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Table of content

Synthesis 5

Biology of the Epigenome 8
MARLA B. SOKOLOWSKI, PHD, F.R.S.C., W. THOMAS BOYCE, MD, NOVEMBER 2017

Gene-Environment Interplay and Epigenetic Processes 14
MARLA B. SOKOLOWSKI, PHD, F.R.S.C., W. THOMAS BOYCE, MD, NOVEMBER 2017

Epigenetic Embedding of Early Adversity and Developmental Risk 20
MARLA B. SOKOLOWSKI, PHD, F.R.S.C., W. THOMAS BOYCE, MD, NOVEMBER 2017

Epigenetics and the Role of Developmental Time 27
MARLA B. SOKOLOWSKI, PHD, F.R.S.C., W. THOMAS BOYCE, MD, NOVEMBER 2017

Epigenetics: comments on Sokolowski and Boyce 32
JEFFREY M. CRAIG, PHD, MAY 2018

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Synthesis

How important is it?

Behavioural or social epigenetics is a new science poised to revolutionize our understanding of how we develop. Genetics is the study of how characteristics are inherited from one generation to the next through DNA. Epi comes from the Greek word meaning upon or over. Epigenetic processes place marks on or nearby DNA; some of these marks can change the amount of gene product (RNA, protein) a gene makes.

Epigenetics is thought to regulate how the brain develops and how it works. Both are critical for our learning, behaviour and health.

One of the central purposes of behavioural epigenetics is to understand how epigenetic marks can change gene expression, and, in turn, the path (trajectory) of development—physical, social and emotional, approaches to learning, thinking, and communication and language. Changes to how we develop can range from being adaptive (positive and functional) to maladaptive (negative and dysfunctional).

Epigenetic changes triggered by adverse childhood experiences (ACEs) are typically maladaptive. These changes can happen from the earliest stages of life, throughout childhood and into adulthood. They occur in our cells and can have a profound effect on lifelong mental and physical health.

Recent studies link child abuse, neglect and ongoing stress to antisocial behaviour, depression and the risk of suicide. Other evidence has found ACEs can increase the risk of mental illness, poorer educational achievements and chronic disease. More research is needed to determine if some epigenetic changes can be passed to future offspring.

By uncovering how our genes (DNA sequence) and our environment (experiences) affect each other, behavioural epigenetics promises to reveal their effect on an individual’s development, behaviour and well-being. Researchers also want to determine if it is possible to identify children at risk and if negative outcomes can be prevented or reversed through positive interventions or drug therapies.

What do we know?

Environment and experiences affect our genes and development.

In children, caring, stable and nurturing environments help build a strong foundation for brain development, lifelong health, learning and normal social and emotional development. At the heart of these environments are caring, stable and nurturing relationships with adults: parents, grandparents, childcare providers, teachers and more.

Similarly, adverse environments and relationships with adults that include poverty, abuse, neglect, stress, and trauma can also change the expression of genes involved in developing and regulating the nervous system. In turn, this can negatively affect a child's brain development, stress responses and the risk of developing illnesses and other challenges. The risks and effects of adverse childhood experiences are highest among those living near, at or below the poverty line.

While many molecular mechanisms control gene expression, epigenetic processes offer a groundbreaking look at how and under what social conditions genes and environment intersect.

Evidence from a variety of studies suggests that epigenetic modifications drive many changes in brain circuitry. For example, stress-related psychiatric conditions, such as suicidal ideation and attempts, depression, post-traumatic stress disorder, schizophrenia and brain changes due to psychoactive and antipsychotic drugs, have induced epigenetic changes.

A growing body of evidence indicates that the number of genetic marks on DNA sequences increases with number of adverse childhood experiences (ACEs) a child has.

Research is also shedding light on how differences in epigenetic susceptibility affect children exposed to harmful stress. Such understanding may offer insight into stress-related disorders, resilience, vulnerability and why health issues affect people differently.

Behavioural epigenetic research is gaining a greater understanding of the periods of development. Critical periods are those in which the presence or absence of important experiences or exposures can change the development of brain circuitry. Sensitive periods are developmental intervals when the brain is especially responsive to experiences and thought to gradually open and gradually close. Both depend on experiences for brain plasticity during

defined windows of early life.

The brain is fragile as it develops. Molecular ‘triggers’ and ‘brakes’ can open and close opportunities for brain plasticity over time. These and other findings have fundamentally shifted thinking about brain plasticity.

