A multiple-levels-of-analysis approach to the study of developmental processes in maltreated children

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Before the early 1970s, scientific investigations of children from high-risk environments, as well as those with mental disorders, portrayed the developmental course of such individuals as deterministic, inevitably eventuating in maladaptive and psychopathological outcomes (1). As researchers discovered that not all high-risk children evinced the dire consequences that the existing theories of psychopathology predicted, comprehending the processes through which children at risk did not develop psychopathology became viewed as important for informing theoretical viewpoints on the development of maladaptation and pathology (2). Indeed, over the past several decades advances have occurred in understanding the complexity of causality, the interaction of risk and protective factors, the heterogeneity of disorders, and the importance of biological and psychological developmental processes and mechanisms (3, 4). The work of Kaufman *et al.* (5) in a recent issue of PNAS illustrates that individual risk factors alone seldom are powerful predictors of later psychopathological outcomes (6, 7). Much more often, adequate prediction of either disturbance or resilience requires considering multiple risks and protective factors and their interplay.

It is now common knowledge that the same risk factors may be associated with different outcomes (i.e., multifinality) and that subgroups of individuals exhibiting similar problems arrived at them from different beginnings (i.e., equifinality) (8). Furthermore, comprehending the factors contributing to positive outcomes despite the presence of significant adversity (i.e., known as resilience; see ref. 1) can help to broaden the understanding of developmental processes that may not be evident in normative environments. The study of child maltreatment, perhaps the greatest failure of the caregiving environment to provide the expectable experiences that are necessary to promote normal developmental processes, provides researchers with a vital opportunity to investigate the pathways to normal and deviant outcomes (9). Child abuse and neglect set in motion a probabilistic path of epigenesis for maltreated children characterized by an increased likelihood of failure and disruption in the successful resolution of salient developmental tasks, resulting in a profile of relatively enduring vulnerability factors that increase the probability of the emergence of maladaptation and psychopathology (10).

The majority of our knowledge about the pathways, developmental trajectories, and ultimate consequences of psychopathology in maltreated children has been informed by investigations that have focused on relatively narrow domains of variables and that have been predominantly psychological in nature (9). To develop a thorough and comprehensive understanding of adaptive and maladaptive functioning, it is essential that scientists increasingly incorporate a multiple-levels-of-analysis perspective into their research (11). Such multiple-levels-of-analysis investigations may reveal the genetic elements that are probabilistically associated with maladaptive developmental outcomes and psychopathology, and, alternatively, those genes that may serve a protective function for individuals experiencing significant adversity.

Genetics, Enviroment, and Resilience

From a genetic perspective, resilience can be conceptualized as the extent to which individuals who possess the genetic risk for maladaptation and psychopathology are not affected (1). To date, research on the correlates of, and contributors to, resilience has focused on discovering the social experiences that may protect some high-risk children from developing maladaptively (12). In addition, there may be genetic contributors to resilient adaptation that protect some individuals in families where there is a high genetic loading for developing maladaptation and mental disorder from succumbing to these deleterious outcomes. Although researchers investigating the genetics of mental disorder have long focused on the vulnerabilities that certain genetic elements may confer, it is equally probable that genes may, from an evolutionary perspective, serve a protective function against environmental insults for some individuals. Consequently, genetic influences on maladaptation and psychopathology operate in a probabilistic and not a deterministic manner.

Caspi *et al.* (13) examined how genetic factors contributed to why some maltreated children grow up to develop antisocial personality disorders, whereas other maltreated children do not. In this longitudinal investigation of males who were studied from birth to adulthood, it was discovered that a functional polymorphism in the promoter of the gene encoding the neurotransmitter, metabolizing enzyme monoamine oxidase A (MAOA) moderated the effect of maltreatment. The link between child maltreatment and antisocial behavior was far less pronounced among males with high MAOA activity than among those with low MAOA activity. Of relevance to research on the biological contributors to resilient adaptation, it is conceivable that the gene for high MAOA activity may confer a protective function against the development of antisocial disorder in males who have been maltreated. Maltreated children grow up in extremely stressful environments. The results of the Caspi *et al.* (13) investigation suggest that a gene-by-environment (G×E) interaction helps to explain why some maltreated children, but not others, develop antisocial behavior via the effect that stressful experiences such as child maltreatment exert on neurotransmitter system development. Specifically, the probability that child maltreatment will eventuate in adult antisocial behavior is greatly increased among children whose MAOA is not sufficient to render maltreatment-induced changes on neurotransmitter systems inactive (13).

