Epigenetic Embedding of Early Adversity and Developmental Risk

Marla B. Sokolowski, PhD, F.R.S.C., W. Thomas Boyce, MD

Co directors of the Child and Brain Development Program, Canadian Institute for Advanced Research (CIFAR), Canada

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Introduction

There is a substantial body of evidence that adversity in early life can lead to epigenetic changes associated with increased risk for disturbances of childhood mental health, more disordered developmental trajectories, poorer educational achievements, and lifelong risks of chronic disorders of health and well-being.[1,2,3]

This report describes evidence that the embedding of adversity-related epigenetic marks is associated with increased susceptibility to compromised development and mental health, and reviews recent research findings about specific disorders in both animal and human studies.[4]

Subject

Genes are long stretches of DNA sequence. Epigenetics processes mark or 'tag' genes without modifying the underlying genetic sequence of DNA. In some cases, these epigenetics marks affect gene expression, the level, timing and place where a gene product is expressed during development. Adverse environments of poverty, neglect and trauma affect the expression of genes involved in the development and regulation of the nervous system in children, which in turn guide brain development, calibrate stress responses and influence lifelong risk of developing mental illnesses and other challenges. Similarly, positive early environments of nurturance, care and stability can affect gene expression, leading to decreased risk for mental health issues and optimized brain preparation for learning and normal social and emotional development.

Problem

Some children show immediate and long-term deficits in health and development in response to adverse environmental conditions, while others thrive and survive without negative consequences.[4,5] By understanding

how genes and the environment interact, it may be possible to identify children at risk and prevent or even reverse negative outcomes through positive environmental interventions or novel drug therapies.

Research Context

Research is shedding light on how individual differences in epigenetic susceptibility relate to how children are affected by harmful stress. Understanding these differences may explain stress-related disorders, shed light on sources of personal resilience and vulnerability and help explain why health issues do not affect all people.

Recent Research Results

Experimental animal studies and human observational studies have found reliable relationships between conditions of early adversity and epigenetic changes to genes associated with stress responses, immunity and the development of mental disorders.[6]

Experimental animal study findings

In a set of transformative studies, researchers used naturally occurring differences in mother rats to illustrate the effect of early maternal care on genes that determine stress responses in their pups. There are two kinds of mother rats: those that lick and groom their pups a lot; and those that do not. In the studies, pups that received lower levels of licking and grooming showed: decreased expression of the genes responsible for regulating stress; increased activity of the gene that controls release of the stress hormone cortisol; and greater activation of the hypothalamic-pituitary-adrenal (HPA) axis, a complex network of interactions between endocrine glands that produce hormones that regulate stress, mood, sexuality, digestion, the immune system and energy storage.[7,8]

Other rodent studies have shown a variety of relationships between early exposures to deprivation, maltreatment and adversity, epigenetic modifications and the development of psychological impairment. In one study, early infant maltreatment was linked to decreased expression of the genes responsible for regulating serotonin, the neurotransmitter that maintains mood balance.[9] In another study, chronic, variable stress during the first trimester of pregnancy in mother rats resulted in heightened expression of stress hormones and increased “depressive” behaviour in their babies, associations that were offset in part by sex-specific differences in epigenetic processes in specific genes.[10] Researchers have also conducted experiments where various epigenetic processes affected the effects of early life stress on adult neurodevelopment in rats.[11]

In non-human primate studies, there is additional evidence of epigenetic modifications in situations of early social adversity. In studies of rhesus macaques, social dominance rankings and rearing conditions were associated with different levels of epigenetic marking in prefrontal cortical neurons (nerve cells in the part of the brain responsible for emotions and judgment) and T lymphocytes (a type of white blood cell involved with immunity).[12,13] Another group of researchers found that infant macaques raised by peers showed increased gene expression for inflammatory processes and suppression of genes involved with antimicrobial defenses.[14] Finally, in a study of bonnet macaques, youngsters that were randomly assigned to an early, stressful condition for finding food showed greater behavioural stress and enhanced epigenetic modifications in the serotonin transporter gene (the gene that regulates the movement of serotonin, a brain chemical responsible for

regulating many body processes, including memory, learning, appetite and mood) and across their whole genomes.[15]

Observational human study findings

In an early observational example, children whose parents were exposed to famine and adversity during the Dutch Winter Hunger of 1944-45 showed a decreased activation of IGF2, the insulin-like growth factor II gene, which has an important role in growth and development.[16] These children had a notably higher risk for metabolic diseases later in life.[17]

Multiple other studies have found heightened, adversity-related epigenetic changes in children. Institutionalized children ages 7-10 years showed whole genome changes compared to children raised by parents.[18] Infants born to mothers with high levels of depressive symptoms during the third trimester of pregnancy showed increased epigenetic marking of NR3C1, an important glucocorticoid receptor (GR) gene related to development, metabolism and immune response.[19] Adolescents whose mothers had been exposed to intimate partner violence during pregnancy showed epigenetic modifications in leukocytes, the white blood cells that fight diseases.[20] Early adolescents who had been physically abused showed increased epigenetic marking of the GR gene compared to peer controls.[21] Similar evidence of epigenetic modifications has been found in studies of brain tissue from suicide victims with a history of child abuse.[22,23] Bullied monozygotic twins showed more extensive epigenetic marking on the serotonin transporter gene compared to their non-bullied co-twins.[24] Finally, other studies have reported that parental loss, maltreatment, and impaired parental care were associated with epigenetic marking of GR.[25]

