A JOURNAL OF THE ASSOCIATION FOR PSYCHOLOGICAL SCIENCE APS

Measured Gene–Environment Interactions and Mechanisms Promoting Resilient Development

Julia Kim-Cohen and Andrea L. Gold

Yale University

ABSTRACT—*Childhood maltreatment elevates risk for antisocial behavior, depression, and other problems over the life span, but a subset of maltreated individuals avoids maladaptive development and shows resilience. Resilience reflects a dynamic confluence of factors that promotes positive adaptation despite exposure to adverse experiences. Recent replicated findings of gene–environment interactions (abbreviated G × E) involving maltreatment have identified two genes, monoamine oxidase A (*MAOA*) and serotonin transporter (*5-HTT*), that moderate the association between childhood maltreatment and psychopathology. Accordingly, G × E raise new questions about potential biological mechanisms by which some individuals are able to cope adaptively and function relatively well despite experiencing early adversity. We summarize advances toward greater specification of G × E mechanisms, including genetic and environmental moderation of G × E effects and imaging genomics that provide clues regarding resilience processes in development.*

KEYWORDS—*resilience; gene–environment interaction; maltreatment; MAOA; 5-HTT*

Each year in the United States, hundreds of thousands of children are victims of abuse and neglect. Although maltreated children are at heightened risk of developing mental and physical health problems, some of these children "beat the odds" and go on to live relatively healthy, productive lives. What biological and environmental processes explain favorable outcomes in some individuals following childhood maltreatment? How can such information be applied to foster resilience in individuals who experience severe adversity?

Resilience reflects a dynamic confluence of factors that promotes positive adaptation—defined as either the absence of psychopathology or the presence of competence—despite exposure to adverse life experiences. In recent years, increasing attention has been drawn to the potential role that genetics and neurobiology might play in determining resilience (Cicchetti & Blender, 2006; Kim-Cohen, Moffitt, Caspi, & Taylor, 2004; Luthar & Brown, 2007; Masten & Obradovic, 2006). This shift toward incorporating biological hypotheses in resilience models has been stimulated by the groundbreaking incorporation of gene–environment interactions (hereafter abbreviated G × E) in behavioral research by Caspi and Moffitt (2006) and their colleagues. In brief, G × E demonstrate that variation in specific genes moderates the impact of environmental risks on psychopathology (or vice versa), such that risk-exposed individuals who carry the "protective" version (or allele) of the gene have significantly reduced levels of psychopathology compared to comparably risk-exposed individuals with the "vulnerable" allele. Here, we review the emerging literature on G × E involving childhood maltreatment and discuss potential G × E mechanisms in resilient development. We then outline future directions that can advance our understanding of resilience phenomena.

G × E

With G × E studies of psychopathology, resilience research is now moving rapidly toward testing empirical models that traverse multiple levels of influence, from DNA sequences to culture (Cicchetti & Blender, 2006). In 2002, Caspi and colleagues (as cited in Caspi & Moffitt, 2006) first demonstrated that the asso-

Address correspondence to Julia Kim-Cohen, Department of Psychology, Yale University, PO Box 208205, New Haven, CT 06520; e-mail: julia.kim-cohen@yale.edu.

