of individuals that moderate environmental influence and thus function as potential markers of plasticity (e.g., difficult temperament). We next turn to work that highlights similar moderational effects of endophenotypic characteristics of individuals, with endophenotype defined as attributes of individuals that lie between the gene and behavior (e.g., physiological reactivity). Finally, we consider evidence from the ever-expanding literature on GXE interaction in which genes moderate environmental effects, again in a for-better-and-for-worse manner, not just in a diathesis-stress or dual-risk manner (see also Uher & McGuffin, 2008).

Perhaps because so much of the work to be cited is new—and was often conducted with a diathesis-stress/dual-risk frame of reference in mind—it is actually rare for investigations to address all or even most of the statistical criteria mentioned above for empirically establishing differential susceptibility to environmental influence, to say nothing of additional ones that are outlined in the concluding section of this report. Indeed, even when investigators detect statistical interactions of a crossover nature, as was the case in all the research to be cited, different strategies of following up and illuminating the nature of such interactions are adopted. Whereas some investigations employ a grouping approach for dealing with the interacting predictor variables, plotting or tabling subgroup means, others calculate and contrast slopes reflecting the differential predictive relation between the continuously measured environmental predictor and outcome for subgroups that differ on the moderating susceptibility factor (e.g., easy vs. difficult infants). Only rarely is it reported whether such slopes differ significantly from each other, as would be preferable when the moderator does not have a natural break point but is a continuous dimension; this, of course, is not needed when the moderator is naturally binary. Perhaps analogously, it is not always reported, when subclass means are plotted, exactly which means differ significantly from which others. And most significantly (see Conclusion), in only one case has an investigatory team explicitly sought to determine whether subclass-mean differences hold at both the "for better" and "for worse" sides of the differential susceptibility equation (Taylor et al., 2006), that is, whether the putatively susceptible group functioned more poorly than the other subgroup under negative environmental conditions and functioned better under positive environmental conditions.

Given this less-than-ideal situation for evaluating differential susceptibility, we adopt a liberal standard of evidence once a significant crossover interaction has been detected when it comes to regarding results as evidence of differential susceptibility to environmental influence. For example, with regard to subgroup means, if one subgroup shows both the highest and lowest mean of all susceptibility-factor-defined subgroups (e.g., short vs. long allele of the *5-HTTLPR*) on an outcome with regard to the environmental effect in question, this is interpreted as being in line with a for-better-and-for-worse, differential-susceptibility patterning of results. Similarly but with regard to slopes, whenever they indicate that one subgroup defined on the basis of the susceptibility factor in question would score highest and lowest, given the environmental influence under investigation (i.e., steepest slope), this, too, is interpreted as evidence of differential susceptibility.

Presented in Tables 1–3 are all the empirical studies and specific findings that inform this review, in order of appearance in the text, though not all will be considered at the same level of detail. Tables 1, 2, and 3, pertain, respectively, to studies and findings involving phenotypic, endophenotypic, and genetic susceptibility factors. In addition to information on (a) study author, (b) publication year, and (c) sample, each table provides information on (d) the specific susceptibility factor (e.g., difficult temperament, *5-HTTPLR*) and plasticity marker (e.g., high difficulty, short allele) being studied; (e) the environmental predictor investigated (e.g., parenting, life events); (f) the extent to which the predictor captured a full range of environmental variation across negative-to-positive poles (i.e., adversity ↔ absence of adversity; adversity ↔ support/enrichment; support/enrichment ↔ absence of support/enrichment); (g) the outcome being predicted (e.g., depression, externalizing behavior); (h) the extent to which the outcome reflected a full range of variation across negative-to-positive poles (i.e., negative ↔ absence of negative; negative ↔ positive; positive ↔ absence of positive); (i) whether the association between susceptibility factor and environmental predictor was significant, not significant, taken

into account statistically, or unreported; (j) the relation between moderator or susceptibility factor and outcome (same categorization); and (k) whether the analysis that followed detection of a significant crossover interaction was based exclusively on contrasting regression lines of subgroups that varied on the susceptibility factor (e.g., high vs. low difficult temperament) or involved contrasting subgroup means on the dependent variable.

Phenotypic Markers of Differential Susceptibility

Evidence of differential susceptibility comes from research showing that temperamental and emotional characteristics of (mostly very young) children moderate the effect of developmental experience on behavioral development (see Table 1). Some of this work highlights the role of early negative emotionality/difficult temperament vis-à-vis parenting effects, some of it the role of other temperamental traits, some of it the moderated influence of child-care experience, some of it individual differences in plasticity beyond the early childhood years, and some of it experimental investigations that manipulated contextual conditions. Each set of evidence is considered in turn. Unless otherwise indicated, the work cited throughout this and the next two major sections was conducted without regard to the differential-susceptibility hypothesis and, if anything, was informed by diathesis-stress thinking.

Negative Emotionality and Difficult Temperament as Plasticity Markers

After advancing the differential-susceptibility hypothesis, which included no claims regarding proximate factors or mechanisms that should make some children more susceptible than others to child-rearing effects, Belsky (1997a, 1997b) sought to identify evidence of differential-susceptibility factors in existing and continually emerging developmental research. Well before any GXE research on humans was reported, attention was called to infant and toddler negative emotionality and difficult temperament as potential differential-susceptibility factors (for review, see Belsky, 2005).

Cross-sectional and longitudinal studies by Kochanska (1993); Belsky, Hsieh, and Crnic (1998); and Feldman, Greenbaum, and Yirmiya (1999) showed, for example, that diverse measures of rearing of infants and toddlers (e.g., discipline, interactional synchrony, positive and negative parenting) accounted for substantially more variance in self-control, externalizing problems, and/or inhibition in the case of more negatively emotional infants/toddlers than of other children, whether operationalized in terms of difficult temperament, irritability, fearfulness, or inhibition. (All but the Kochanska, 1993, study were explicitly designed to test differential susceptibility.) But it was not just in research on very young children that such moderating effects of negativity emerged. Morris et al. (2002) found, for example, that harsh and hostile mothering also proved to be a stronger predictor of teacher-reported externalizing problems in first and second grade when children scored high rather than low on irritable distress.

Even though most of the research reviewed by Belsky (2005) showed 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 reviewed often did not afford determination of whether this result was itself a function of a for-better-and-for-worse pattern of parenting effects. In consequence, it remained unclear whether individual differences in plasticity—or just vulnerability—were responsible for the repeatedly detected finding that more variance was explained in one group's functioning than in another's by the environmental factor investigated.

Fortunately, a growing number of studies have overcome this limitation, revealing for-better-and-for-worse rearing effects and thus differential susceptibility. Van Aken, Junger, Verhoeven, van Aken, and Dekovic (2007) found, for example, that 16- to 19-month-old boys with difficult temperament showed 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.

In a series of investigations Kochanska, Aksan, and Joy (2007) evaluated whether child temperament moderated parenting effects on positive developmental outcomes. In one study, children's fearfulness, maternal power assertion, and mother–child positive relations were assessed behaviorally when children were 22 and 33 months old, and children's moral self was measured (via puppet interview) at 56 months. Although no parenting effects emerged in the case of children who, as toddlers, scored low in fear, those who were highly fearful evinced a greater moral sense if their mothers (at 22 months only) relied little on power assertion to regulate their behavior but a limited one if their mothers relied heavily on power to control earlier child behavior. Similar fear-moderated findings emerged when Kochanska et al. (2007) investigated effects of fathers' power-assertive behavior (15 months) on children's rule-compatible conduct (38 months). Because child fearfulness was itself significantly and negatively related to maternal power assertion in the first study summarized, questions arise about the confidence that can be placed in an interpretation highlighting individual differences in plasticity. A preferable way to proceed in this circumstance would be to statistically adjust the environmental predictor (i.e., maternal power assertion) for the susceptibility factor (i.e., child fearfulness), thereby controlling for the evocative effect of the latter on the former before testing Temperament × Parenting interactions.

A series of reports using data from the large-scale National Institute of Child Health and Human Development (NICHD) Study of Early Child Care and Youth Development (NICHD Early Child Care Research Network, 2005) and focusing upon maternally reported difficult temperament at 1 and/or 6 months explicitly tests differential susceptibility to parenting. In one study, Bradley and Corwyn (2008) found that quality of parenting (observed and averaged across multiple measurement occasions from infancy through first grade) negatively predicted teacher-reported problems in first grade but that this anticipated parenting effect was moderated by early temperament. Thus, evidence showing that better quality parenting predicted fewer problems and that poorer quality parenting predicted more problems proved strongest for those with difficult temperaments, weaker for those with intermediate levels of difficult temperament, and weaker still for those scoring very low on difficult temperament (i.e., easy temperament). This suggests that rather than categorically conceptualizing some children as malleable (i.e., difficult temperament) and others as not (i.e., easy temperament), studies might more appro-

Table 1
Characteristics of Study Findings Providing Empirical Evidence for Differential Susceptibility as a Function of Phenotype

Study characteristics								Statistical criteria for differential susceptibility		Follow-up analysis[a]
Author	Year	Sample	Susceptibility: Plasticity marker	Environmental predictor	Range of predictor	Outcome	Range of outcome	Moderator/ predictor correlation	Moderator/ outcome correlation	Subgroup contrasts
van Aken et al.	2007	115 16- to 19-month-old boys	Temperament: difficult	Maternal sensitivity,	A ↔ S	Change in externalizing	N ↔ P	ns	significant	regression lines
				Negative control	A ↔ S	behavior				
Kochanska et al.	2007	Study 1: 74 4.5-year-old boys and girls	Temperament: high fearfulness	Maternal power assertion	A ↔ S	Child moral self	N ↔ P	significant	ns	regression lines
		Study 2: 100 3-year-old boys and girls		Paternal power assertion	A ↔ S	Rule-compatible conduct	N ↔ P	ns	ns	regression lines
Bradley & Corwyn	2008	929 6-year-old boys and girls	Temperament: difficult	Maternal sensitivity, Productive activity	A ↔ S	Externalizing behavior	N ↔ AN	not reported	ns	regression lines
Dopkins-Stright et al.	2008	1,007 6-year-old boys and girls	Temperament: difficult	Parenting quality	A ↔ S	Academic competence,	P ↔ AP	significant	significant	regression lines
						Social skills,	P ↔ AP	significant	ns	
						Teacher–child relationships,	N ↔ P	significant	ns	
						Peer status	N ↔ P	significant	ns	
Pluess & Belsky	2009a	1,364 10- to 11-year-old boys and girls	Temperament: difficult	Parenting quality,	A ↔ S	Reading, social competence	N ↔ P	significant (adjusted)	ns	regression lines
				Child-care quality	A ↔ S	Externalizing behavior, teacher–child conflicts	N ↔ AN	ns	ns	regression lines
Lengua et al.	2000	231 9- to 12-year-old boys and girls	Temperament: high impulsivity	Maternal inconsistent discipline	A ↔ S	Depression symptoms	N ↔ AN	significant	significant	regression lines
Smeekens et al.	2007	116 5-year-old boys and girls	Temperament: high anger proneness	Parental effective guidance	A ↔ S	Externalizing behavior	N ↔ AN	ns	ns	regression lines
Volling & Feagans	1995	36 14- to 48-month-old boys and girls	Temperament: social fear	Child-care quality	A ↔ S	Nonsocial activity	N ↔ P	not reported	ns	regression lines
Pluess & Belsky	2009	761–915 4.5- to 5-year-old boys and girls	Temperament: difficult	Child-care quality	A ↔ S	Externalizing behavior,	N ↔ AN	ns	ns	regression lines
						Social competence	P ↔ AP	ns	ns	regression lines
Lengua	2008	118 8- to 12-year-old boys and girls	Temperament: high anxiousness, high frustration, low frustration	Maternal parenting style	A ↔ S	Externalizing behavior,	N ↔ AN	significant	ns	regression lines
						Internalizing behavior	N ↔ AN	significant	significant	

