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Genetic differential susceptibility to the effects of parenting

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Intervention efforts aimed at remediating or preventing problems in children typically prove only moderately effective due to substantial heterogeneity in their efficacy. It thus becomes important to account for such variation in intervention efficacy. Here we summarize illustrative evidence that, due to their genetic make-up, some children benefit more from interventions targeting parenting than do others. Whereas some work documents the role of single, 'candidate' genes, other work reveals the utility of compositing multiple genes and genetic pathways. Collectively, this research extends prior observational work indicating that children most negatively affected by adverse experiences also benefit the most from supportive ones, while underscoring the need for research illuminating underlying neurobiological mechanisms that instantiate differential susceptibility to environmental influences.

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Students of child development have long appreciated that parenting (and other environmental sources of influence) may not affect all children to the same degree. Indeed, this view is central to the long-standing and highly influential diathesis-stress or dual-risk model of person-X-environment interaction which stipulates that some individuals, caused by their personal characteristics (*e.g.*, temperament, physiology, genotype), are more likely than others to be adversely affected by negative environmental exposures, including harsh and insensitive parenting [1]. It is this framework, in fact, that leads to the expectation that infants with highly negative, difficult temperaments are most likely to succumb to the developmentally compromising effects of poverty, parental neglect or harsh parenting [2•]. The solid horizontal red and dotted blue lines in Figure 1 graphically depict this conceptual model.

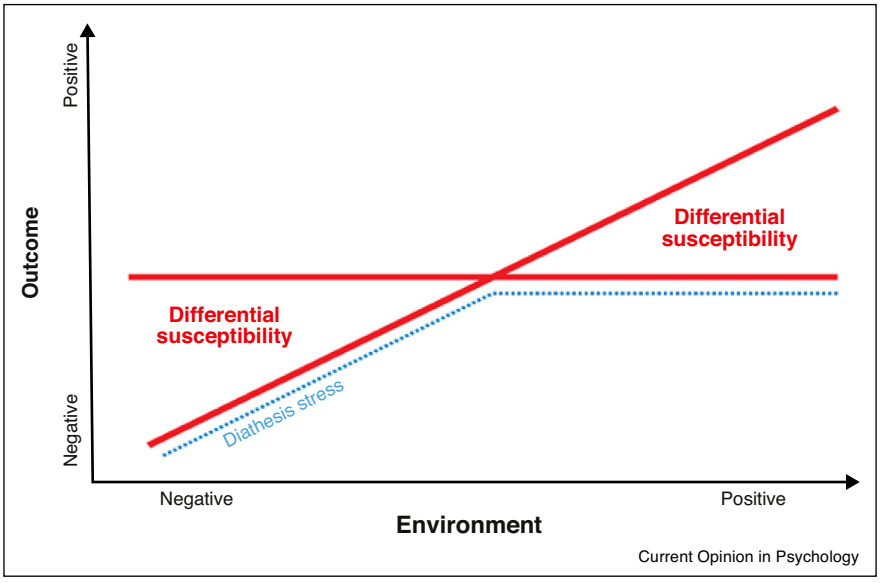
Whatever the real contributions of diathesis-stress thinking to our understanding of parenting effects and human development more generally, there are fundamental conceptual challenges to this theoretical framework [3••,4,5••]. If diathesis-stress is generalized to genetic 'risk' factors (*i.e.*, genetically rooted vulnerabilities), the crucial question becomes why would nature—meaning natural selection—craft a species in which some individuals are especially susceptible only to the negative effects of contextual adversity? Such a one-sided susceptibility to adverse environments would undermine the individual's likely success in passing genes to future generations (*i.e.*, reproductive fitness), including genes carrying the vulnerabilities.

These conceptual challenges to the prevailing diathesis-stress model of person-X-environment interaction gave birth to an alternative conceptual framework, that of *differential susceptibility to environmental influences*, including parenting. This theoretical perspective stipulates, as depicted graphically by the two red lines in Figure 1, that some children are not only more vulnerable to adversity than are others, but that these putatively 'vulnerable' children are also disproportionately likely to benefit from environmental support and enrichment. In other words, they are more developmentally plastic or malleable—'for better *and* for worse' [6••].