Evidence from a variety of studies suggests that underlying epigenetic modifications drive many changes in brain circuitry. Stress-related psychiatric conditions, such as suicidal ideation and attempts,[26] depression,[27] post-traumatic stress disorder,[28] schizophrenia[29] and brain changes due to psychoactive and antipsychotic drugs have been noted to induce epigenetic changes.[27] Genome-wide observational research has detected long-term associations between childhood disadvantage and genome-wide epigenetic marking in mid-life, between parental stress in infancy and increased epigenetic marking in adolescence, and between early socioeconomic status and elevated transcription of genes responsible for immune responses.[30,31,32,33]

Individual variation in epigenetic susceptibility

A substantial body of recent research shows that there is a subset of fragile children, called ‘orchid children,’ who are more sensitive to both negative and positive environmental factors than their more resilient counterparts, called ‘dandelion children.[34,35,36,37] Orchid children show either the most maladaptive or the most positive outcomes, depending on the character of their social environments. In negative environments, orchid children have a heightened risk for developmental disorders, but in positive, supportive environments, they can thrive impressively and outperform less-susceptible peers. Dandelion children, on the other hand, are hardy and thrive in any situation, but do not ‘bloom’ as beautifully as orchid children.

Research Gaps

While there are a growing number of experimental animal studies and observational human studies showing

heightened epigenetic marking when adversity is present in early developmental stages, the findings are not uniform and often, the differences are quite modest. Some findings seem to contradict others, and this might be due to confounding factors, such as the proportions of different cell types measured in peripheral blood on which the epigenetic analysis is performed.[38]

Adversity-related epigenetic modification may actually be highly specific and depend on the type and timing of the adversity.[39] Further, an important question is whether epigenetic modifications are acquired as a consequence of early environmental conditions or linked to underlying susceptibilities. Furthermore, human studies are correlational and don't reflect a causal relationship between adversity, epigenetic marks and behavioural and health outcomes. Future studies that address causation in animal models and humans are required.

Conclusions

There is increasing evidence that adverse conditions in early childhood affect the number and placement of epigenetic marks on the DNA sequence. The developmental and health effects of early exposures to adversity and stress are socioeconomically partitioned, with children from the lower ranks of social class sustaining greater and more severe threats to normative development. Epigenetic processes that affect gene expression almost certainly have an impact on adversity-related, maladaptive outcomes.

Implications

Adverse early childhood experiences can leave lasting marks on genes that are involved with stress responses, immunity and mental health, underscoring the importance of creating an optimal early childhood environment for each and every child.

References

1. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *Journal of the American Medical Association* 2009;301(21):2252-2259.
2. Hertzman C, Boyce WT. How experience gets under the skin to create gradients in developmental health. *Annual Review of Public Health* 2010;31:329-347.
3. Boyce WT, Sokolowski MB, Robinson GE. Toward a new biology of social adversity. *Proceedings of the National Academy of Sciences, USA* 2012;109(Suppl. 2):17143-17148.
4. Rutter M. Resilience as a dynamic concept. *Development and Psychopathology* 2012;24(2):335-344.
5. Masten AS. Global perspectives on resilience in children and youth. *Child Development* 2014;85(1):6-20.
6. Monk C, Spicer J, Champagne FA. Linking prenatal maternal adversity to developmental outcomes in infants: the role of epigenetic pathways. *Development and Psychopathology* 2012;24(4):1361-1376.
7. Weaver IC, Diorio J, Seckl JR, Szyf M, Meaney MJ. Early environmental regulation of hippocampal glucocorticoid receptor gene expression: characterization of intracellular mediators and potential genomic target sites. *Annals of the New York Academy of Sciences* 2004;1024:182-212.
8. Meaney M.J. Epigenetics and the biological definition of gene 9 environment interactions. *Child Development* 2010;81(1):41-79.
9. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biological Psychiatry* 2009;65(9):760-769.
10. Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. *Journal of Neuroscience* 2008;28(36):9055-9065.
11. Korosi A, Naninck EF, Oomen CA, Schouten M, Krugers H, Fitzsimons C, Lucassen PJ. Early-life stress mediated modulation of adult

neurogenesis and behavior. *Behavioural Brain Research* 2012;227(2):400-409.