(table continues)

Table 1 (*continued*)

Study characteristics								Statistical criteria for differential susceptibility		Follow-up analysis[a]
Author	Year	Sample	Susceptibility: Plasticity marker	Environmental predictor	Range of predictor	Outcome	Range of outcome	Moderator/ predictor correlation	Moderator/ outcome correlation	Subgroup contrasts
Mezulis et al.	2006	289 11-year-old boys and girls	Temperament: high withdrawal negativity	Negative life events (peer domain)	A ↔ S	Negative cognitive style	N ↔ AN	ns	ns	regression lines
Leve et al.	2005	373 17-year-old boys and girls	Temperament: high impulsivity, low fear/shyness	Harsh discipline	A ↔ AA	Externalizing behavior slope	N ↔ AN	significant	significant (only impulsivity)	regression lines
Gilissen et al.	2008	170 4- or 7-year-old boys and girls	Temperament: high fearfulness	Attachment quality	A ↔ S	Skin conductance level reactivity	N ↔ P	not reported	ns	means
Aron et al.	2005	213 male and female students	Sensory-processing sensitivity: high sensitivity	Adverse parental environment,	A ↔ AA	Shyness	N ↔ AN	significant	significant	regression lines
				Experimentally induced stress	A ↔ S	Negative affectivity	N ↔ AN	not reported	not reported	regression lines
Velderman et al.	2006	81 mothers	Temperament: high reactivity	Parenting intervention	S ↔ AS	Attachment security of child	N ↔ P	ns	ns	means

Note. A = adversity; AA = absence of adversity; S = support/enrichment; AS = absence of support/enrichment; N = negative outcome; AN = absence of negative outcome; ns = nonsignificant; P = positive outcome; AP = absence of positive outcome.

[a] After detecting significant crossover interaction between moderator and predictor on outcome.

priately conceptualize and measure individual differences in plasticity dimensionally, in terms of a plasticity gradient (Belsky, 2000).

Notably, Dopkins Stright, Cranley Gallagher, and Kelley (2008) extended work on parenting effects in this sample by documenting similar temperament-moderated, differential-susceptibility-like effects on positive, not just negative, developmental outcomes (i.e., teacher-rated academic competence, social skills, teacher–child relationships, and peer status at first grade). The fact, though, that the temperament susceptibility factor proved related to the parenting predictor (as well as at least one outcome measured) in this work raises questions about conclusions the investigators drew regarding differential susceptibility. Pluess and Belsky (2009a) overcame this problem in their study of differential susceptibility using the same sample (but not measures). After finding that parenting quality prior to school entry predicted reading and social competence in fifth grade and socioemotional functioning in sixth grade more strongly for children with difficult temperaments as infants than for those with easy temperaments—and in a for-better-and-for-for worse manner—they reran the analyses, discounting discerned evocative effects of a putative susceptibility factor (i.e., temperament) on the environmental predictor (i.e., parenting quality). After adjustment of the parenting predictor for the effect of infant difficult temperament, differential-susceptibility findings remained virtually unchanged.

Beyond Negative Emotionality/Difficult Temperament

Negative emotionality/difficult temperament is not the only temperamental trait that apparently moderates rearing influence in a manner consistent with differential susceptibility, thereby highlighting individual differences in plasticity. Impulsivity emerged as such a susceptibility factor in Lengua, Wolchik, Sandler, and West's (2000) cross-sectional study of recently divorced mothers and their 9- to 12-year-old children. Highly impulsive children manifested the least depressive symptoms when their mothers provided consistent discipline but the most when discipline proved highly inconsistent. And here, too, a plasticity gradient emerged, with the parenting–depression relation proving strongest for the most impulsive, weakest (and insignificant) for those least impulsive, and intermediate for those in between.

In longitudinal work with toddlers, anger proneness, which is conceptually related to impulsivity (and negative emotionality), emerged as a plasticity marker (Smeekens, Riksen-Walraven, & van Bakel, 2007). Toddlers who scored high in proclivity to get angry at 15 and 28 months were more and less likely than other children to manifest behavior problems at age 5 years (according to averaged parent and teacher report) if they had experienced, respectively, ineffective and effective parental guidance during the toddler years. Effective guidance involved the provision of structure and limit setting, clear instructions, and a supportive presence.

Beyond Parenting: Child-Care Quality

All the rearing effects considered through this point pertain to parenting. But as children, especially in the contemporary Western world, are routinely cared for by alternative caregivers in child-care settings, the question arises as to whether similar differential-susceptibility-like effects emerge in this context. In perhaps the earliest pertinent study, Volling and Feagans (1995) detected a relevant and thus noteworthy interaction between children's social fear (i.e., negative emotionality), as rated by mothers, and the observed quality of center-based child care in the prediction of observed nonsocial activity (i.e., solitary play, onlooker behavior) a year later when children were 14–48 months of age. The highly fearful children manifested both the most and least nonsocial activity, depending upon the quality of child care, whereas no such effect emerged in the case of the low-fear children.

Given Volling and Feagan's (1995) limited sample size, perhaps more convincing evidence that differential susceptibility characterizes some effects of child care comes from a recent analysis of data from the large-sample NICHD Study of Early Child, which examined both negative and positive developmental outcomes (Pluess & Belsky, 2009b). In this work explicitly testing differential susceptibility, the effect of observed quality of care (averaged across measurements at 6, 15, 24, 36, and 54 months) on behavior problems and social competence rated by caregivers in the year before school entry and by teachers in the first year of school was moderated by child temperament. Children with difficult temperament (averaged across the first 6 months) had more behavior problems when reared in low-quality environments and fewer problems when quality was high than did children with easy temperaments, and the regression lines (i.e., slopes) proved significant only for the children who scored high on difficult temperament as infants. Similar results emerged when Pluess and Belsky (2009a) extended this research to determine if differential susceptibility to the effects of good- and poor-quality child care in the first 4.5 years of life extended to teacher-reported behavior problems and teacher–child conflicts when children were 10–11 years of age.

Beyond the Early Childhood Years

Although the just-cited research indicates that differential-susceptibility effects pertaining to early parenting and child-care experience and involving phenotypic susceptibility factors extend beyond the early childhood years, the question arises as to whether rearing and related experiences thereafter operate in a similar manner. Indication that they do comes from Lengua's (2008) Temperament × Parenting interaction study, which sought to explain change in internalizing and externalizing problems using a community sample of 8- to 12-year-old boys and girls (see also Mezulis, Hyde, & Abramson, 2006). The effects of mothers' parenting style, as reported by children (i.e., rejection/acceptance, inconsistent discipline), on change over a 1-year period in mother-reported internalizing and externalizing problems varied by child temperament. Children highly prone to negative emotion in the form of frustration increased in externalizing problems over time when mothers were rejecting but decreased in externalizing problems when mothers manifested little rejection; no such effects of rejection emerged in the case of children scoring low on frustration. Inconsistent discipline did not affect the development of internalizing problems in low-anxious boys but did so in the case of high-anxious ones and in a manner consistent with differential susceptibility. It needs to be noted, however, that not all of Lengua's (2008) results were in line with these indicating that children scoring higher on some index of negativity prove more susceptible to the effects of more and less competent parenting. Leve, Kim,

and Pears's (2005) work on the determinants of behavior-problem trajectories from ages 5 to 17 documents similarly contrasting findings.

Perhaps especially worthy of consideration is research treating endophenotypic traits, rather than just behavioral functioning, as developmental outcomes shaped by developmental experience. Gilissen, Bakermans-Kranenburg, van IJzendoorn, and van der Veer (2008) detected a significant interaction between child fearfulness (parent report) and observed parent–child relationship quality in the prediction of skin conductance level (SCL) reactivity in response to a fear-inducing film clip. This cross-sectional investigation of 4- and 7-year-olds—specifically testing differential susceptibility—found that more fearful children manifest lower and higher SCL reactivity than do all low-fear children, depending upon whether their parent–child relationships were, respectively, secure or insecure. Of indisputable interest is that SCL reactivity—a marker for the activity of the sympathetic nervous system—has been found to moderate effects of the environment in a differential susceptibility manner, as is reported in the next major section dealing with endophenotypes. The Gilissen et al. (2008) findings would thus seem consistent with Boyce and Ellis's (2005) claim that plasticity may itself be a function of environmental influence (Belsky & Pluess, 2009).

Intriguingly, there is also suggestive evidence of the legacy or even operation of differential susceptibility in early adulthood. Especially worthy of consideration is a series of cross-sectional studies testing hypothesized interactions between sensory-processing sensitivity, a personality characteristic measureable by means of the Highly Sensitive Person Scale (see 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 individuals are characterized by a high-sensitive personality; this 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 studies of most relevance to this report (Aron et al., 2005, Study 2 and 3) indicated that a problematic (and retrospectively reported) child-rearing history predicted high levels of (self-reported) shyness and negative affectivity among undergraduate students, whereas its absence predicted low levels of these same dependent constructs; this relation obtained principally in the case of students scoring high on sensory-processing sensitivity, resulting in significant differences between regression lines (i.e., slopes) for high- and low-sensitivity groups.

Beyond Field Studies: Experimental Evidence

Evidence of a similar differential-susceptibility effect emerged in other research on sensory-processing sensitivity when the environmental influence, stress (or lack thereof), was experimentally induced by requiring students to take easy and difficult tests before negative affectivity was assessed (Aron et al., 2005, Study 4). In view of the fact that all research considered through this point can be regarded as limited due to its correlational (and often cross-sectional) nature, such an experimental demonstration of an environmental effect operating in a differential-susceptibility-like manner must regarded as important. After all, the possibility exists that that relations detected between experience and development in virtually all the work cited through this point could be a function of some unmeasured third variable, most notably, perhaps, genes that both elicit environmental experiences and influence development.

For this very reason, particular importance is accorded to two additional experimental studies, each of which explicitly tested Belsky's (1997a, 2005) differential-susceptibility-derived proposition that negatively emotional infants would disproportionately benefit from supportive environments. In one, Velderman, Bakermans-Kranenburg, Juffer, and van IJzendoorn (2006) sought to enhance the sensitivity of mothers at risk for rearing insecure infants due to their own less-than-secure state of mind regarding attachment. Results revealed that improvements in parenting following participation in a video-feedback-based intervention translated, as theorized, into secure attachment but only for infants who scored high on negative reactivity (before the intervention).