The evolutionary logic underlying the differential-susceptibility framework is twofold [5••]. First, because a developmental process whereby future development is shaped by earlier experiences may or may not pay off—depending on whether contextual conditions in the future prove consistent with those of childhood ('match') or not ('mismatch')—nature should 'hedge its bets', varying developmental plasticity across individuals, and thereby insuring that not all individuals are compromised when it comes to passing on their genes in the face of mismatch [7]. The second reason why there should be variation in susceptibility to the effects of parenting and other environmental influences involves the evolutionary process of frequency-dependent selection: if everyone were highly susceptible—or unsusceptible—to environmental influences, there would be disproportionate reproductive benefits to deviating from the common 'strategy' [8].

It is one thing to advance theoretical claims as to why parenting effects should vary across children and that the

Figure 1



Theoretical models of person-X-environment interaction.
Models of differential susceptibility (*red lines*) and diathesis stress. The differential susceptibility model hypothesizes that susceptible individuals are disproportionately influenced by both negative and positive environments (*diagonal line*), whereas non-susceptible individuals are not influenced (strong version) or less influenced (weak version) by both negative and positive environments (*horizontal line*). The diathesis-stress or cumulative risk model (*blue dotted line*) contends that vulnerable and resilient individuals function similarly in a positive environment but diverge in negative environments, with vulnerable individuals showing worse outcomes (based on Bakermans-Kranenburg and Van IJzendoorn [12••]).

very personal characteristics that make some children especially vulnerable to contextual adversity should also make them especially likely to benefit from environmental support and enrichment, but quite another to document empirically such for-better-and-for-worse effects. Here we limit our discussion to *genetic* markers of differential susceptibility, with an emphasis on parenting as a major component of children's environment. We present illustrative evidence linking (single) candidate genes with enhanced developmental plasticity vis-à-vis parenting, before turning to polygenetic approaches, introducing the concept of Polygenic Susceptibility Scores (PSS). We conclude by highlighting the need for examining the cascade of neurobiological mechanisms instantiating genetic differential susceptibility.

Candidate genes and differential susceptibility

More than 10 years ago the first study on genetic differential susceptibility investigated the influence of parental insensitivity observed at home in infancy on preschooler externalizing behavior. The dopamine-system related *DRD4* polymorphism was selected as a marker of differential susceptibility based on neurobiological reasoning. Preschoolers with DRD4-7repeats showed the *highest* levels of externalizing behavior if reared by *insensitive* parents while preschoolers with the same *DRD4* variant but with highly *sensitive* parents manifested the *lowest* externalizing levels. Preschoolers without *DRD4*-7repeat seemed relatively indifferent for variations in parenting and showed average externalizing levels [9].

A subsequent meta-analysis covering 12 GxE studies of some 1232 children up to 10 years of age and involving dopaminergic genes (*DRD2*, *DAT*, and *DRD4*) provided clear-cut evidence of genetic differential susceptibility. Children with the putative 'risky' genetic variants did worse in negative rearing environments than agemates without these genotypes, but they also benefited most from positive environments, with these respective 'dark' and 'bright' sides of susceptibility yielding equally large effect sizes [10]. Similarly, in a meta-analysis of 22 GxE studies of some 9361 children up to 18 years of age focusing on the serotonin-related *5HTTLPR* genotype, evidence of genetic differential susceptibility also emerged, at least in samples of mainly European descent [11]. In line with diathesis-stress thinking, children with the ss or s/l genotypes were most vulnerable to negative environments, but as predicted by the differential susceptibility model, they also benefited most from positive environments.