CURRENT DIRECTIONS in Psychological Science

ciation between childhood maltreatment and later antisocial behavior was moderated by a functional polymorphism in the promoter (or regulatory) region of the gene encoding the monoamine oxidase A (MAOA) enzyme. Specifically, maltreated children whose genotype conferred relatively low levels of MAOA expression had significantly higher levels of antisocial behavior in adolescence and adulthood compared to maltreated children carrying the high-activity version of the *MAOA* gene. In 2003, Caspi and colleagues (as cited in Caspi & Moffitt, 2006) reported a second G × E involving a functional polymorphism in the promoter region of the serotonin transporter (*5-HTT*) gene. Individuals with one or two copies of the *5-HTT* "short" allele had more depressive symptoms, higher rates of diagnosable depression, and more suicidality subsequent to stressful life events or childhood maltreatment compared to similarly stressed individuals with two copies of the "long" allele. In both of these studies, the genes showed no effect on the mental health outcomes in individuals who had not been exposed to risk. Although debate continues regarding the veracity of G × E models (Tabery, 2007) and further study is needed before these G × E hypotheses can be definitively confirmed, both findings have been replicated in several independent studies and a meta-analysis (Kim-Cohen et al., 2006; Taylor & Kim-Cohen, 2007; Uher & McGuffin, 2007), indicating that, rather than having a direct and linear association to mental health outcomes, genetic variation predicts variation in how individuals respond to adverse experiences.

To date, virtually all G × E studies involving childhood maltreatment have focused on polymorphisms in *MAOA* and *5-HTT*, two principal genes implicated in early brain maturation and the regulation of mood, behavior, and stress response. The MAOA enzyme metabolizes serotonin primarily, but also norepinephrine and dopamine (Buckholtz & Meyer-Lindenberg, 2008). Serotonin transporter plays an analogous role by clearing serotonin in the synapse, the intracellular space between neurons. As both the long *5-HTT* and the high-activity *MAOA* alleles are associated with relatively lower levels of active serotonin in the synapse and predict less psychopathology in maltreated individuals, an intriguing hypothesis is that optimal regulation of serotonin during development is one of the processes leading to good adjustment among those who experience suboptimal care early in life.

SPECIFYING MECHANISMS OF G × E AND RESILIENCE

As emerging studies continue to test Caspi and colleagues' original G × E hypotheses, researchers have also called for greater specification of effects in several ways.

Specifying Features of the Environmental "Pathogen" in G × E

Research is being conducted to further delimit the environmental risks that interact with genes to predict vulnerability and resilience. Epidemiological cohort studies typically yield small numbers of maltreated individuals, leading to the impracticality of teasing out specific features of maltreatment that predict G × E effects. In contrast, Cicchetti, Rogosch, and Sturge-Apple (2007) specifically recruited a large sample of maltreated children ($N = 207$) and nonmaltreated controls. Although overall maltreatment status did not interact significantly with *5-HTT* genotype to predict depressive symptoms, the authors identified specific components of the maltreatment experience that did. Namely, levels of depressive symptoms were especially heightened among carriers of the low-activity *MAOA* allele who had experienced three or four maltreatment subtypes. Additionally, among adolescents carrying two copies of the *5-HTT* short allele, sexual abuse had a greater effect than physical abuse (with no sexual abuse) or neglect on increasing internalizing symptoms. In this study, the sexual-abuse group was the broadest category and could include co-occurring physical abuse, neglect, and emotional abuse. Taken together, these results suggest that having experienced multiple types of maltreatment may indicate a risk factor that is most likely to "get under the skin" and trigger a genetically mediated biological process leading to the development of psychopathology. At the same time, these findings raise the possibility that putative resilience could be an artifact of variability in exposure to the environmental risk factor (Rutter, 2006), which emphasizes the importance of continuing to specify and measure risk exposure accurately.

Diversity of methods and approaches used to measure environmental risk may explain inconsistencies in results across G × E studies that have attempted to replicate Caspi and Moffitt's (2006) findings (Uher & McGuffin, 2007). Recently, Brown and Harris (2008) highlighted a similarity across studies that have failed to replicate the *5-HTT*-by-life-stress G × E—that is, these studies measured the occurrence of stressful life events in the months immediately preceding the depressive outcomes. In contrast, positive replication studies have more closely followed Caspi and Moffitt (2006) and colleagues' strategy by measuring stressful life events occurring in the 5 years prior to the depressive episode, which are significantly associated with childhood maltreatment. Thus, a 5-year index of severe life stress may be a marker of childhood maltreatment that may be the actual environmental "pathogen" involved in the *5-HTT*-by-stress interaction. Brown and Harris (2008) propose a developmental interpretation of this G × E in which *5-HTT* polymorphisms influence natural variation in brain maturation and sensitivity to adversity in early development. If childhood maltreatment occurs, it is this genetically influenced variation in brain structure and function in interaction with stress that predicts depression or promotes resilience, rather than the current status of serotonin functioning in the adult brain when stressful life events occur.