The second experimental study involved a reanalysis of data from the Infant Health and Development Program (1990), a well-known early intervention that involved the random assignment of poor, low-birth-weight infants and their families to treatment or control condition, putatively generating positive, across-the-board program effects. Blair (2002) found, as predicted, that experimental-group infants—exposed to educational day care in the second and third year of life and home visiting and parent support over their first 3 years—who were highly negatively emotional scored substantially lower on externalizing problems at 3 years of age than did similarly tempered infants randomly assigned to the control group; no such treatment effect occurred in the case of other infants. Especially intriguing given the fact that virtually all research considered through this point has focused on differential susceptibility vis-à-vis social and emotional functioning is that exactly the same results emerged when the outcome in question was severely impaired cognitive functioning. Highly negative infants assigned to the experimental intervention were five times less likely to score at or below 75 on an IQ test at age 3 than were their negatively emotional counterparts assigned to the control condition. No such experimental effect was detected in the case of infants scoring low on negative emotionality.

Comment

The repeatedly discerned moderational effect of negative emotionality/difficult temperament in the case of parenting, child-care quality, and other environmental experiences raises the question of why this should be the case. This issue is especially significant given the fact that even though the differential-susceptibility hypothesis stipulates that children should vary in their susceptibility to environmental influences (i.e., plasticity) for evolutionary-biological reasons (Belsky, 1997a, 2005), it does not predict that more negatively emotional children or those with difficult temperament would prove especially malleable; this was an empirical observation (Belsky, 2005). One possible reason why those high in negative emotionality, operationalized as it has been in a variety of ways, may prove most susceptible to environmental influence is because a negatively emotional/difficult temperament reflects a highly sensitive nervous system, one on which experience registers especially strongly; this is so irrespective of whether the experience is positive and growth promoting or negative and undermining of well-being (Aron & Aron, 1997; Belsky, 2005).

Whatever the mechanisms involved in making more negatively emotional children seemingly more malleable—in an often for-better-and-for-worse manner, consistent with differential-susceptibility thinking—it would be a mistake to conclude that this is the most important phenotypic marker of plasticity. Even though this could be the case, it could well be an artifact of the disproportionate attention that investigators guided by diathesis-stress/dual-risk perspective have devoted to investigating individual "risk factors" that interact with contextual adversity in producing problematic functioning (Belsky & Pluess, 2009). If this is so, then it certainly behooves the field to consider other potential behavioral markers of plasticity/malleability rather than reify one. Nevertheless, the evidence considered through this point clearly suggests that differential susceptibility is operative—and not just perhaps in the opening years of life—and that conceptualizing negatively emotional or difficult infants and children as "at risk" and "vulnerable" may misrepresent their more general highly malleable/plastic nature.

Endophenotypic Markers of Differential Susceptibility

Recall that central to Boyce and Ellis's (2005) biological-sensitivity-to-context proposition is the claim that children who are highly physiologically reactive to stress manifest the most developmental plasticity. Given that many such children probably begin life as highly negative infants or ones with difficult temperaments, it seems likely that many of the very same children Belsky (1997a, 2005) first called attention to in this regard are being identified by different means. In any event, what Boyce and Ellis's (2005) viewpoint highlights is that endophenotypic characteristics, not just the behavioral ones considered in the preceding section, might moderate environmental influences and thereby function as plasticity markers. In this section, we consider evidence consistent with the claim (see Table 2) after providing a brief summary of the two separate physiological systems—the autonomous nervous system and the neuroendocrine system—and their specific functions.

The so-called fight-or-flight response to stress is primarily controlled by the autonomous nervous system, which is further divided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS controls those activities that are mobilizing during stress and anxiety (e.g., accelerated heart rate, increased blood pressure, enhanced blood flow to the skeletal muscles/decreased blood flow to the internal organs and extremities, sweating). Physiologically opposing activities under PNS control serve the basic functions of rest, repair, and relaxation of the body and restoration of energy stores (e.g., decreases in heart rate and blood pressure, stimulation of the digestive system, sexual arousal, sleep). The neuroendocrine response to stress is primarily controlled by the hypothalamus–pituitary–adrenal axis (HPA). Corticotropin releasing hormone (CRH)—which is released from the hypothalamus in response to stress—activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which then causes the adrenal cortex to release cortisol into the general bloodstream. Finally, cortisol leads to a large number of diverse physiological and metabolic changes in order to prepare the organism for optimal functioning under stressful conditions (e.g., increase of blood pressure and blood sugar, breakdown of lipids and proteins, mobilization of amino acids, reduction of immune responses).

In the earliest pertinent investigation of physiological reactivity presenting differential-susceptibility-like effects, Gannon, Banks, Shelton, and Luchetta (1989) studied undergraduates on whom a range of SNS markers of physiological reactivity were obtained (before and after a math-problems' stress test; plasticity factor). These students also reported on daily hassles (environmental factor), as well as common physical symptoms and depression. Compared to individuals showing low reactivity of blood volume pulse amplitude, high-reactive students reported both few physical symptoms when experiencing few daily hassles and many physical symptoms when experiencing many hassles. Those students showing slow heart rate recovery after the stress test reported fewer depressive symptoms when experiencing fewer daily hassles and more symptoms when experiencing more daily hassles than did individuals with a fast recovery, a result also consistent with differential-susceptibility thinking.

Findings in line with those just presented, but evident at much younger ages, emerged in Boyce et al.'s (1995) test of the hypothesis that mean arterial blood pressure reactivity to a stress test at age 3–5 years would interact with a composite measure of child-care quality (measured across a 2-year period) in predicting frequency of respiratory illness during the 6 months following the physiological-reactivity assessment. In particular, children with higher blood pressure reactivity exhibited higher rates of respiratory illness than other children when growing up in stressful rearing contexts, yet under low-stress conditions such high-reactive children had a significantly lower incidence of respiratory illnesses than did other children.

Reactivity-moderated effects of environmental experiences are also evident when SCL reactivity serves as the index of physiological functioning. This seems noteworthy in view of the fact that SCL is controlled solely by the SNS, in contrast to the other cardiovascular-reactivity measures, which are generally innervated and controlled by both SNS and PNS. Thus, El-Sheikh, Keller, and Erath (2007) investigated associations between SCL reactivity (assessed during a star-tracing problem-solving task), marital conflict (parent report), and change (from 9 to 11.5 years) in adjustment problems (parent report). Compared to girls with low SCL reactivity, highly reactive girls showed the largest increase in internalizing problems if from highly conflicted homes but the smallest increase when marital conflict was low in their families.

The same research team also used vagal tone (indexed by respiratory sinus arrhythmia; RSA) and vagal suppression (during exposure to an audio recording of a male–female verbal conflict) to investigate whether and how PNS measures moderate effects of marital conflict on child adjustment in middle childhood (El-Sheikh, Harger, & Whitson, 2001). Compared to children with high vagal tone (who were not seemingly affected by marital conflict), those scoring low in vagal tone proved less anxious when growing up in families with little marital conflict but more anxious when residing in high-conflict homes. Similar crossover-interaction results emerged with respect to vagal suppression but for boys only.

In a recent, large cross-sectional study of 5-year-olds, Obradovic, Bush, Stamperdahl, Adler, and Boyce (in press) provided yet more evidence of the role of RSA in moderating environmental effects, along with some pertaining to cortisol reactivity (both assessed during a stress test). In this research, a composite index of childhood adversity (based on parental reports of financial

Table 2
Characteristics of Study Findings Providing Empirical Evidence for Differential Susceptibility as a Function of Endophenotype

Study characteristics								Statistical criteria for differential susceptibility		Follow-up analysis[a]
Author	Year	Sample	Susceptibility factor: Plasticity marker	Environmental predictor	Range of predictor	Outcome	Range of outcome	Moderator/ predictor correlation	Moderator/ outcome correlation	Subgroup contrasts
Gannon et al.	1989	50 male and female students	Cardiovascular reactivity: high blood volume pulse amplitude reactivity, slow heart rate recovery	Daily hassles	A ↔ AA	Physical symptoms	N ↔ AN	not reported	ns	regression lines
						Depression symptoms	N ↔ AN	not reported	ns	regression lines
Boyce et al.	1995	137 3- to 5-year-old boys and girls	Cardiovascular reactivity: high arterial blood pressure reactivity	Child-care stressors	A ↔ AA	Respiratory illness incidence	N ↔ P	not reported	ns	regression lines
El-Sheikh et al.	2007	110 9-year-old boys and girls	SNS reactivity: high skin conductance reactivity	Marital conflict	A ↔ AA	Internalizing and externalizing problems	N ↔ AN	ns	ns	regression lines
El-Sheikh et al.	2001	75 8- to 12-year-old boys and girls	PNS reactivity: low vagal tone	Marital conflict	A ↔ AA	Anxiety	N ↔ AN	ns	ns	regression lines
Obradovic et al.	in press	338 5-year-old boys and girls	PNS reactivity: high RSA reactivity, cortisol reactivity	Childhood adversity	A ↔ AA	Prosocial behavior,	N ↔ P	ns	ns	regression lines
						School engagement,	N ↔ P	ns	ns	regression lines
						Change in academic competence	N ↔ P	ns	ns	regression lines

Note. A = adversity; AA = absence of adversity; S = support/enrichment; AS = absence of support/enrichment; N = negative outcome; AN = absence of negative outcome; ns = nonsignificant; P = positive outcome; AP = absence of positive outcome; SNS = sympathetic nervous system; PNS = parasympathetic nervous system; RSA = respiratory sinus arrhythmia.
[a] After detecting significant crossover interaction between moderator and predictor on outcome.

stress, parenting overload, marital conflict, negative/anger expressiveness, maternal depression, and harsh and restrictive parenting) proved predictive of externalizing symptoms, prosocial behaviors, school engagement, and academic competence (based on parent, teacher, and child self-reports); this proved true more so in the case of children with a more reactive PNS (for contrasting evidence, see El-Sheikh, Erath, & Keller, 2007; El-Sheikh et al., 2001). In particular, children with high RSA reactivity were rated as more prosocial under low-adversity conditions and as less prosocial under high-adversity conditions than were children with low RSA reactivity. High RSA reactivity children also scored higher on school engagement under low-adversity conditions and lower under high-adversity conditions than did children with low RSA reactivity.

Despite the fact that multiple PNS investigations have provided evidence in line with the differential-susceptibility hypothesis, only a single investigation involving the neuroendocrine system appears to provide comparable evidence. In the just summarized work by Obradovic et al. (in press), children with high cortisol reactivity were rated as more prosocial under low adversity and less prosocial under high adversity relative to children with low cortisol reactivity. It is difficult to be sure that this apparent imbalance in evidence across the autonomous nervous system and the neuroendocrine system is due to the two stress reactivity systems playing fundamentally different roles vis-à-vis environmental influences; the alternative possibility is that one has just received more empirical attention as a moderator of environmental effects. This would seem likely, given that most developmentalists measuring cortisol reactivity treat it as an outcome to be explained by environmental factors rather than as a moderator of environmental influences (Fernald, Burke, & Gunnar, 2008; Gunnar & Quevedo, 2007).

Genetic Markers of Differential Susceptibility

Whereas almost all the evidence cited through this point derives from research on children, GXE interaction findings consistent with the differential-susceptibility hypothesis typically come from studies of adults; this is especially true of psychiatric research focused upon pathological outcomes (e.g., depression, antisocial behavior). The fact that most of this work has been guided by traditional diathesis-stress thinking means that on many occasions evidence that those carrying a putative "risk allele" actually function better than others when not exposed to the risk condition being studied (e.g., negative life events) frequently goes unnoticed or at least is not discussed in primary reports. Recently, Uher and McGuffin (2008) called attention to such differential-susceptibility-like findings (but not in those terms) in their review of GXE work on life events, the serotonin-transporter gene, and depression. Here we call attention to many more GXE findings seemingly reflective of differential susceptibility across a diverse array of candidate genes (see Table 3).