Most GxE studies included in these two meta-analyses were correlational and like all observational work open to alternative interpretation—due to the fact that child characteristics may themselves affect parenting (*i.e.*, active or passive GE correlations), meaning that parenting

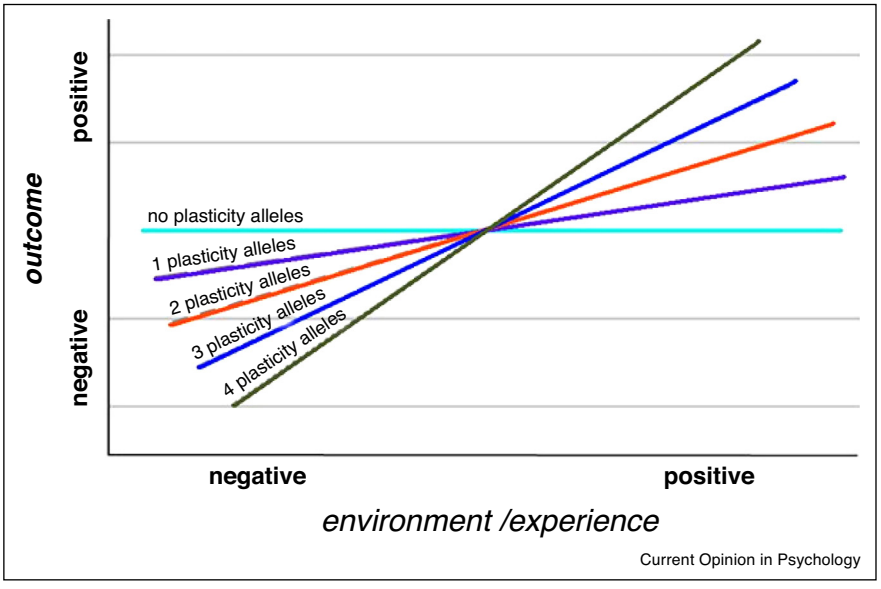
effects and putative child susceptibility factors may be confounded. Experimental intervention research with random assignment of children and families to treatment and control conditions eliminates such confounding, thereby affording strong causal inference. Also, the statistical power of experimental GxE studies is superior to that of correlational investigations, as correlational research requires up to 13 times more participants for the same power [12••]. Bakermans-Kranenburg *et al.* [13,14] pioneered the experimental study of GxE or GxeE (*i.e.*, experimental E) interaction, finding that children carrying the 7-repeat of the *DRD4* allele disproportionately benefited from a video-feedback parenting intervention aimed at fostering positive discipline and sensitive parenting and, thereby, reducing externalizing behavior among toddlers showing moderate to high levels of problems pre-treatment. In subsequent years more than 20 other randomized control GxE experiments (N = 3257) were published, and meta-analysis of resulting intervention effects proved much stronger in individuals with the susceptible genotypes (combined effect size of r = .33) than in the non-susceptible genotype carriers (non-significant combined effect size of r = .08), leading to the conclusion that the efficacy of interventions might be underestimated or even go undetected when it is obscured by GxE interactions [12••,15]. More recent GxeE studies involving parenting support not included in this meta-analysis also document genetic differential susceptibility using *5HTTLPR* as a marker [16,17].

Polygenic susceptibility scores (PSS)

The earliest work indicating that genes function not just as vulnerability but as for-better-and-for-worse plasticity factors focused on single candidate genes. This research eventually stimulated a polygenic approach to more adequately address the complexities of genetics, behavioral phenotypes and environmental influences. The first differential-susceptibility work to composite multiple genes into a multi-locus score was done by Belsky and Beaver [18•] who aggregated a cumulative score of five candidate genes previously identified as plasticity factors. Notably, evidence revealed that the more of the putative plasticity allelic variants adolescents carried, the more their self-control was associated with the quality of parenting to which they were exposed—in a for-better-and-for-worse manner. Perhaps more than anything else, this work suggested that children vary along a continuum of susceptibility to parenting effects rather than there being, as heuristically depicted in Figure 1, some children who are highly susceptible and others who are not at all susceptible. This 'susceptibility gradient' is depicted in Figure 2 when considering five susceptibility genotypes; it should be appreciated however, that some studies have used many more, as made clear below.

Polygenic scores have not only been used in correlational studies but also in randomized control trials. In a recent large trial using the Incredible Years parenting intervention program, Overbeek and his team [19,20] investigated whether children scoring higher on a polygenic plasticity

Figure 2



Theoretical model of genetic plasticity gradient.
Hypothesized for-better-and-for-worse effects of environment/experience on development depicting the proposition that the strength of predictor-outcome association is greater the more plasticity/sensitivity alleles an individual carries. In other words, there is a dose-response relation between number of such alleles and strength of for-better-and-for-worse, environment/experience effects.

index based on five dopaminergic genes (*DRD4*, *DRD2*, *DAT1*, *MAOA*, and *COMT*) benefited the most from the parenting program. The 341 4–8 years olds were screened for moderate-to-high levels of externalizing problem behavior. The intervention proved most effective in decreasing parent-reported (but not observed) externalizing behavior in boys (but not girls) carrying more rather than fewer dopaminergic plasticity alleles.