Moderation of G × E by Other Genes and Environments

Genes are unlikely to act in isolation in explaining complex behavioral phenomena, and G × E effects might be moderated

by additional genes. Examples of epistasis (or gene–gene interaction) in G × E research are now available. For instance, Kaufman et al. (2006) reported that the *5-HTT*-by-childhood-maltreatment interaction predicting depression is further moderated by a polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene. Moreover, Cicchetti et al. (2007) found that sexually abused adolescents with one or two copies of the *5-HTT* short allele had significantly reduced levels of internalizing symptoms if they also had the high-activity version of the *MAOA* gene. Such findings indicate that resilience imparted by genotype is still possible even among those who might be considered genetically at risk because of a single gene.

G × E effects might also be moderated by other, nongenetic variables (Masten & Obradovic, 2006). In a key demonstration of this principle, Kaufman et al. (2006) reported that having a supportive relationship with an adult protected maltreated children from developing depression, even among genetically at-risk children. The complexity of possible multigene and multienvironment effects on vulnerability and resilience makes conjecture about pharmacological interventions challenging at this time. However, as Kaufman et al.'s (2006) study shows, psychosocial interventions may ameliorate the "double whammy" of risk conferred by a vulnerable genetic allele combined with environmental disadvantage.

Imaging Genomics: Neural Substrates Underlying Mechanisms of Risk and Resilience

In recent years, the joining of G × E research with neuroscience theory and methods (Caspi & Moffitt, 2006; Viding, Williamson, & Hariri, 2006) has generated new hypotheses regarding neural bases of resilience. Imaging genomics studies of psychiatrically healthy adults have reported similar effects for the risk-conferring variants of *MAOA* and *5-HTT* genotype on the reactivity and structure of brain regions associated with emotion processing. Neuroscientists have demonstrated the tendency of the low-activity *MAOA* allele (Buckholtz & Meyer-Lindenberg, 2008) and the *5-HTT* short allele (Hariri et al., 2005) to predict exaggerated amygdala responses to fearful or angry faces. Meyer-Lindenberg and colleagues (as cited in Buckholtz & Meyer-Lindenberg, 2008) also found that carriers of the low-activity *MAOA* variants exhibited diminished responsivity to threat in regions of the frontal cortex and had reduced volumes of limbic-system structures that include connections to cortical regions associated with cognitive-control processes. These neural features themselves do not represent biomarkers for psychopathology because they are found in typical, healthy samples. Rather, they suggest a mechanism by which genotype influences brain-based variation in sensitivity to and regulation of emotional experiences. In the absence of aberrant caregiving experiences, neither high nor low reactivity to threat is maladaptive. However in the presence of maltreatment, a relatively more dampened, controlled response to threat associated with the high-activity *MAOA* or long *5-HTT* alleles may be the adaptive, resilience-promoting attribute.

Imaging genomics studies are essential to our understanding of the developmental timing of G × E effects. Converging evidence warrants further research regarding the specificity of *MAOA* and *5-HTT* influences on brain development as the backdrop for vulnerability or resilience to environmental risk exposure. Specifically, G × E mechanisms may represent (a) an "in the moment" biochemical process between gene expression and environmental risk exposure; (b) an interaction of brain development shaped by the presence of vulnerable or protective alleles and the environmental risk; or (c) both processes, given that they are not mutually exclusive. Imaging genomics findings and Brown and Harris's (2008) argument for severe life stress in adulthood as a marker for childhood maltreatment (as discussed earlier) both point toward the importance of developmental timing in G × E effects.