MAOA

The neurotransmitter-metabolizing enzyme monoamine oxidase A gene, or *MAOA*, 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; this is exactly what they discovered in their groundbreaking GXE research carried out on a New Zealand birth cohort followed into young adulthood. It was principally young men—young women were not studied—with one form of the gene, that associated with low *MAOA* activity, who proved most violence prone if they had been subjected to child maltreatment. 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 seem to 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 rather than just greater vulnerability to adversity. This interpretation is buttressed by results of a reasonably large number of studies that sought to replicate the Caspi et al. (2002) findings. For example, Kim-Cohen et al. (2006) found that 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 symptoms of attention-deficit/hyperactivity disorder (ADHD)—if they had been victims of abuse, but fewer problems if they had not, than were boys with the high-*MAOA*-activity genotype. In a large longitudinal study of adolescent twin boys age 8–17 years, Foley et al. (2004) observed that compared to boys with the high-*MAOA*-activity allele, those with the low-*MAOA*-activity allele were more likely to be diagnosed with conduct disorder if exposed to higher levels of childhood adversity and were less likely if exposed to lower levels of adversity. Similar results emerged in Nilsson et al.'s (2006) cross-sectional investigation of adolescent boys when the predictor was psychosocial risk, operationalized in terms of maltreatment experience and living arrangement, and the outcome to be explained was criminal behavior (composite of vandalism, violence, stealing).

Three additional studies generated results documenting the heightened susceptibility to environmental influences of individuals carrying the low-*MAOA* allele. One was a prospective investigation of the long-term effects of (court-substantiated) child abuse and neglect on White male and female violent and antisocial behavior in adolescence and through the early 40s (Widom & Brzustowicz, 2006). The second was a retrospective study of adult psychiatric outpatients and healthy controls linking trauma experienced in childhood with physical aggression in adulthood (Frazzetto et al., 2007). And the third was a retrospective study of female American Indians that investigated effects of childhood sexual abuse on symptoms of antisocial personality disorder (Ducci et al., 2008).

5-HTTLPR

Far more studied 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. Most 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 is 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 *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 s alleles proved most adversely affected, whereas effects on l/l genotypes were weaker or entirely absent. Of special significance, however, is that carriers of the s/s 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.

Multiple 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; many have succeeded (see below) but certainly not all (Risch et al., 2009; Surtees et al., 2006). The data presented in quite a number of studies indicate, however, that individuals carrying short alleles (s/s, s/l) not only functioned most poorly when exposed to many stressors but functioned best—showing least problems—when they encountered few or none (e.g., Wilhelm et al., 2006; Zalsman et al., 2006). Calling explicit attention to such a pattern of results, Taylor et al. (2006) reported that young adults homozygous for short alleles (s/s) manifested greater depressive symptomatology than did individuals with other allelic variants when they had been exposed to early adversity (i.e., problematic child-rearing history), as well as many recent negative life events, yet manifested the fewest symptoms when they had experienced a supportive early environment or recent positive experiences. The same for-better-and-for-worse pattern of results concerning depression was evident—and noted—in Brummett et al.'s (2008) investigation of middle-aged and aging adults who did and did not serve as caregiver of a relative with Alzheimer's disease and in Eley et al.'s (2004) research on adolescent girls who were and were not exposed to risky family environments.

The effect of *5-HTTLPR* in moderating environmental influences in a manner consistent with differential susceptibility is not restricted to depression and its symptoms. It also emerges, perhaps unsurprisingly, in studies of anxiety (Gunthert et al., 2007; Stein, Schork, & Gelernter, 2008) and ADHD, particularly of ADHD that persists into adulthood (Retz et al., 2008). In all these cases, whether studies examined effects of negative life events (Gunthert et al., 2007), emotional abuse in childhood (Stein et al., 2008), or a generally adverse child-rearing environment (Retz et al., 2008), it proved to be those individuals carrying short alleles who responded to developmental or concurrent experiences in a for-better-and-for-worse manner, depending on the nature of the experience in question.

The final differential-susceptibility-relevant finding involving *5-HTTLPR* to be considered that emanates from a field study comes from Manuck, Flory, Ferrell, and Muldoon's (2004) investigation of the effect of socioeconomic status on adult central nervous serotonergic responsivity. Central serotonergic responsivity was measured indirectly by means of the fenfluramine challenge test. Fenfluramine increases serotoneric neurotransmission by release of serotonin stores and reuptake inhibition. Such stimulation of hypothalamic serotonin receptors promotes as well the pituitary release of the hormone prolactin. This relative release in circulating prolactin concentration provides an index of the serotonergic responsivity in the HPA axis. Consistent with all the findings summarized above pertaining to depression, anxiety, and persistent ADHD, s/s individuals manifested the most and least serotonergic responsivity, depending on whether they were, respectively, of low or high socioeconomic status (SES).

Experimental evidence that those carrying short alleles benefit disproportionately from a supportive environment comes from Brody, Beach, Philibert, Chen, and Murry (2009), who evaluated effects of a family-based intervention designed to reduce adolescent risk taking among rural African American children at high risk for engaging in such behavior. The multisession intervention conducted at a community center sought to promote nurturant–involved parenting practices and children's proclivities to follow family rules and establish goals for the future. Results revealed that those explicitly labeled as at "genetic risk" due to the fact that they carried one or two short alleles on *5-HTTLPR* were the ones most likely to benefit from the program. These participants engaged in substantially less drinking, drug use, or sexual activity than did those carrying the same alleles who were not randomly assigned to the intervention.

HTR2A

Additional evidence consistent with differential-susceptibility thinking emerges from GXE studies of another serotonergic gene, the serotonin receptor gene (*HTR2A*), which comes in two forms: the C and T alleles. Whereas some research has revealed an association between the C allele and depression (see, e.g., Du, Bakish, Lapierre, Ravindran, & Hrdina, 2000), other studies have found the T allele to confer depression risk (Eley et al., 2004). Recent work by Jokela and associates (Jokela, Keltikangas-Jarvinen, et al., 2007; Jokela, Lehtimaki, & Keltikangas-Jarvinen, 2007a, 2007b)—drawing on data from a large-scale, population-based, longitudinal study in Finland, the Cardiovascular Risk in Young Finns Study—suggests that individuals carrying the T allele are generally more affected than others by environmental factors in a for-better-and-for-worse manner. When nurturance reported by mother was averaged across baseline (i.e., when study participants were 3–8 years old) and again 3 years later, offspring with at least one T allele scored highest and lowest on self-reported depression some two decades after baseline, depending on whether they had experienced, respectively, more or less nurturant care (Jokela, Keltikangas-Jarvinen, et al., 2007). Similar results emerged when the effects of residence in very rural Finland were contrasted with those of living in urban Finland (Jokela et al., 2007a). And the same differential-susceptibility-like results occurred when the predictor was family SES and the outcome to be explained was self-reported harm avoidance; those carrying one or more T alleles scored highest on harm avoidance if they had grown up in low-SES households but lowest if they had grown up in high-SES ones (Jokela et al., 2007b). This latter finding led the investigators to suggest that this allele might function as an "opportunity" allele, not just a risk gene.

Table 3
Characteristics of Study Findings Providing Empirical Evidence for Differential Susceptibility as a Function of Genotype

Study characteristics								Statistical criteria for differential susceptibility		Follow-up analysis[a]
Author	Year	Sample	Susceptibility factor: Plasticity marker	Environmental predictor	Range of predictor	Outcome	Range of outcome	Moderator/ predictor correlation	Moderator/ outcome correlation	Subgroup contrasts
Caspi et al.	2002	442 26-year-old men	*MAOA*: low-activity allele	Childhood maltreatment	A ↔ AA	Antisocial behavior	N ↔ AN	ns	ns	regression lines
Kim-Cohen et al.	2006	975 7-year-old boys	*MAOA*: low-activity allele	Physical abuse	A ↔ AA	Mental health problems, ADHD	N ↔ AN	ns	significant	regression lines
Foley et al.	2004	514 8- to 17-year-old boys	*MAOA*: low-activity allele	Childhood adversity	A ↔ AA	Conduct disorder	N ↔ AN	ns	ns	regression lines
Nilsson et al.	2006	81 adolescent boys	*MAOA*: low-activity allele	Maltreatment and living conditions	A ↔ AA	Criminal behaviors	N ↔ AN	ns	ns	regression lines
Widom & Brzustowicz	2006	631 male and female adults	*MAOA*: low-activity allele	Childhood abuse/neglect	A ↔ AA	Antisocial behavior	N ↔ AN	ns	ns	means
Frazzetto et al.	2007	235 male and female adults	*MAOA*: low-activity allele	Childhood traumatic life events	A ↔ AA	Physical aggression	N ↔ AN	ns	ns	regression lines
Ducci et al.	2008	291 adult women	*MAOA*: low-activity allele	Childhood sexual abuse	A ↔ AA	Antisocial personality	N ↔ AN	ns	ns	means
Caspi et al.	2003	847 26-year-old men and women	*5-HTTLPR*: s allele	Stressful life events	A ↔ AA	Depression symptoms, suicide ideation	N ↔ AN	ns	ns	regression lines
Wilhelm et al.	2006	127 male and female adults	*5-HTTLPR*: s allele	Stressful life events	A ↔ AA	Probability for major depression	N ↔ AN	ns	ns	regression lines
Zalsman et al.	2006	316 male and female adults	*5-HTTLPR*: s allele	Stressful life events	A ↔ AA	Depression symptoms	N ↔ AN	ns	significant	regression lines
Taylor et al.	2006	118 young adult men and women	*5-HTTLPR*: s allele	Early family risk, stressful life events	A ↔ S	Depression symptoms	N ↔ AN	ns	ns	means
Brummett et al.	2008	215 male and female adults	*5-HTTLPR*: s allele	Caregiver of Alzheimer patient	A ↔ AA	Depression symptoms	N ↔ AN	ns	ns	regression lines
Eley et al.	2004	377 female and male adolescents	*5-HTTLPR*: s allele	Family environmental risk	A ↔ AA	Depression symptoms	N ↔ AN	ns	significant	regression lines
Gunthert et al.	2007	350 male and female students	*5-HTTLPR*: s allele	Daily event stress	A ↔ AA	Evening anxiety	N ↔ AN	ns	ns	regression lines
Stein et al.	2008	247 male and female students	*5-HTTLPR*: s allele	Childhood emotional abuse	A ↔ AA	Anxiety sensitivity	N ↔ AN	ns	ns	regression lines

(table continues)

Table 3 (*continued*)