A newer understanding indicates that the brain is naturally plastic and during normal development plasticity is suppressed except when critical periods are open. These periods can be thought of as ‘windows’ of opportunity during which the brain is sculpted by experience. Critical and sensitive periods open and close as the brain’s circuitry is established.

Epigenetic processes may also transmit risk and disorder from one generation to the next, although more research is needed in this area. Risks and protective factors can be passed from parents to children through behavioural and social factors, or possibly by inherited epigenetic marks.

What can be done?

More research into epigenetics is needed, but it is clear that adverse childhood experiences can affect the genes that are involved with stress responses, immunity and mental and physical health. It’s important for each and every child to live in a caring, stable and nurturing environment and to have similar relationships with adults.

Biology of the Epigenome

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Introduction

The new scientific field of behavioural or social epigenetics is poised to revolutionize our understanding of human development. We describe the biology of the epigenome and recent findings on epigenetic processes that affect gene expression as early as the embryonic stage of human development.

Subject

DNA lies deep within the nuclei of cells, like books on a library shelf waiting to be opened, read and transcribed to reveal the instructions used to make the substances of life our bodies require.[1] The word ‘epigenetics’ consists of the word ‘genetics’ and the Greek root epi, which means upon or over. There are a number of different types of epigenetic mechanisms. These include DNA methylation, histone modification and the regulation of gene expression by small RNA molecules that do not code for proteins (ncRNA). The science of epigenetics looks at processes that mark DNA and can change gene expression without modifying the underlying genetic sequence of the DNA.[2] Epigenetics has a long history in development research. Its contributions to gene regulation are known to play a role in the differentiation of cells into distinctive cell types during embryonic development.[3]

Problem

One of the goals of research in the field is to understand how changes in the epigenome can contribute to the developmental path (trajectory) that a child is on. These developmental trajectories can range from being adaptive to maladaptive. Epigenetic modifications can have consequences for child well-being including cognition and social emotional development as well as mental and physical health.

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Context

The term ‘epigenetics’ was used in 1869 by the French biologist-anthropologist Armand de Quatrefages who wrote: “Nowadays I admit, with everybody, the doctrine of epigenesis. Every normal egg which gives birth to an abnormal individual is influenced by external agents whatever they are; this is what I call action of the milieu.”[4] Epigenetics was then used in a developmental context by Conrad Waddington where he suggested that the development of the embryo unfolded through what he termed an “epigenetic landscape”.[5] His model illustrated the developmental pathways that an undifferentiated cell might take toward its differentiation (becoming for example a brain or liver cell). In his metaphor there are number of balls (cells) rolling down a hill. Individual balls slow down in the grooves on the slope, and come to rest at the lowest points. These lowest points are the tissue types-each cell eventual becomes, its cell fate. The shape of the landscape (the contours of the hill) is a consequence of the interactions between the embryo’s genes and the environment. The metaphor revealed how gene regulation modulates development. Although knowledge of molecular biology and gene-environment interplay was lacking in Waddington’s time, his insights are still relevant today. Recent epigenetic research has identified the molecular processes involved in development and cellular differentiation.

After cell differentiation, many more changes occur in pre and postnatal development that involve the interplay between genes and the environment. A new field of epigenetic of Behavioural or Social Epigenetics focuses on how our experiences get embedded into our biology.[6]

Recent Research Results

Epigenetic processes

Three epigenetic processes are described here that alter gene expression. The first, DNA methylation, is most highly studied in mammals. DNA methylation operates as a structural overlay on the DNA. It adds a mark to the DNA and depending on where it is situated on the DNA sequence it can change gene expression, the amount of messenger RNA (mRNA) that the gene makes. Gene regulation is also important for determining which genes are expressed at which times and locations in the developing organism. Scientists have recently discovered that DNA methylation is reversible.[7]