FUTURE DIRECTIONS

Gene–environment interaction studies have opened a new avenue for investigation into resilience processes across development, but important questions remained unanswered. We propose several future steps that can capitalize further on the promise of genetic and environmental co-action for elucidating developmental mechanisms of resilience.

First, G × E in psychiatry are relevant for resilience because they demonstrate how genes can lead to escape from psychopathology in individuals who have experienced maltreatment. The absence of psychopathology, however, is both conceptually distinct from good adjustment, indicated by the presence of competent functioning, and likely to lead to different conclusions regarding predictors and pathways toward resilient outcomes (Luthar & Brown, 2007). To our knowledge, no studies have tested whether particular genotypes might enhance the development of competencies in the presence of maltreatment or other adversities. However, it is conceivable that genes may promote the development of psychological strengths that surface in response to adversity and generate the so-called "steeling" effect, or the notion that the experience of stress bolsters resistance to future adverse experiences (Rutter, 2006). Thus, in order to increase the relevance of G × E for resilience research, studies must not rely solely on the absence-of-psychopathology criterion but must also include specific measures of competencies that are likely to be influenced by genetic variation (Fig. 1).

This discussion relates to the allied concepts of *differential susceptibility* and *biological sensitivity to context*—that is, the idea that some children, perhaps because of their genetic makeup, might be more affected by their rearing experiences, either good or bad (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Boyce & Ellis, 2005). Recently, these theoretical models have received an innovative application in the interpretation of G × E studies, which reveal genotypic differences rendering

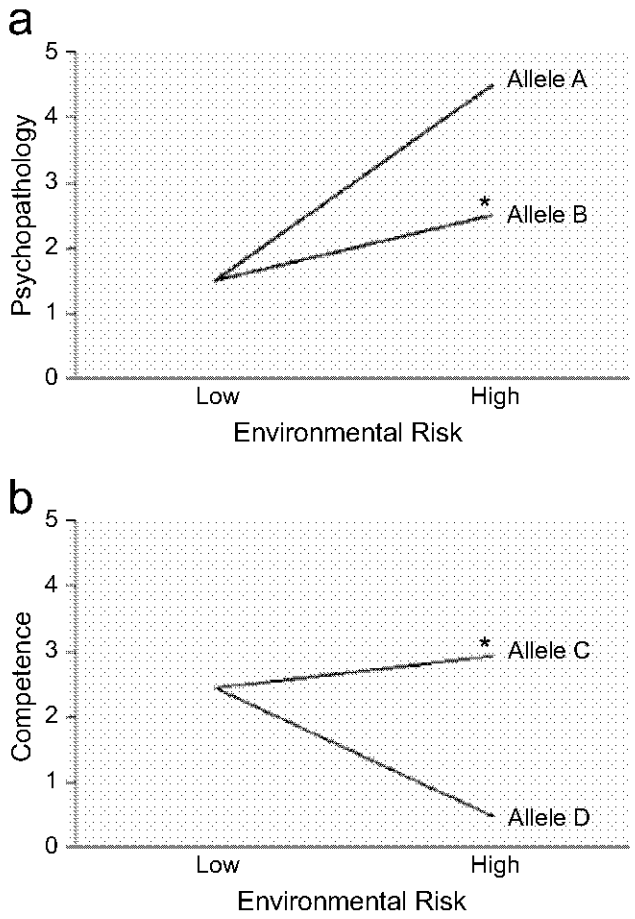

Fig. 1. Illustrative gene × environment interaction (G × E) effects predicting resilience in two ways: (a) resilience defined as the relative absence of psychopathology compared to the nonresilient group, and (b) resilience defined as maintaining or showing some elevation of competence despite exposure to adversity. The x-axes in both graphs indicate the degree of environmental risk exposure from low to high; the y-axes indicate the outcomes, and lines represent different genotype groups (alleles). Resilience is denoted in each figure by an asterisk.