Study characteristics								Statistical criteria for differential susceptibility		Follow-up analysis[a]
Author	Year	Sample	Susceptibility factor: Plasticity marker	Environmental predictor	Range of predictor	Outcome	Range of outcome	Moderator/ predictor correlation	Moderator/ outcome correlation	Subgroup contrasts
Retz et al.	2008	184 adult male delinquents	*5-HTTLPR*: s allele	Childhood adverse environment	A ↔ AA	ADHD	N ↔ AN	not reported	not reported	regression lines
Manuck et al.	2004	139 male and female adults	*5-HTTLPR*: s allele	Socioeconomic status	A ↔ AA	Central nervous serotonergic responsivity	N ↔ P	ns	ns	means
Jokela, Keltikangas-Järvinen, et al.	2007	820–1212 male and female adults	*HTR2A*: T allele	Maternal nurturance	S ↔ AS	Depression symptoms	N ↔ AN	ns	ns	means
Jokela, Lehtimaki, et al.	2007a	1185–1224 male and female adults	*HTR2A*: T allele	Rural/urban residency	A ↔ S	Depression symptoms	N ↔ AN	ns	ns	means
Jokela, Lehtimaki, et al.	2007b	966–1246 male and female adults	*HTR2A*: T allele	Parental socio-economic status	A ↔ S	Harm avoidance	N ↔ P	ns	significant	means
Jokela, Räikkönen, et al.	2007	341 male and female adults	*THP1*: A allele	Social support	S ↔ AS	Depression symptoms	N ↔ AN	ns	ns	regression lines
Keltikangas-Järvinen et al.	2007	341 male and female adults	*THP1*: A allele	Hostile child environment	A ↔ AA	Harm avoidance	N ↔ P	ns	ns	regression lines
van IJzendoorn & Bakermans-Kranenburg	2006	63 male and female toddlers	*DRD4*: 7-repeat allele	Maternal unresolved loss/trauma	A ↔ AA	Disorganized attachment	N ↔ AN	ns	ns	means
Bakermans-Kranenburg & van IJzendoorn	2006	47 male and female infants	*DRD4*: 7-repeat allele	Maternal sensitivity	A ↔ S	Externalizing behavior	N ↔ AN	ns	ns	regression lines
Propper et al.	2007	169 male and female children	*DRD4*: short allele	Parenting quality	A ↔ S	Externalizing behavior	N ↔ AN	not reported	ns	regression lines
Sheese et al.	2007	45 male and female infants	*DRD4*: 7-repeat allele	Parenting quality	A ↔ S	Sensation seeking	N ↔ P	ns	ns	regression lines
Bakermans-Kranenburg, van IJzendorn, Pijlman, et al.	2008	157 male and female toddlers	*DRD4*: 7-repeat allele	Parenting intervention	S ↔ AS	Externalizing behavior	N ↔ AN	ns	ns	regression lines

(table continues)

Table 3 (*continued*)

Study characteristics								Statistical criteria for differential susceptibility		Follow-up analysis[a]
Author	Year	Sample	Susceptibility factor: Plasticity marker	Environmental predictor	Range of predictor	Outcome	Range of outcome	Moderator/ predictor correlation	Moderator/ outcome correlation	Subgroup contrasts
Bakermans-Kranenburg, van IJzendoorn, Mesman, et al.	2008	130 male and female toddlers	*DRD4*: 7-repeat allele	Parenting intervention	S ↔ AS	Salivary cortisol	N ↔ P	ns	ns	means
van IJzendoorn et al.	2008	176 mothers	*DRD4*: 7-repeat allele *COMT*: Val allele	Daily hassles	A ↔ AA	Maternal sensitivity	N ↔ P	ns (significant for *COMT* Val)	ns	regression lines
Berman & Noble	1997	168 10- to 13-year-old boys	*DRD2*: A1 allele	Family stress	A ↔ AA	Visuospatial ability, P300 amplitude	N ↔ P	ns	ns	regression lines
Elovainio et al.	2007	1,636 male and female adults	*DRD2*: A2 allele	Stressful life events	A ↔ AA	Depression symptoms	N ↔ AN	ns	ns	regression lines
Mills-Koonce et al.	2007	172 3-year-old boys and girls	*DRD2*: A1 allele	Maternal sensitivity	A ↔ S	Affective problems	N ↔ AN	significant	significant	regression lines
Propper et al.	2008	206 male and female infants	*DRD2*: A1 allele	Maternal sensitivity	A ↔ S	RSA	N ↔ P	significant	ns	regression lines
Keltikangas-Järvinen et al.	2007	1,512 male and female adults	*DRD2*: A1 allele	Birth weight	A ↔ S	Educational achievement	N ↔ P	ns	ns	regression lines
Sonuga-Barke et al.	2009	728 5- to 17-year-old boys	*DAT1*: 9R allele *5-HTTLPR*: s allele	Maternal expressed emotion	S ↔ AS	Conduct disorder	N ↔ AN	ns	ns	means
Belsky et al.	2009c	183 male and female adults	*DRD2*: A1 allele *DRD4*: 7 repeat allele *COMT*: Val allele	Parental divorce	A ↔ AA	Adult relationship stability	N ↔ AN	ns	ns	regression lines

Note. A = adversity; AA = absence of adversity; S = support/enrichment; AS = absence of support/enrichment; N = negative outcome; AN = absence of negative outcome; P = positive outcome; AP = absence of positive outcome; ADHD = attention-deficit hyperactivity disorder; RSA = respiratory sinus arrhythmia.

[a] After detecting significant crossover interaction between moderator and predictor on outcome.

THP1

The same Finish research group, drawing on the same population-based sample, identified similar interaction effects involving yet another serotonin gene, a polymorphism in the tryptophane hydroxylase 1 gene (*THP1*; Jokela, Raikkonen, Lehtimaki, Rontu, & Keltikangas-Jarvinen, 2007); this gene codes for a rate-limiting enzyme in the biosynthesis of serotonin. Of the two variants A and C, the A allele has been associated with low serotonin levels (Jönsson et al., 1997) and suicidal behavior/depression, though findings are not consistent across studies (see, e.g., Bellivier, Chaste, & Malafosse, 2004; Lalovic & Turecki, 2002).

Jokela, Raikkonen, et al. (2007) detected a moderating effect of *TPH1* on the association between social support and depressive symptoms. Depressive symptoms and social support were assessed when participants were between 20 and 35 years of age, with the former measurements taken again 4 years later. Compared with all other individuals, A/A individuals experienced the most and least depression, whenever depression was assessed, depending on whether they had experienced, respectively, low or high social support. This proved to be even more the case when change in depressive symptoms was the outcome to be explained. Comparable differential-susceptibility-like results emerged when the environmental predictor was hostile childhood environment (based on maternal report) and harm avoidance in adulthood was the outcome to be explained (Keltikangas-Jarvinen, Puttonen, et al., 2007).

DRD4

We now move 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 has stimulated much GXE research. Variants of *DRD4* differ by the number of 48-base-pair tandem repeats in exon III, which ranges from 2 to 1. 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.

A number of studies indicate that individuals carrying this putative risk allele not only are more adversely affected by poorer environmental conditions, broadly conceived, but also benefit more than others from good-quality ones (van IJzendoorn & Bakermans-Kranenburg, 2006). Four related inquiries focused on parenting are considered particularly important, because a "good" environment was operationalized not just as the absence of adversity but in terms of high-quality parenting. In a longitudinal investigation, maternal sensitivity observed when children were 10 months of age predicted externalizing problems reported by the mother more than two years later, but only for children carrying the 7-repeat *DRD4* allele (Bakermans-Kranenburg & van IJzendoorn, 2006). Whereas such children displayed the most externalizing behavior of all children when mothers were judged insensitive, they also manifested the least externalizing behavior when mothers were highly sensitive (for contradictory results, see Propper, Willoughby, Halpern, Carbone, & Cox, 2007). A cross-sectional study of sensation seeking in 18- to 21-month-old children generated results in line with those just summarized. Toddlers carrying the 7-repeat allele were rated by parents as showing, compared to children without the 7-repeat allele, less sensation-seeking behavior when parenting quality was high but more when it was low (Sheese, Voelker, Rothbart, & Posner, 2007).

Experimental intervention research designed to enhance parenting also reveals a moderating effect of the 7-repeat allele. 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- to 3-year-olds who scored high on externalizing problems—they found that the intervention succeeded in promoting more sensitive parenting and positive discipline. Moreover, this intervention effect translated into improvements in child behavior but only for those children carrying the *DRD4* 7-repeat allele. The same was true when, at posttreatment follow up, stress reactivity was measured by means of change in salivary cortisol before and after the administration of an experimental stressor (Bakermans-Kranenburg, van IJzendoorn, Mesman, Alink, & Juffer, 2008). In fact, children in the experimental group who carried the *DRD4* 7-repeat allele not only showed the least physiological stress reactivity of all children but showed the most if their mothers had been assigned to the control group.

Of special interest is that the most pronounced reduction in children's problem behavior occurred when two conditions obtained: (a) the parenting intervention substantially improved the mother's use of positive discipline techniques and (b) the child carried the 7-repeat allele. One cannot but wonder why some mothers benefited more from the experimental treatment than others in terms of (substantially) improved parenting. Recent evidence that the effect of daily hassles on sensitive parenting is dependent on the mother's own genotype and operates in a for-better-and-for-worse manner certainly raises the possibility that GXE processes could account for why some mothers proved to benefit, in terms of their parenting, more from the intervention than did others (van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2008). Thus, could an untested GXGXE interaction have been responsible for the problem-behavior findings discerned in the Bakermans-Kranenburg, van IJzendoorn, Pijlman, et al. (2008) intervention study? Indeed, could it have been that mothers with certain susceptibility genes proved most responsive to the intervention and that it was this responsiveness, in combination with their child's genetic susceptibility to rearing, that generated the results described? These questions raise a more general one: When parenting interventions prove effective in changing child behavior, is a small subset of parent–child dyads responsible for the overall treatment effect (i.e., those comprising a parent and a child who are both highly malleable for genetic reasons)? As no intervention investigation has considered parent as well as child genotype, this possibility remains to be evaluated.

DRD2

Another polymorphism in the dopaminergic system that has been a focus of GXE research is located on the *DRD2* gene, which encodes the D2 subtype of the dopamine receptor. Of special interest is the Taq1A (A1) polymorphism—a C to T substitution

located in a noncoding region of the *DRD2* locus—which is thought to affect dopamine receptor D2 availability in postmortem striatal samples (Thompson et al., 1997). The A1 allele has been associated with low dopamine density and lower mean relative glucose metabolic rate in dopaminergic regions in the human brain (Noble, Gottschalk, Fallon, Ritchie, & Wu, 1997), high novelty seeking (Suhara et al., 2001), and a number of substance use disorders, particularly alcoholism (Bowirrat & Oscar-Berman, 2005).

A number of study findings suggest that the *DRD2* polymorphism moderates environmental influences in differential susceptibility terms (Berman & Noble, 1997; Elovainio et al., 2007), with individuals carrying the A1 allele proving more susceptible to environmental influences in a for-better-and-for-worse manner. Mills-Koonce et al. (2007) found this in research linking sensitive mothering when infants were 6 and 12 months of age with children's affective problems at age 3 years. Propper et al. (2008) chronicled the same moderating influence using maternal sensitivity at 6 months to predict 12-month-olds' RSA. And finally, Keltikangas-Jarvinen, Elovainio, et al. (2007), drawing on the large Finnish study, also reported differential-susceptibility-like effects upon examining the association between birth weight, presumed to reflect quality of the uterine environment to which the fetus has been exposed, and educational achievement at age 27–34.

