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Gene-environment Interplay and Risk and Resilience During Childhood

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Introduction

Developmental scientists have long acknowledged that genetically-based characteristics of the child contribute to developmental processes associated with risk and resilience. For example, quantitative behaviour-genetic (e.g., twin and adoption) studies have highlighted genetic influences on children's behaviour and development, increasingly with a focus on resilience-related outcomes.[1] However, such studies often assume that genetic and environmental influences operate independently of one another. Recently, focus has shifted towards the idea that development is shaped by ongoing, reciprocal influences across multiple levels of analysis, spanning from the child's sociocultural context to molecular and cellular processes.[2-5] Studying the complex interplay between genetic and environmental influences has increasingly focused the field on the contributions of molecular variations within specific genes.

Subject

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One class of gene-environment interplay is the interactions between measured genetic variations and environmental experiences. Gene-by-environment interaction (G×E) refers to the idea that genetic variations might not shape development outcomes directly but rather confer vulnerabilities and protections against the effects of adverse experience.[6] Research on G×E processes has implications for our understanding of risk and resilience because these studies have the potential to explain children's heterogeneous responses to adversity. Indeed, recent advances in our understanding and measurement of molecular genetic variations have ushered in a growing number of genetically informed investigations of risk and resilience in children's development.

Research Context

To date, research on G×E processes has focused on a relatively small but expanding number of genetic variations. Moreover, nearly all of the genetic markers investigated to date transcribe proteins that regulate the availability and functioning of neurotransmitters such as serotonin, dopamine, and norepinephrine. In this way, current G×E research has emphasized the idea that the effects of adverse experiences on later adaptation and functioning may be, at least partially, accounted for by neurobiological processes.[7,8]

Key Research Questions

Although children may experience many kinds of adversity, maltreatment is one that has been observed to overwhelm the child's adaptive capacities, therefore leading to a host of problematic developmental outcomes.[9,10] However, not all maltreated children develop maladaptively. Some abused and neglected youth function in a competent manner despite the pernicious experiences they have encountered. Recent investigations have begun to shed light on how G×E processes may account for the variability in outcomes associated with child maltreatment.[11-16]

Recent Research Results

In a groundbreaking study, Caspi and colleagues reported that a functional variation in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) moderated the consequences of child maltreatment on later antisocial behaviour.[11] More specifically, individuals who experienced maltreatment were at an increased risk for antisocial behaviour if their genotype conferred low levels of MAOA expression. There were no associations between MAOA genetic variation and antisocial behaviour in the absence of maltreatment. Thus, the

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combination of genetic vulnerability and childhood maltreatment posed the greatest risk for antisocial outcomes. In a second study, Caspi and colleagues observed that individuals carrying one or two copies of the less efficient version of a serotonin related genetic marker exhibited more depressive symptoms following childhood maltreatment compared to maltreated individuals with the more efficient version.[12] Once again, genetic variations were not associated with mental health outcomes among individuals who had not experienced maltreatment earlier in development.

Subsequent attempts to replicate these findings in independent samples have not produced a uniform body of evidence, thus sparking a debate about the magnitude and replicability of G×E effects for children's development.[17-20] However, consensus is building around the possibility that measurement issues play a critical role in researchers' ability to detect G×E effects.[21] For example, recent longitudinal studies that include prospectively collected information about child maltreatment have supported the hypotheses that MAOA and serotonin transporter genetic variations moderate the associations between child maltreatment and antisocial and depression outcomes, respectively.[13-16] For both developmental outcomes, the maladaptive consequences of child maltreatment are most pronounced among genetically susceptible individuals. These results have ushered in a wave of research interest in the possibility of G×E effects involving other child development outcomes and other types of stressors.[22] However, the findings from many of these studies have not yet been thoroughly replicated, so the prevalence of G×E effects for children's development remains uncertain.