12. Provencal N, Suderman MJ, Guillemin C, Massart R, Ruggiero A, et al. The signature of maternal rearing in the methylome in rhesus macaque prefrontal cortex and T cells. *Journal of Neuroscience* 2012;32(44):15626-15642.
13. Tung J, Barreiro LB, Johnson ZP, Hansen KD, Michopoulos V, Toufexis D, Michelini K, Wilson ME, Gilad Y. Social environment is associated with gene regulatory variation in the rhesus macaque immune system. *Proceedings of the National Academy of Sciences, USA* 2012;109(17):6490-6495.
14. Cole SW, Conti G, Arevalo JM, Ruggiero AM, Heckman JJ, Suomi SJ. Transcriptional modulation of the developing immune system by early life social adversity. *Proceedings of the National Academy of Sciences, USA* 2012;109(50):20578-20583.
15. Kinnally EL, Feinberg C, Kim D, Ferguson K, Leibel R, Coplan JD, John Mann J. DNA methylation as a risk factor in the effects of early life stress. *Brain, Behavior, and Immunity* 2011;25(8):1548-1553.
16. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proceedings of the National Academy of Sciences, USA* 2008;105(44):17046-17049.
17. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, Slagboom PE, Heijmans BT. DNA methylation differences after exposure to prenatal famine are common and timing-and sex-specific. *Human Molecular Genetics* 2009;18(21):4046-4053.
18. Naumova OY, Lee M, Koposov R, Szyf M, Dozier M, Grigorenko EL. Differential patterns of whole-genome DNA methylation in institutionalized children and children raised by their biological parents. *Development and Psychopathology* 2012;24(1):143-155.
19. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress response. *Epigenetics* 2008;3(2):97-106.
20. Radtke KM, Ruf M, Gunter HM, Dohrmann K, Schauer M, Meyer A, Elbert T. Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. *Translational Psychiatry* 2011;1:e21.
21. Romens SE, McDonald J, Svaren J, Pollak SD. Associations between early life stress and gene methylation in children. *Child Development* 2015;86(1):303-309.
22. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience* 2009;12(3):342-348.
23. Sasaki A, de Vega WC, McGowan PO. Biological embedding in mental health: an epigenomic perspective. *Biochemistry and Cell Biology* 2013;91(1):14-21.
24. Ouellet-Morin I, Wong CC, Danese A, Pariante CM, Papadopoulos AS, Mill J, Arseneault L. Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: a longitudinal study of discordant monozygotic twins. *Psychological Medicine* 2013;43(9):1813-1823.
25. Tyrka AR, Price LH, Marsit C, Walters OC, Carpenter LL. Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: preliminary findings in healthy adults. *PLoS One* 2012;7(1):e30148.
26. Murphy TM, Mullins N, Ryan M, Foster T, Kelly C, et al. Genetic variation in DNMT3B and increased global DNA methylation is associated with suicide attempts in psychiatric patients. *Genes, Brain, and Behavior* 2013;12(1):125-132.
27. Olsson CA, Foley DL, Parkinson-Bates M, Byrnes G, McKenzie M, et al. Prospects for epigenetic research within cohort studies of psychological disorder: a pilot investigation of a peripheral cell marker of epigenetic risk for depression. *Biological Psychology* 2010;83(2):159-165.
28. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, et al. Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proceedings of the National Academy of Sciences, USA* 2013;110(20):8302-8307.
29. Tsankova N, Renthal W, Kumar A, Nestler EJ. Epigenetic regulation in psychiatric disorders. *Nature Reviews Neuroscience* 2007;8(5):355-367.
30. Borghol N, Suderman M, McArdle W, Racine A, Hallett M, et al. Associations with early life socio-economic position in adult DNA methylation. *International Journal of Epidemiology* 2012;41(1):62-74.
31. Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, et al. Epigenetic vestiges of early developmental adversity: childhood stress exposure and DNA methylation in adolescence. *Child Development* 2013;84(1):58-75.
32. Lam LL, Emberly E, Fraser HB, Neumann SM, Chen E, et al. Factors underlying variable DNA methylation in a human community cohort. *Proceedings of the National Academy of Sciences, USA* 2012;109(Suppl. 2):17253-17260.
33. Powell ND, Sloan EK, Bailey MT, Arevalo JM, Miller GE, et al. Social stress up-regulates inflammatorygene expression in the leukocyte transcriptome via beta-adrenergic induction of myelopoiesis. *Proceedings of the National Academy of Sciences, USA* 2013;110(41):16574-16579.
34. Boyce WT, Chesney M, Alkon-Leonard A, Tschann J, Adams S, et al. Psychobiologic reactivity to stress and childhood respiratory illnesses:

results of two prospective studies. *Psychosomatic Medicine* 1995;57:411-422.

35. Belsky J. Differential susceptibility to rearing influence: an evolutionary hypothesis and some evidence. In: Ellis BJ, Bjorklund DF, eds. *Origins of the social mind: Evolutionary psychology and child development.* New York: Guilford; 2005:139-163
36. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology* 2005;17(2):271-301.
37. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary-neurodevelopmental theory. *Development and Psychopathology* 2011;23(1):7-28.
38. Witzmann SR, Turner JD, Meriaux SB, Meijer OC, Muller CP. Epigenetic regulation of the glucocorticoid receptor promoter 1(7) in adult rats. *Epigenetics* 2012;7(11):1290-1301.
39. Klengel T, Pape J, Binder EB, Mehta D. The role of DNA methylation in stress-related psychiatric disorders. *Neuropharmacology* 2014;80:115-132.