Cumulative Genetic Plasticity

Through this point, all GXE investigations cited have examined the interaction of some environmental factor and a single gene. In view of the fact that an individual could carry multiple plasticity alleles—say short alleles in the case of *5-HTTLPR* and 7-repeat alleles in the case of *DRD4*—the possibility arises that the more plasticity alleles an individual carries, the more susceptible he or she will prove to be to environmental influences. Some evidence consistent with this proposition comes from two recent studies, one addressing this issue in a post hoc fashion and the other on an a priori basis. In the former, Sonuga-Barke et al. (2009) discovered, after identifying two separate GXE interactions, that children carrying alleles other than 10R/10R in the case of *DAT1 and* other than two long alleles in the case of *5-HTTLPR* proved most susceptible to the anticipated adverse effects of high levels of maternal expressed (negative) emotion on conduct disorder in their study of 5- to 17-year-olds diagnosed with ADHD. In the second study (Belsky, Pluess, Comings, & MacMurray, 2009), individuals were scored in terms of whether they carried 0, 1, 2, or 3 putative plasticity alleles—*DRD4* 7-repeat, *DRD2* A1, and *COMT* Val—to test the hypothesis that those with more plasticity alleles would be more affected than those carrying fewer by childhood exposure to divorce when the outcome to be explained was relationship instability in adulthood; this is exactly what was found. More than anything else, what these two preliminary inquiries suggest is that individuals carrying more plasticity alleles do appear more susceptible to at least some environmental influences than do those individuals carrying fewer. Indeed, the Belsky, Pluess, et al. (2009) work suggests that further efforts should be made to measure cumulative genetic plasticity by creating a composite score based on multiple plasticity alleles, in much the same way that multiple environmental risk factors are often combined to create indices of cumulative contextual risk (e.g., Belsky & Fearon, 2002).

Conclusion

The preceding review was designed to highlight findings consistent with the differential-susceptibility hypothesis that have appeared—mostly recently—within much larger literatures addressing principally, even if not exclusively, Parenting × Temperament and Gene × Environment interactions. The research considered should be regarded as providing at least suggestive even if not conclusive evidence that there exist individual differences in plasticity. That is, some individuals are more affected than others by rearing experiences and, apparently, environmental circumstances more generally. In particular, some individuals appear more susceptible to the adverse effects of unsupportive contextual conditions and the beneficial effects of supportive ones.

One of the most striking features of the work reviewed is the diversity of the evidence base suggesting that individuals differ in their plasticity. As indicated in Tables 1–3, the evidence pertaining to environmental factors highlights differential-susceptibility-related effects of parenting, child-care quality, life events, rural-versus-urban residence, and even birth season. That pertaining to outcomes seemingly affected by these diverse environmental influences includes disorganized infant attachment; externalizing problems in the toddler, preschool, and childhood years; antisocial behavior in adolescence, young adulthood, and even middle age; depression throughout adulthood, children's respiratory health, and endophenotypes like RSA. Findings pertaining to moderators of diverse environmental effects on these diverse outcomes, so-called susceptibility—not just vulnerability—factors, include temperamental and other phenotypic attributes of children, endophenotypic characteristics, and genotypic ones.

The contention that some individuals are more susceptible than others to both the adverse and beneficial effects of, respectively, unsupportive and supportive contextual conditions is strikingly different from diathesis-stress/dual-risk thinking. The latter model regards some individuals as simply more vulnerable to adversity with respect to problematic outcomes and has informed, if not directly guided, so much Parenting × Temperament and GXE interaction research, including much of that considered herein. The traditional view seems so deeply entrenched that some investigators have failed to notice when their own data reveal differential-susceptibility-like findings, not just vulnerability-related ones. Indeed, two secondary analyses of such studies have shown that the beneficial effects of a benign environment on children presumed to be vulnerable for genetic reasons are actually larger than the originally—and exclusively—anticipated, detected and discussed negative effects of the contextual adversity under investigation (Belsky et al., 2009; Pluess, Belsky, & Neuman, 2009).

Because of the inherent limits of so many of the studies considered, both in terms of what has been measured and of how data have been analyzed and presented in primary publications, it remains impossible to know how much confidence should be placed in the differential-susceptibility interpretation given to the findings assembled in this paper. Recall in this regard that rather liberal standards of interpretation have, by necessity, been applied to virtually all the evidence cited, most of which emerged from investigations designed to evaluate diathesis-stress hypotheses. In order to enable both primary researchers and reviewers of the literature, including meta-analysts, to better address this fundamental issue about how human development operates, investiga-

tory and reporting practices must change. We hope that this selective review, by calling attention to the possibility of differential susceptibility, will stimulate such change. Toward that end, in the remainder of this section we consider (a) additional statistical and measurement criteria for evaluating differential susceptibility, (b) potential mechanisms responsible for it, and (c) still-to-be-illuminated unknowns in the differential-susceptibility equation.

Statistical and Measurement Criteria for Evaluating Differential Susceptibility

Future studies should pursue several research desiderata while meeting the criteria for establishing differential susceptibility, summarized earlier, that informed the interpretation of study findings considered herein (Belsky et al., 2007). First, studies should measure not just the presence of adversity and its absence but environmental support, as Taylor et al. (2006) did in assessing positive life events and Bakermans-Kranenburg and van IJzendoorn (2006) did in measuring sensitive parenting. Second, human functioning should be measured along a continuum ranging from dysfunction to competence, whenever possible, not just from dysfunction to its absence. Such measurement should avoid the masking of differential susceptibility by ceiling effects. Should this not prove possible for some reason (e.g., positive pole of depression), separate measurements of negative and positive functioning should be obtained and examined.

Additionally, once a Temperament × Parenting, GXE, or other interaction has been discerned, follow-up analysis should determine whether significant differences in the functioning of individuals hypothesized to be more and less susceptible to environmental influence obtain when environmental circumstances are supportive, as well as when they are adverse (i.e., at both ends of the environmental spectrum). Those putatively susceptible should differ from those putatively not so (or less so) under both supportive and unsupportive conditions. It is when significant differences are obtained for both comparisons, revealing a for-better-and-for-worse pattern of environmental effects, that differential susceptibility rather than diathesis stress would be the correct inference. Only a single study reviewed considered—and met—this criterion (Taylor et al., 2006).

Mediating Mechanisms

As much as anything else, the central thesis upon which this effort is based and the evidence assembled suggesting that individuals differ in plasticity and thus susceptibility to environmental influence raise many issues in need of further investigation. One concerns whether some individuals could be especially susceptible to just adversity, some to just environmental support and enrichment, some to both, and some to neither. Another is whether investigators working in different fields and studying the moderating effects of different susceptibility factors are actually identifying the same more-and-less-susceptible individuals by different means. Consider in this regard that the very children who score high in negative emotionality and physiological stress reactivity and who have short alleles on the *5-HTTPLR* gene could often be one and the same (Auerbach et al., 1999).

This possibility raises the critical issue of mechanism or process, one mentioned only in passing in this effort reviewing evidence of differential susceptibility. Recall that this review was stimulated by two evolutionary-based propositions. Whereas one stipulated that there should be individual differences in developmental plasticity, not just vulnerability, and advanced no hypotheses concerning process (Belsky, 1997a, 1997b, 2005), the other highlighted physiological reactivity as a plasticity mechanism (Boyce & Ellis, 2005). Although evidence that negative emotionality and short alleles on the serotonin-transporter gene (*5-HTTLPR*) should be considered plasticity markers raises the possibility that these traits function, at least partly, via this putative mechanism when it comes to environmental inputs shaping developmental and behavioral outcomes, it seems unlikely that this is the only process involved in differential susceptibility. Therefore, much more work on mediating mechanisms is clearly required. Some may contend, in contrast, that jumping into the study of mechanism is premature before evidence of differential susceptibility stronger than that reviewed herein is reported.

Nevertheless, here we offer some indisputably speculative comments on the issue of mechanism. It occurs to us that perhaps the reason why some are more responsive than others to environmental conditions is because they have lower thresholds for experiencing pleasure and/or displeasure and thus are more sensitive and responsive than others to, respectively, rewards and/or punishments, very broadly conceived (Gray, 1981, 1982). Although it is rather easy to see how having a lower threshold for discomfort might make an individual more likely to respond in a negative, problematic way to adverse and displeasure-inducing experiences, perhaps by becoming depressed, anxious, and/or antisocial, it is perhaps more difficult to see why such individuals would also be more likely to prove susceptible, as the differential-susceptibility viewpoint presupposes, to the benefits of positive environments. By the same token, although it is easy to imagine how having a low threshold for pleasure might increase an individual's responsiveness to rewards and thus enable that individual to benefit more from positive, supportive experiences, it is difficult to imagine how this proclivity could translate into being more adversely affected by negative experiences. Perhaps, though, this conundrum is more apparent than real, if only because the reduction of discomfort and the loss or denial of a rewarding experience may register most powerfully on those who have low thresholds for, respectively, displeasure and pleasure.

The GXE work highlighting differential susceptibility may be consistent with this line of reasoning. After all, it calls attention to both the serotonergic system (i.e., 5-*HTTLPR, HTR2A, MAOA, THP1*), which is implicated in the experience of displeasure (e.g., depression, anxiety), and the dopaminergic one (i.e., *DRD4, DRD2, MAOA*), which has been linked to reward sensitivity and sensation seeking (Robbins & Everitt, 1999). Our line of reasoning, along with the GXE evidence implicating these two neurotransmitter systems, would seem not unrelated to Gray's (1981, 1982) behavioral inhibition and behavioral activation systems and to Bakermans-Kranenburg and van IJzendoorn's (2009) model with dopamine-related variance in attention and the processing of positive versus negative feedback (Klein et al., 2007; Tripp & Wickens, 2008) as mechanisms.

The amygdala also seems likely to be involved in at least some differential-susceptibility-related processes. Not only have differences in the amygdala been linked to responsiveness to fearful stimuli in healthy adults, but individuals with *5-HTTLPR* short

alleles—a putative plasticity marker—are the ones who manifest the greatest amygdala activity/reactivity. The same is true of yet another putative plasticity gene, one conferring low *MAOA* activity (Meyer-Lindenberg et al., 2006). In fact, the observation that several putative plasticity genes are associated with negative emotionality in infancy (e.g., *5-HTTLPR* short alleles, *DRD4* 7-repeat: Auerbach, Faroy, Ebstein, Kahana, & Levine, 2001) and a more reactive amygdala (e.g., *5-HTTLPR* short alleles: Hariri et al., 2002, 2005; *MAOA* low-activity allele: Meyer-Lindenberg et al., 2006) lends empirical support to the hypothesis that heightened susceptibility to environmental influences may be characterized and driven by a more sensitive central nervous system (e.g., serotonoergic, dopaminergic systems).

Unknowns in the Differential Susceptibility Equation

It is not just mediating mechanisms involved in the process of differential susceptibility for which more research is required. There is also a need for future work to determine whether individual differences in plasticity are best conceptualized in typological or dimensional terms. Adopting evolutionary terminology pertaining to reproductive strategy, we can ask whether there exist "plastic and fixed strategists" who are and are not, respectively, susceptible to environmental experiences, thereby following "conditional" and "alternative" pathways of development (Belsky, 2000). But perhaps it makes more sense to think in terms of a "plasticity gradient," as mentioned earlier, with individuals varying in degree of susceptibility to environmental influences? Conceivably, the choice between a typological and dimensional conceptualization and a parameterization of plasticity is a false one, as the approach that proves best will vary across conceptual purposes and empirical inquiries.