The investigation of Kaufman *et al.* (5) provides an especially important exemplar of the great value accrued by incorporating a multiple-levels perspective into investigations of the processes that contribute to maladaptive or resilient outcomes. The Kaufman *et al.* (5) study was conducted with children, thereby extending a previous experiment conducted by Caspi *et al.* (14) with adults in which a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was shown to moderate the influence of stressful life events on depression. Specifically, individuals with one or two copies of the short (s) allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, depressive disorders, and suicidality than individuals homozygous for the long (l) allele when confronted with high stress. The s allele in the polymorphic region is associated with

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lower transcriptional efficiency of the promoter compared with the l allele (15).

This study, a large-scale prospective, longitudinal investigation of a representative birth cohort, provides evidence of a G×E interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup (16). Moreover, Caspi *et al.* (14) found that, congruent with a G×E hypothesis, adult depression was predicted by the interaction between the s allele in the 5-HTT gene-linked polymorphic region and child maltreatment that occurred during the first decade of life. The interaction revealed that child maltreatment predicted adult depressive disorder only among individuals carrying an s allele (i.e., s/s or s/l), but not among l/l homozygotes.

The results of Kaufman *et al.* (5) that, in children, the s allele in the 5-HTT gene-linked polymorphic region only confers vulnerability to depression in individuals with a history of significant life stress replicates the G×E result found in Capsi *et al.* (14) with adults. Furthermore, the findings of Kaufman *et al.* (5) demonstrate that social support, in concert with this genetic factor, additionally moderate the risk for depression in maltreated children. Specifically, maltreated children who were homozygous for the s allele and who had a dearth of positive social supports, had depressive symptoms that were nearly twice as high as maltreated children with the s/s genotype and positive social supports. The latter group of maltreated children had levels of depressive symptoms that were comparable to those of nonmaltreated children in the comparison group with the same s/s genotype. The risk for depression in maltreated children was moderated by the interplay of genetic and environmental factors. Thus, the negative developmental sequelae associated with child maltreatment are not inevitable. There are many factors that contribute significantly to the ultimate developmental course embarked on by maltreated children (9). Importantly, the quality and availability of social supports were environmental factors that promoted resilience in maltreated children, even in the presence of a genotype that might otherwise be expected to confer vulnerability to psychiatric disorder.

Multiple Levels of Analysis

The development of mental disorders is generally expected to be caused by genetic predispositions along with the impact of an individual's past and present life experiences (3, 4). Genetic influence is likely complex, involving many genes in concert. Ideally, future research should examine multigene–environment interactions. Moreover, environmental variables must be precisely defined and clearly specified to permit investigators to discover ways in which genes may moderate environmental experiences, or vice versa.

Advances have been made in the measurement and operationalization of child maltreatment subtypes (10, 17). Future investigations of G×E interactions with maltreated children must be sufficiently large to enable investigators to examine maltreatment subtypes to ascertain whether G×E interactions vary for children with different types of maltreatment experiences. For example, in the Kaufman *et al.* (5) study, variations in outcome might have been detected between children who had experienced different forms, duration, or severity of maltreatment (10, 17).

Furthermore, future G×E investigations should examine brain endophenotypes that may be intermediate between the 5-HTT gene and depression (18). Because of their expense, magnetic resonance imaging studies may be difficult to conduct with large population-based samples; however, the examination of gene–brain interactions would make an invaluable contribution to a multiple-levels-of-analysis perspective on psychopathology.

Likewise, children born with normal brains may encounter a number of experiences, including child maltreatment, that can exert a deleterious impact on developing brain structure, function, and organization. These experiences may contribute to distorting these children's experiences of the world (19). Pathological experience may become part of a vicious cycle, as the pathology induced in brain structure may distort the child's experience, with subsequent alterations in cognition or social interactions causing additional pathological experience and added brain pathology.

Finally, incidents of maltreatment, especially co-occurring physical, sexual, and emotional abuse, may engender massive stress in vulnerable children. The development of behavior problems that often accompanies stress-induced hypercortisolism is partially a consequence of hormonal effects on gene expression (10). Investigators have documented the role of stress hormones, such as cortisol, in the expression of genes that govern brain function. Neuronal glucocorticoid receptors are responsible for the influence of stress hormones on the expression of genes (20). When stress hormones bind to nuclear receptors, these hormones can trigger transcription and protein synthesis of certain genes. The resulting proteins, in turn, influence neuronal structure and function, including neuronal growth, neurotransmitter synthesis, receptor density and sensitivity, and neurotransmitter reuptake.

The incorporation of assessments of the hypothalamic–pituitary–adrenal axis functioning into research on G×E interactions could further enhance the predictive efficiency of such investigations. For example, maltreated children who demonstrate stress-induced neuroendocrine dysregulation (i.e., hypocortisolism or hypercortisolism), have a paucity of social supports and have the s/s genotype for the 5-HTT gene may be even more likely to develop depressive disorder. Once stress-sensitive neural processes have been more fully delineated, this may pave the way for the formulation of pharmacological and behavioral prevention and intervention efforts to ameliorate the harmful impact that early stressful experiences exert on neurobiological development.

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