One exciting new avenue for research on genetic contributions to risk and resilience is the possibility that children's genetic characteristics moderate the effectiveness of preventive interventions. For example, Bakermans-Kranenburg and colleagues reported that children's genotype moderated their responses to an intervention designed to reduce children's behaviour problems by training parents to provide responsive care and sensitive discipline.[23] Children who were randomly assigned to the intervention showed significant reductions in externalizing behaviour problems compared a control group only if they carried the less efficient version of a dopamine-related genetic marker. This finding, among others, points to the possibility that genotypic differences may contribute to children's differential responses to positive interventions as well as adversities.[24,25] Future research in this area may uncover avenues of tailoring prevention and intervention efforts to the needs of the individual.

Research Gaps

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Altogether, the studies of gene-by-environment interactions are beginning to shed light on genetic factors that might moderate the impact of early adverse experiences for children's behavioural and mental health. However, this is still a new research area and several gaps remain. First, many of the findings still await thorough replication. This is important because molecular genetic investigations have generally been difficult to replicate in both the biomedical and psychological sciences.[26,27] Corroborating evidence from diverse samples is vital to the development of empirically supported interventions and preventions. Second, it has been argued that some genetic variations confer increased susceptibility to all contextual influences, not only adversity.[22] According to this perspective, genetic variants formerly viewed as vulnerability factors may actually heighten susceptibility to positive environments as well. If confirmed, this would have far-reaching implications for our understanding of genetic contributions to risk or resilience.

Conclusions

Increased knowledge about the genome promises to elucidate how children's resilience in the face of adversity is shaped by the complex interplay between their genetic makeup and experiences. In particular, the research on gene-by-environment interactions indicates that genetic variations may not have direct associations with children's developmental outcomes but instead predispose individuals to be especially susceptible to the harmful effects of adversities such as child maltreatment. Although the available evidence is still limited in some respects, this area of research has already begun to enhance our understanding of children's heterogeneous responses to their experiences. Still, it is important to remember that the processes of resistance and recovery from adversity are shaped by multiple factors, not just the child's genetic makeup. As such, the risks associated with an individuals' genome or early childhood experiences may be buffered by experiences later in life.[28] Also, the interplay between genetic and environment factors involves more than just gene-by-environment interactions. Another type of interplay that is receiving increased attention among developmental researchers is the environmental regulation of genomic functioning, a phenomenon referred to as epigenetics.[29] Although research in this area is still in its infancy, investigations of epigenetic modification may shed light on neurobiological mechanisms by which early adverse experiences exert a detrimental influence on children's adaptation across the life-course.

Implications

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The hope for many involved in research on gene-environment interplay is that increased knowledge of genetic contributions to risk and resilience will eventually yield practical applications for prevention and intervention programs aimed at reducing the burden of mental illness and improving the quality of life for individuals in higher risk contexts. For example, genetic information could potentially be used to identify and selectively target individuals who are at the greatest risk for problematic outcomes. In addition, it may be possible in the future for intervention and prevention programs to customize their treatment protocols based on each individual's genotype. However, scientific understanding remains a long way from being able to make suggestions about how to tailor interventions to specific groups of children on the basis of genotype. Nonetheless, advances in our conceptual understanding of the factors (genetic and otherwise) that account for individuals' varied responses to their environments will provide clues for aiding efforts that treat the wide range of problems associated with childhood adversity.