some children especially vulnerable to the effects of maltreatment on risk for psychopathology. However, new G × E findings suggest that under conditions of warm, supportive caregiving, the same children who would be genetically vulnerable actually function more advantageously than do similar children with the presumed protective allele (Bakermans-Kranenburg, van IJzendoorn, Pijlman, Mesman, & Juffer, 2008). That is, genetic variation confers differential susceptibility to environments "for better and for worse" (Belsky et al., 2007), and no single allele is risk-inducing under all contexts. What will be essential to distinguish for purposes of understanding resilience is how some individuals, because of their genotype, may respond more competently and advantageously under suboptimal rearing conditions.

Second, G × E studies involving adversities in human populations will frequently suffer the limitations of correlational or quasi-experimental designs that cannot identify true causes. However, experimental designs are ethically possible when the "environment" in the G × E equation is an intervention to which participants who vary on genotype are randomly assigned. Randomized controlled trials of effective treatments can join forces with G × E research to identify genetic alleles that predict treatment efficacy. To date, we know of one study involving a psychosocial treatment that has tested this possibility. Bakermans-Kranenberg and colleagues (2008) recently showed that an intervention to increase sensitive responding in parents was more successful in reducing behavior problems in children carrying the version of a dopamine receptor gene (i.e., *DRD4* 7-repeat allele) that is typically associated with increased risk for hyperactivity, impulsivity, and inattention.

Third, G × E studies tend to focus primarily on how genes may moderate the impact of environmental pathogens. However, genes may also moderate positive, health-promoting environments. For instance, the benefits of breastfeeding in infancy for boosting IQ scores are found only in individuals who carry a specific allele of a gene involved in the metabolism of fatty acids, the presumed "active ingredient" in breast milk that supports optimal cognitive development (Caspi et al., 2007). Two points are worth noting here. First, although no G × E studies have directly investigated resilience per se, G × E are likely to shape the development of normative adaptive systems in the presence of a positive caregiving context (Masten & Obradovic, 2006). Second, when normative adaptive systems develop well, they can in turn foster adaptive coping when hardship, adversity, and stress arise. Thus, in some cases, genes may be involved in promoting resilient outcomes indirectly by influencing which individuals benefit most from salubrious environments and will be best prepared to deal effectively with misfortune.

Since its inception, a major motivating force for resilience research has been to prevent mental disorders and promote competent, healthy development (Luthar & Brown, 2007; Masten & Obradovic, 2006). There is optimism that G × E research will aid this mission, but there is skepticism as well. We hope that as information regarding both biological and environmental mechanisms of G × E effects continues to emerge, the promise of intervening more effectively with the most disadvantaged children in our society will be fulfilled.

Recommended Reading

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H.L., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*, 386–389. Already a classic, this study empirically demonstrates methodological strategies for a strong test of G × E effects.

Kim-Cohen, J. (2007). Resilience and developmental psychopathology. *Child and Adolescent Psychiatric Clinics of North America, 16*, 271–283. A concise overview of resilience with emphasis on implications for developmental theory and clinical practice, written for the nonexpert.

Lester, B.M., Masten, A., & McEwen, B. (Eds.). (2006). *Resilience in children. Annals of the New York Academy of Sciences (1094).* Hoboken, NJ: Wiley. A recent, highly accessible book-length collection of theoretical and empirical conference papers.

Luthar, S.S., & Brown, P.J. (2007). (See References). An excellent discussion of strategies for advancing transdisciplinary and applied resilience research.

Moffitt, T.E., Caspi, A., & Rutter, M. (2006). Measured gene-environment interactions in psychopathology: Concepts, research strategies, and implications for research, intervention, and public understanding of genetics. *Perspectives on Psychological Science*, *1*, 5–27. A thorough description of the logic behind G × E research and recommendations for conducting G × E studies of high quality.