Another question that arises is whether to regard more and less plasticity as a global, macro, traitlike characteristic of individuals or to consider it in more domain-specific terms. Are some people simply more malleable than others across the board, almost irrespective of the environmental factor and aspect of functioning under consideration? Or are individuals a complex mosaic of components that are more and less susceptible to particular environmental influences vis-à-vis particular aspects of functioning, thus making them both more and less malleable relative to others? Whereas the latter conceptualization might make more intuitive sense, of interest is the aforementioned simulation study designed to determine whether individual differences in susceptibility to environmental influences could evolve through natural selection (Wolf et al., 2008). In addition to revealing that they could, this work further indicated that such evolution would occur in a more domain-general, across-the-board manner rather than a domain-specific one.

A final issue of the many that could be raised for future research pertains to whether, or at least the extent to which, plasticity should be regarded as principally a function of nature or of nurture. Certainly the GXE evidence calls attention to heritable individual differences in plasticity, as well as to the fact that so-called vulnerability genes or risk alleles might in many cases be better conceptualized as "plasticity genes" (Belsky et al., 2009). After all, and with regard to the latter point, why would natural selection, for example, maintain much less select genes that functioned only to foster depression in the face of negative life events or antisocial behavior in the face of child maltreatment? Were these perhaps downside costs of selecting and preserving genes that engendered benefit in the face of supportive contextual conditions or that even operated as adaptations when also functioning in a diathesis-stress-like manner, it would seem to make more sense for them to be selected.

Although GXE studies are replete with evidence, often unnoticed, of differential susceptibility, this should not lead to the presumption that plasticity is only a function of genetics. Central to Boyce and Ellis's (2005) thinking, it will be recalled, is the role of extremely supportive and unsupportive environments in fostering physiological reactivity and, thereby, developmental plasticity. Especially notable, in fact, is recent research on the putatively adverse effects of maternal stress during pregnancy. This is because so-called fetal programming appears to influence several of the very susceptibility factors identified in this review (Belsky & Pluess, 2009; Pluess & Belsky, 2009c). Consider in this regard research showing (a) that maternal stress during pregnancy predicts difficult temperament at 3 months of age (Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002); (b) that stressful life events during pregnancy predict toddler fearfulness at age 17 months (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007); (c) that prenatal maternal depression and elevated cortisol levels in late pregnancy predict negative reactivity at age 2 (Davis et al., 2007); and (d) that maternal prenatal anxiety predicts awakening cortisol in 10-year-olds (O'Connor et al., 2005).

On one hand, such data suggest that very early experience—in the womb—may shape plasticity, as the "outcomes" just mentioned are among the very child characteristics found in work cited herein to demarcate heightened susceptibility to environmental influences. Just as important, this reinterpretation of putatively negative effects of prenatal stress raises fundamental questions about the problem-centered perspective that pervades virtually all research and theory on fetal programming: Is it the case that prenatal stressors compromise later development, as prevailing thinking presumes, or do these prenatal experiences promote plasticity—and thus the organism's openness to future experiential input, be it positive or negative in character? That is, is there prenatal programming of postnatal plasticity (Pluess & Belsky, 2009c)? Oberlander et al.'s (2008) recent epigenetic findings showing that maternal depressed mood in pregnancy predicts increased methylation of the human glucocorticoid receptor gene (*NR3C1*, measured in neonatal cord blood), which itself forecasts elevated cortisol stress reactivity at age 3 months, illuminates at least one biological mechanism that may be central to such fetal programming of postnatal plasticity, in fact, the very one that Boyce and Ellis (2005) heralded in their biological-sensitivity-to-context thesis.

Before concluding on the basis of fetal programming research that plasticity is a function of experience as much as a function of genetics, we should not lose sight of the fact that GXE interaction may characterize the fetal programming process (Gluckman & Hanson, 2005). New evidence showing that prenatal smoking effects on ADHD in childhood are genetically moderated (Neuman et al., 2007)—in fact, in a differential-susceptibility manner (Pluess et al., 2009)—certainly provides reason to suppose that fetal programming of postnatal plasticity could be genetically moderated, too. This leads to the final unanswered differential-susceptibility question to be raised: Are some fetuses more sus-

ceptible to fetal programming than others, for genetic reasons? If they are—and as of yet we simply do not know—it would suggest that plasticity is a function not just of nature or nurture but of their interaction (Belsky & Pluess, 2009). That is, some individuals may be more likely than others to be affected by experience, most notably perhaps, fetal experience, in ways that subsequently affect whether or to what degree they will be influenced by the postnatal world they encounter.

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For Better *and* For Worse

Differential Susceptibility to Environmental Influences

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ABSTRACT—*Evidence that adverse rearing environments exert negative effects particularly on children presumed "vulnerable" for temperamental or genetic reasons may actually reflect something else: heightened susceptibility to the negative effects of risky environments* **and** *to the beneficial effects of supportive environments. Building on Belsky's (1997, 2005) evolutionary-inspired proposition that some children are more affected—both for better and for worse—by their rearing experiences than are others, we consider recent work on child vulnerability, including that involving measured genes, along with evidence showing that putatively vulnerable children are especially susceptible to both positive and negative rearing effects. We also consider methodological issues and unanswered questions in the differential-susceptibility equation.*

KEYWORDS—*differential susceptibility; gene–environment interaction; parenting; temperament*

Most students of child development probably do not presume that all children are equally susceptible to rearing effects; a long history of research on interactions between parenting and temperament, or *parenting-by-temperament interactions*, clearly suggests otherwise. Nevertheless, it remains the case that most work still focuses on parenting effects that apply equally to all children—so-called main effects of parenting—thus failing to consider interaction effects, which reflect the fact that whether, how, and how much parenting influences the child may depend on the child's temperament or some other characteristic of individuality.

Like classic work in educational and clinical psychology on interactions between learning aptitude and treatment, research on parenting-by-temperament interactions is based on the premise that what proves effective for some individuals in fostering the development of some valued outcome—or preventing some problematic one—may simply not do so for others. Commonly tested are hypotheses derived from multiple-risk/transactional frameworks in which individual characteristics that make children "vulnerable" to adverse experiences—placing them "at risk" of developing poorly—are mainly influential when there is at the same time some contributing risk from the environmental context.

After highlighting some research of just this kind, we raise questions—on the basis of other findings—about how the first set of data has been interpreted. We advance the evolutionary-inspired proposition that some children, for temperamental or genetic reasons, are actually more susceptible to *both* (a) the adverse effects of unsupportive parenting *and* (b) the beneficial effects of supportive rearing. The validity of this claim cannot be determined, however, so long as research focuses disproportionately on *vulnerable* (as opposed to merely *susceptible*) child characteristics and evaluates effects of *adverse* environments on *problematic* outcomes. What, then, would be required to distinguish vulnerability from susceptibility? We consider the answer after first reviewing research that meets the criteria for differential susceptibility. Finally, we draw conclusions and highlight some "unknowns in the differential-susceptibility equation."

DUAL-RISK CONDITIONS AND CONSEQUENCES

The view that infants and toddlers manifesting high levels of negative emotion are at special risk of problematic development when they experience poor-quality rearing is widespread. Evidence of this comes from Morrell and Murray (2003), who showed that it was only highly distressed and irritable 4-month-old boys who experienced coercive and rejecting mothering at this age who continued to show evidence, 5 months later, of emotional and behavioural dysregulation. Relatedly, Belsky, Hsieh, and Crnic (1998) observed that infants who scored high in negative emotionality at 12 months of age and who experienced the least supportive mothering and fathering across their second and third years of life scored highest on externalizing problems

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at 36 months of age. And Deater-Deckard and Dodge (1997) reported that children rated highest on externalizing-behavior problems by teachers across the primary-school years were those who experienced the most harsh discipline prior to kindergarten entry and who were characterized by mothers at age 5 as being negatively reactive infants.

The adverse consequences of the co-occurrence of a child risk factor (e.g., negative emotionality) and problematic parenting also is evident in Caspi and Moffitt's (2006) ground-breaking research on gene-by-environment interaction. Young men followed from early childhood were most likely to manifest high levels of antisocial behavior when they had both a history of child maltreatment and a particular variant of the *MAO-A* gene, a gene previously linked to aggressive behaviour. Such results led Rutter (2006), like others, to speak of "vulnerable individuals," a concept that also applies to children putatively at risk for compromised development due to their behavioral attributes. But is "vulnerability" the best way to conceptualize the kind of parenting-by-child interactions under consideration?

VULNERABILITY OR DIFFERENTIAL SUSCEPTIBILITY?

Working from an evolutionary perspective, Belsky (1997, 2005) theorized that children, especially within a family, should vary in their susceptibility to both adverse and beneficial effects of rearing influences: Because the future is uncertain, in ancestral times, just like today, parents could not know for certain (consciously or unconsciously) what rearing strategies would maximize reproductive fitness. To protect against all children being steered, inadvertently, in a parental direction that proved disastrous at some later point in time, developmental processes were selected to vary children's susceptibility to rearing.

Belsky (1997, 2005) further observed that children high in negative emotion, particularly in the early years, appeared to benefit disproportionately from supportive rearing environments (Boyce & Ellis, 2005). Crockenberg (1981) showed that social support predicted infant attachment security but only in the case of highly irritable infants. Denham et al. (2000) reported that the beneficial effects of proactive parenting (i.e., supportive presence, clear limit setting) at age 7 and/or age 9 were most pronounced in the case of children who scored high on externalizing problems (i.e., disobedient, aggressive, angry) at an earlier time of measurement (i.e., mean age 55 months), even after controlling for problem behavior at the initial measurement occasion.

Experimental studies designed to test Belsky's (1997) theory are even more suggestive of differential susceptibility than the longitudinal-correlational evidence. Blair (2002) discovered that it was highly negative infants who benefited most—in terms of both reduced levels of externalizing behavior problems and enhanced cognitive functioning—from a multifaceted infant-toddler intervention program whose data he reanalyzed. More recently, Klein Velderman, Bakermans-Kranenburg, Juffer, and Van IJzendoorn (2006) found that experimentally induced changes in maternal sensitivity exerted greater impact on the attachment security of highly negatively reactive infants than it did on other infants. In both experiments, environmental influences on "vulnerable" children were for better instead of for worse.

Better Evidence of Differential Susceptibility

Even though studies highlight the heightened susceptibility of temperamentally negative or genetically vulnerable offspring to either positive or negative rearing influences, more compelling would be data on a single sample substantiating the for-better-*and*-for-worse predictions of the differential-susceptibility hypothesis. Feldman, Greenbaum, and Yirmiya (1999) found that 9-month-olds scoring high on negativity who experienced low levels of synchrony in mother–infant interaction manifested more noncompliance during clean-up at age two than other children did. When such infants experienced mutually synchronous mother–infant interaction, however, they displayed greater self-control than did children manifesting much less negativity as infants. More recently, Kochanska, Aksan, and Joy (2007) observed that highly fearful 15-month-olds experiencing high levels of power-assertive paternal discipline were most likely to cheat in a game at 38 months, yet when cared for in a supportive manner such negatively emotional, fearful toddlers manifested the most rule-compatible conduct.

Recent studies involving measured genes and measured environments also document both-for-better-and-for-worse rearing effects in the case of susceptible infants, specifically those with a particular allele (variant) of a gene called *DRD4*, which codes for a type of dopamine receptor. Because the dopaminergic system is engaged in attentional, motivational, and reward mechanisms and the variant in question, the 7-repeat allele, has been linked to lower dopamine reception efficiency, Van IJzendoorn and Bakermans-Kranenburg (2006) predicted this allele would moderate the association between maternal unresolved loss or trauma and infant attachment disorganization. Having the 7-repeat *DRD4* allele substantially increased risk for disorganization in children exposed to maternal unresolved loss/trauma, as expected; but when children with that allele were raised by mothers who had no unresolved loss, they displayed significantly less disorganization than agemates without the allele, regardless of mothers' unresolved-loss status (Bakermans-Kranenburg & Van IJzendoorn, in press).