References

1. Kim-Cohen J, Moffitt TE, Caspi A, Taylor A. Genetic and environmental processes in young children's resilience and vulnerability to socioeconomic deprivation. *Child Dev*. 2004;75(3):651-668.
2. Cicchetti D, Blender JA. A multiple levels of analysis perspective on resilience. *Ann N Y Acad Sci*. 2006;1094(1):248-258.
3. Gottlieb G. Probabilistic epigenesis. *Developmental science*. 2006;10(1):1-11.
4. Masten AS. Resilience in developing systems: Progress and promise as the fourth wave rises. *Dev Psychopathol*. 2007;19(3):921-930.
5. Sameroff A. A unified theory of development: A dialectic integration of nature and nurture. *Child Dev*. 2010;81(1):6-22.
6. Rutter M, Moffitt TE, Caspi A. Gene–environment interplay and psychopathology: Multiple varieties but real effects. *Journal of Child Psychology and Psychiatry*. 2005;47(3-4):226-261.
7. Cicchetti D. How a child builds a brain: Insights from normality and psychopathology. In: Hartup W, Weinberg RA, eds. *The Minnesota symposia on child psychology. Child psychology in retrospect and prospect: In celebration of the 75th anniversary of the Institute of Child Development. Volume 32*. Mahwah, NJ: Lawrence Erlbaum Associates Publishers; 2002:23-71.
8. Feder A, Nestler EJ, Charney DS. Psychobiology and molecular genetics of resilience. *Nature Reviews Neuroscience*. 2009;10(6):446-457.
9. Cicchetti D., Valentino. K. An ecological-transactional perspective on child maltreatment: Failure of the average expectable environment and its influence on child development. In: Cicchetti D, Cohen DJ, eds. *Developmental psychopathology. Volume three: Risk, disorder, and adaptation*. 2nd ed. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2006:129-201.
10. Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Child maltreatment 1: Burden and consequences of child maltreatment in high-income countries. *Lancet*. 2009;373(9657):68-81.
11. Caspi A, McClay J, Moffitt TE, et al. Role of genotype in the cycle of violence in maltreated children. *Science*. 2002;297(5582):851-854.

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12. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-389.

13. Cicchetti D, Rogosch FA, Thibodeau EL. The effects of child maltreatment on early signs of antisocial behavior: Genetic moderation by tryptophan hydroxylase, serotonin transporter, and monoamine oxidase A genes. *Dev Psychopathol*. 2012;24(3):907-928.

14. Kim-Cohen J, Caspi A, Taylor A, et al. MAOA, maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta-analysis. *Mol Psychiatry*. 2006;11(10):903-913.

15. Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: Evidence of genetic moderation.*Arch Gen Psychiatry*. 2011;68(5):444-454.

16. Cutuli J, Raby KL, Cicchetti D, Englund MM, Egeland B. Contributions of maltreatment and serotonin transporter genotype to depression in childhood, adolescence, and early adulthood. *J Affect Disord*. 2013;149(1-3):30-37.

17. Risch N, Herrell R, Lehner T, et al. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression. *JAMA: The journal of the American Medical Association*. 2009;301(23):2462-2471.

18. Uher R, McGuffin P. The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Mol Psychiatry*. 2010;15(1):18-22.

19. Munafò MR, Durrant C, Lewis G, Flint J. Gene× environment interactions at the serotonin transporter locus. *Biol Psychiatry*. 2009;65(3):211-219.

20. Rutter M, Thapar A, Pickles A. Gene-environment interactions: Biologically valid pathway or artifact? *Arch Gen Psychiatry* . 2009;66(12):1287-1289.

21. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: The case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry*. 2010;167:509-527.

22. Belsky J, Pluess M. Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychol Bull*. 2009;135(6):24.

23. Bakermans-Kranenburg MJ, Van IJzendoorn MH, Pijlman FTA, Mesman J, Juffer F. Experimental evidence for differential susceptibility: Dopamine D4 receptor polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. *Dev Psychol*. 2008;44(1):293.

24. Cicchetti D, Rogosch FA, Toth SL. The effects of child maltreatment and polymorphisms of the serotonin transporter and dopamine D4 receptor genes on infant attachment and intervention efficacy. *Development and Psychopathology*. 2011;23:357-372.

25. van IJzendoorn MH, Bakermans-Kranenburg MJ. Differential susceptibility experiments: Going beyond correlational evidence--comment on beyond mental health, differential susceptibility articles. *Dev Psychol*. 2012;48(3):769-774.

26. Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry*. 2011;168(10):1041-1049.

27. Ioannidis J. Genetic associations: False or true? *Trends Mol Med*. 2003;9(4):135-138.

28. Kaufman J, Yang B, Douglas-Palumberi H, et al. Brain-derived neurotrophic factor–5-HTTLPR gene interactions and environmental modifiers of depression in children. *Biol Psychiatry*. 2006;59(8):673-680.

29. Meaney MJ. Epigenetics and the biological definition of gene× environment interactions. *Child Dev*. 2010;81(1):41-79.

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