Polygenic scores may be derived bottom-up, in a combination of genetic markers of differential susceptibility no matter what biological and functional genetic pathway they belong to [18•,21] or they can be aggregated top-down according to their 'biological relatedness' in an a priori defined coherent 'gene-set' [19,22]. Polygenic *Risk* Scores (PRS) have been developed bottom-up by diathesis-stress researchers using GWAS data to reveal what combination of SNPs relates to a psychiatric disorder such as depression or schizophrenia [23]. A radically novel approach to testing differential susceptibility has been introduced by a UK team [24••], based on a genome-wide analysis (GWAS) of more than 1000 monozygotic twins. The within-twin phenotypic variability in symptoms of anxiety was associated with whole-genome SNPs yielding a polygenic score of sensitivity to environmental pressures (*i.e.*, Polygenic *Susceptibility* Score, PSS), in behavioral genetic terms part of the unique environment. Depending on cut-off criteria the various polygenic scores included 400 to more than 100 000 SNPs. Following identification of these SNPs using twin data, the resulting polygenic scores were used in an observational study with an independent sample, with findings indicating that PSS moderated the effect of parenting on emotional problems in a differential-susceptibility-related manner. PSS was then used to predict therapeutic efficacy in yet another sample. Notably, for those patients with low PSS, treatment type had little effect on outcome, whereas for those with high PSS therapeutic success varied with type of treatment.

If these findings prove replicable, this is a very promising approach, which might be used to investigate effects of environmental changes or treatments on other phenotypes. The percentage explained variance of the polygenic score in interaction with therapeutic treatment was modest, less than 5% at most, and replication efforts will require large samples to reproduce this finding. In a first replication attempt, data from a longitudinal population-based cohort study (Generation R) were used, including almost 3000 children for whom GWAS data on about half a million SNPs and CBCL internalizing scores were available, as well as scores for harsh parenting, and socio-economic status. Using polygenic susceptibility scores based on the same SNPs as the UK team [24••] in predicting children's internalizing behavior in a family context of less or more harsh parenting, or higher or lower SES, the expected GxE interactions could not be confirmed (I Pappa, personal communication). More exact replications are sorely needed, because this polygenic approach clearly is a major conceptual and methodological advance.

Yet another approach would be to combine several large RCTs with similar interventions (*e.g.*, parent training) and phenotypic outcomes (*e.g.*, child behavior problems) to predict intervention success. For each participant a residual score could be computed that indicates how the individual contributes to intervention success. For some individuals residuals will be large and negative, implying that they were least affected by the intervention, whereas for others the residuals will be large and positive, indicating greatest intervention efficacy. This residual score could then be correlated with GWAS data. A related non-experimental 'data-mining' approach would be to use so-called logistic Bayesian lasso techniques to search for the best set of markers of GxE interaction from GWAS data in a hypothesis-free manner ([25], M Meaney, personal communication).

Conclusion: in search of mechanisms

In the face of evidence documenting genetic differential susceptibility, there is a need for research illuminating neurobiological mechanisms which instantiate this phenomenon (see Boyce [26] and Moore and Depue [27] for recent multi-level models, see Ref. [28] for pertinent animal models). Numerous ones, no doubt, are involved. Indeed, there is suggestive evidence implicating attentional processes, like bias toward positive and negative emotional cues [29,30]; cognitive processes, like rumination [31], feedback processing [32], and reward sensitivity [33]; physiological processes, including stress reactivity [34,35,36•]; and brain functioning involving the hippocampus and amygdala [37–39], as well as DNA methylation [12••,40,41]. What is required, though, are models and evidence illuminating whether and how such multi-level neurobiological processes operate in concert to produce individual differences in environmental susceptibility across development.

Conflict of interest

The authors do not have any conflict of interest.

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