Similar results emerged when the interplay between *DRD4* and observed parental insensitivity in predicting externalizing problems was studied in a group of 47 twins (Bakermans-Kranenburg & Van IJzendoorn, 2007). Children with the 7-repeat *DRD4* allele and insensitive mothers displayed more externalizing behaviors than children without that allele (irrespective of maternal sensitivity); and children with the 7-repeat *DRD4* allele and sensitive mothers showed the lowest

levels of externalizing problem behavior (Bakermans-Kranenburg & Van IJzendoorn, 2007). Such results suggest that conceptualizing the 7-repeat *DRD4* allele exclusively in risk-factor terms is misguided, as this variant of the gene seems to heighten susceptibility to a wide variety of environments, with supportive and risky contexts promoting, respectively, positive and negative outcomes.

DETECTING DIFFERENTIAL SUSCEPTIBILITY

An environmental effect, be it involving parenting or something else, moderated by an organismic characteristic, be it temperamental negativity or genetic makeup, is a necessary condition for differential susceptibility but not a sufficient one. It would thus be a mistake to presume that all gene-by-environment (or temperament-by-parenting) interactions are examples of differential susceptibility. Differential susceptibility needs to be distinguished from other interaction effects, including that of "dual risk," which arises when the most "vulnerable" individuals (i.e., risk #1) are disproportionately affected in an adverse manner by a negative environment (i.e., risk #2) but do not also benefit disproportionately from positive environmental conditions). It is also important that there be no association between the moderator (i.e., the susceptibility factor) and the environment (i.e., the predictor). Belsky et al. (1998) tested the independence of negative emotionality and parenting as a step in their investigation of differential susceptibility. Had these factors been correlated, then the evidence would not have shown that the predictive power of parenting was greater for highly negative infants; it would instead have indicated either that high-negativity infants elicit negative parenting or that negative parenting fosters infant negativity. Similarly, Caspi and Moffitt (2006) determined that boys' *MAO-A* genotype did not elicit maltreatment.

The formal test of differential susceptibility consists of five steps (see Box 1). The first step concerns the application of conventional statistical criteria for evaluating genuine moderation (Dearing & Hamilton, 2006), with some emphasis on excluding interactions with regression lines that do not cross (sometimes referred to as *removable* interactions). The next steps distinguish differential susceptibility from gene–environment correlations that may reflect rearing experiences evoked by genotypes (step 2) and from dual-risk models (steps 3 and 4), as defined above. If the susceptibility factor and the outcome are related, dual risk (or gain, when positive factors are involved) is suggested (Fig. 1, model d). For example, early negativity would itself lead to externalizing behavior, but even more so when combined with negative parenting. The specificity of the effect is demonstrated (step 5) if the model is not replicated when other susceptibility factors (i.e., moderators) and outcomes are used (Caspi & Moffitt, 2006; Rutter, 2006). Differential susceptibility is demonstrated when the moderation reflects a cross-over interaction (Fig. 1, model a) that covers both the positive and the negative aspects of the environment (i.e., susceptibility instead of dual risk). The slope for the susceptible subgroup should be significantly different from zero and at the same time significantly steeper than the slope for the nonsusceptible subgroup (i.e., differential instead of general susceptibility). If both slopes are significantly different from zero but in opposite directions, contrastive effects are indicated (Fig. 1, model c), as in the case of positive and negative effects of harsh discipline on, respectively, African American and White children (Deater-Deckard & Dodge, 1997).

BOX 1

Stepwise Testing for Differential Susceptibility

Distinguishing true differential susceptibility from other types of interaction proceeds in five steps, as follows:

1. Statistical test for genuine (cross-over) interaction
2. Test of the independence of the susceptibility factor and the predictor
3. Test of the association between the susceptibility factor and the outcome; if the association is nonzero, there is no support for differential susceptibility
4. Comparison of the regression plot with the prototypical graphical displays shown in Figure 1; only the first model (a) represents differential susceptibility
5. Test of the specificity of the model by replacing susceptibility factors and outcomes

UNKNOWNS IN THE DIFFERENTIAL-SUSCEPTIBILITY EQUATION

The notion of differential susceptibility, derived as it is from evolutionary theorizing, has only recently been stated in a clear and testable form (Belsky, 1997, 2005). Although research summarized here suggests that the concept has utility, there are many "unknowns," four of which are highlighted.

Domain General or Domain Specific?

Is it the case that some children, perhaps those who begin life as highly negatively emotional, are more susceptible both to a wide variety of rearing influences and with respect to a wide variety of developmental outcomes—as is presumed in the use of concepts like "fixed" and "plastic" strategists (Belsky, 2005), with the latter being highly malleable and the former hardly at all? Boyce and Ellis (2005) contend that a general psychobiological reactivity makes some children especially vulnerable to stress and thus to general health problems. Or is it the case, as Belsky (2005) wonders and Kochanska et al. (2007) argue, that different children are susceptible to different environmental influences (e.g., nurturance, hostility) and with respect to different outcomes? Pertinent to this idea are findings of Caspi and Moffitt (2006) indicating that different genes differentially moderated the effect of child maltreatment on antisocial behavior (*MAO-A*) and depression (*5HTT*).

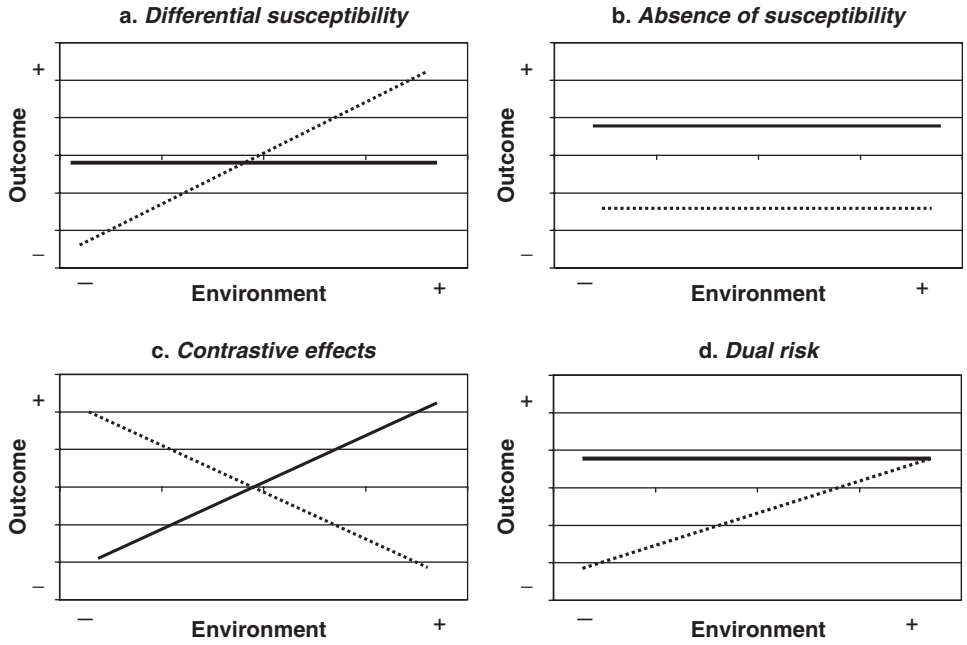

Fig. 1. Graphical display of different moderation effects. The x-axis indicates variation in the environmental factor from negative to positive; the y-axis indicates the outcome from negative to positive; and the lines depict the two groups differing on the susceptibility factor. Model a represents differential susceptibility. Model b depicts absence of susceptibility (fixed strategies)—that is, the two groups show different outcomes but variation in the environmental factor does not affect the outcome. In model c, the regression lines reflect contrastive effects. Model d represents a fan-shaped interaction, with the moderator affecting the outcome in just one direction.

Also worth considering is the prospect that heritable (or experientially induced) variation in positive emotionality (e.g., exuberance) moderates effects of rearing experiences on positive developmental outcomes (e.g., empathic concern). Perhaps negative emotionality emerges as a differential-susceptibility marker due to the disproportionate focus upon negative developmental outcomes in so much research.

Continuous Versus Discrete Plasticity?

The central argument that children vary in their susceptibility to rearing influences raises the question of how to conceptualize differential susceptibility: categorically (some children highly plastic and others not so at all) or continuously (some children simply more malleable than others)? It may even be that plasticity is discrete for some environment–outcome relations, with some individuals affected and others not at all (e.g., gender-specific effects), but that plasticity is more continuous for other susceptibility factors (e.g., in the case of the increasing vulnerability to stress of parents with decreasing dopaminergic efficiency; Van IJzendoorn, Bakermans-Kranenburg, & Mesman, 2007).

Mechanisms

Susceptibility factors are the moderators of the relation between the environment and developmental outcome, but they do not elucidate the mechanism of differential influence. Several (non-mutually exclusive) explanations have been advanced for the heightened susceptibility of negatively emotional infants. Suomi (1997) posits that the timidity of "uptight" infants affords them extensive opportunity to learn by watching, a view perhaps consistent with Bakermans-Kranenburg and Van IJzendoorn's (2007) aforementioned findings pertaining to *DRD4*, given the link between the dopamine system and attention. Kochanska et al. (2007) contend that the ease with which anxiety is induced in fearful children makes them highly responsive to parental demands. And Belsky (2005) speculates that negativity actually reflects a highly sensitive nervous system on which experience registers powerfully—negatively when not regulated by the caregiver but positively when coregulation occurs—a point of view somewhat related to Boyce and Ellis' (2005) proposal that susceptibility may reflect prenatally programmed hyperreactivity to stress.

Within-Family Differences in Susceptibility

In light of evolutionary thinking about differential susceptibility (e.g., parental "bet hedging" or the trading off of costs and benefits), it is crucial to investigate within-family variation in susceptibility (Sulloway, 1996). Studies that include twins and other siblings from the same family might prove especially powerful, as they could distinguish genetically and environmentally induced variations in susceptibility. This will be especially the case if, in addition to measuring genes and

environments, studies also measured hypothesized moderators, thereby enabling investigators to move beyond globally attributing variance to "nonshared" family environment (i.e., those experiences that make children in the same family different from each other).

At best, work on differential susceptibility has only just begun. Issues raised here remain to be addressed empirically. Doing so may shed further light on why environmental effects seem so much smaller than they are often presumed to be.

Recommended Reading

Belsky, J. (2005). (See References). A comprehensive presentation of theory and research on differential susceptibility that goes into more detail than the current article.

Boyce, W.T., & Ellis, B. (2005). (See References). A thoughtful evolutionary analysis of differential susceptibility, advancing the original claim that heightened susceptibility may itself be environmentally induced, not just genotypically determined.

Caspi, A., & Moffitt, T. (2006). (See References). A clearly written scholarly review of recent gene-by-environment interaction findings involving psychiatric disturbances in humans.

Rutter, M. (2006). (See References). A book-length treatment of "gene–environment interplay" for non-geneticists, highlighting work on genotypic vulnerability to adverse rearing environments (and much more).

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