REFERENCES

Bakermans-Kranenburg, M.J., van IJzendoorn, M.H., Pijlman, F.T.A., Mesman, J., & Juffer, F. (2008). Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Developmental Psychology*, *44*, 293–300.

Belsky, J., Bakermans-Kranenburg, M.J., & van IJzendoorn, M.H. (2007). For better *and* for worse: Differential susceptibility to environmental influences. *Current Directions in Psychological Science*, *16*, 300–304.

Boyce, W.T., & Ellis, B.J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development & Psychopathology*, *17*, 271–301.

Brown, G.W., & Harris, T.O. (2008). Depression and the serotonin transporter 5-HTTLPR polymorphism: A review and a hypothesis concerning gene-environment interaction. *Journal of Affective Disorders*, *111*, 1–12.

Buckholtz, J.W., & Meyer-Lindenberg, A. (2008). MAOA and the neurogenetic architecture of human aggression. *Trends in Neurosciences*, *31*, 120–129.

Caspi, A., & Moffitt, T.E. (2006). Gene-environment interactions in psychiatry: Joining forces with neuroscience. *Nature Reviews Neuroscience*, *7*, 583–590.

Caspi, A., Williams, B., Kim-Cohen, J., Craig, I.W., Milne, B.J., Poulton, R., et al. (2007). Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proceedings of the National Academy of Sciences, USA*, *104*, 18860–18865.

Cicchetti, D., & Blender, J.A. (2006). A multiple-levels-of-analysis perspective on resilience: Implications for the developing brain, neural plasticity, and preventive interventions. *Annals of the New York Academy of Sciences*, *1094*, 248–258.

Cicchetti, D., Rogosch, F.A., & Sturge-Apple, M.L. (2007). Interactions of child maltreatment and serotonin transporter and monoamine oxidase A polymorphisms: Depressive symptomatology among adolescents from low socioeconomic status backgrounds. *Development & Psychopathology*, *19*, 1161–1180.

Hariri, A.R., Drabant, E.M., Munoz, K.E., Kolachana, B.S., Mattay, V.S., Egan, M.F., et al. (2005). A susceptibility gene for affective disorders and the response of the human amygdala. *Archives of General Psychiatry*, *62*, 146–152.

Kaufman, J., Yang, B.Z., Douglas-Palumberi, H., Grasso, D., Lipschitz, D., Houshyar, S., et al. (2006). Brain-derived neurotrophic factor-5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biological Psychiatry*, *59*, 673–680.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I.W., et al. (2006). *MAOA*, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry*, *11*, 903–913.

Kim-Cohen, J., Moffitt, T.E., Caspi, A., & Taylor, A. (2004). Genetic and environmental processes in young children's resilience and vulnerability to socioeconomic deprivation. *Child Development*, *75*, 651–668.

Luthar, S.S., & Brown, P.J. (2007). Maximizing resilience through diverse levels of inquiry: Prevailing paradigms, possibilities, and priorities for the future. *Development & Psychopathology*, *19*, 931–955.

Masten, A.S., & Obradovic, J. (2006). Competence and resilience in development. *Annals of the New York Academy of Sciences*, *1094*, 13–27.

Rutter, M. (2006). Implications of resilience concepts for scientific understanding. *Annals of the New York Academy of Sciences*, *1094*, 1–12.

Tabery, J. (2007). Biometric and developmental gene-environment interactions: Looking back, moving forward. *Development & Psychopathology*, *19*, 961–976.

Taylor, A., & Kim-Cohen, J. (2007). Meta-analysis of gene-environment interactions in developmental psychopathology. *Development & Psychopathology*, *19*, 1029–1037.

Uher, R., & McGuffin, P. (2007). The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: Review and methodological analysis. *Molecular Psychiatry*, *13*, 131–146.

Viding, E., Williamson, D.E., & Hariri, A.R. (2006). Developmental imaging genetics: Challenges and promises for translational research. *Development & Psychopathology*, *18*, 877–892.