The second process is histone modification. Histones are proteins that serve to wind DNA strands into bundled units like beads on a necklace. Reversible chemical tags can modify specific sections of histone proteins, causing the DNA packaging to relax, allowing genes to be more readily transcribed and expressed, or to constrict, making gene transcription and expression more difficult. Scientists have recently proposed a working theory about a 'histone language,' where different combinations of histone modifications may be responsible for driving certain processes associated with the storage and retrieval of memories, and behaviours associated with cognitive impairment, schizophrenia and depression.[8,9] Of interest, some recent research has demonstrated that it is possible to reverse brain changes due to histone modification of a specific gene known to be related to chronic stress with an antidepressant medication.[10]

mRNA molecules are responsible for conveying DNA instructions for the manufacture of proteins. A third, newly discovered epigenetic process involves small, non-coding RNAs (ncRNAs) that interfere with the expression of specific genes by encouraging the compaction of DNA or by causing transcribed messenger RNA to degrade.[11] These ncRNA molecules have been discovered in plentiful numbers in the brain. Epigenetic marking processes by ncRNAs have been linked to several disorders of cognition and behaviour, for example, Fragile X syndrome.

These three epigenetic processes — DNA methylation, histone modification and ncRNAs — do not operate entirely independently. Recent research has found that DNA methylation encourages other substances to come to the site that decrease histone modification, and the two processes then work together to impede gene transcription. Histone modification can also suppress nearby DNA methylation. Further, small ncRNAs and DNA methylation can also influence each other's presence and effects.[12]

Epigenetic differentiation of cells in embryogenesis

Early embryonic development depends on critical epigenetic programming that occurs within the earliest stages of cell differentiation and development.[13] Before fertilization occurs, an egg and a sperm cell both undergo extensive and complex epigenetic remodeling processes.[14] Epigenetic modifications that mark the genes of a sperm or egg cell can result in only one parental gene copy being expressed and this impact has been observed across nearly 400 human genes. After conception, a further, highly regulated epigenetic calibration process takes place, affecting the expression of about 20,000-25,000 genes responsible for coding proteins.[2]

Research Gaps

Neurodevelopment, dynamic variation and an epigenetics

Brain development in mammals requires a precisely coordinated sequence of gene regulation events, some of which are epigenetic, in order to produce and spatially locate neurons and glial cells.[2] Epigenetic regulation in the brain can also influence a variety of complex neural functions, such as memory formation, learning and the calibration of stress response circuitry.[15] The causal mechanisms involved in the relationships between epigenetic marks, how the brain develops and functions remain to be elucidated.

Widespread and regionalized shifts in DNA methylation and histone modifications have been shown to take place with key phases of normal brain development[16,17] and with specific disorders of development and mental health.[18,19,20] DNA methylation, histone modifications and ncRNAs may explain differences in susceptibility to various forms of psychopathology between males and females.[21,22] Scientists have also found a correlation between distinctive epigenetic marks within hundreds of gene loci among patients with autism spectrum disorder and other neurodevelopmental syndromes.[23,24] Epigenetic processes may also explain why Down syndrome children do not show an expected 50 per cent greater expression of the triplication of chromosome,[21] indicating that co-occurring cognitive deficits might be due to epigenetic processes and therefore, be potentially modifiable with targeted drug interventions.

Research challenges

There are significant challenges for scientists studying the human epigenome. Epigenetic marks are most often not associated with changes in gene expression. Changes in gene expression can arise from many mechanisms only some of which involve epigenetic modifications. The epigenome can activate or deactivate genes in response to environmental signals and conditions. Different tissue types have different epigenetic profiles, so conclusions cannot be drawn reliably from one type to another. For example, epigenetic states in brain cells are not the same as those found in epithelial cheek cells. Some tissue types like brain tissue are only available on a post-mortem basis, so large-scale studies must rely on surrogate tissue. Most animal and human studies of the relationship between the epigenome and experience show correlation rather than causation; new research must aim to take these correlations to the level of causations. Since it has been easier to focus on studying DNA methylation to date, there is still much to discover

about the functions of other epigenetic marking processes.

Conclusions

The epigenome can alter the expression of genes without changing the underlying DNA sequence and is responsible for cell differentiation in early embryonic development. Experiences and environmental exposures, especially those early in life, can result in the placement or removal of epigenetic marks, which is thought to regulate the neurodevelopment that underlies learning, behaviour and risks for compromised mental health.

Implications

Given recent discoveries that some epigenetic processes are reversible and demonstrate potential mechanisms of developmental plasticity,[7] scientists are working on targeted drugs for the treatment of chronic stress,[9] cancer, neurological and psychiatric disorders.[24]

References

1. Champagne FA, Mashoodh R. Genes in Context: Gene-Environment Interplay and the Origins of Individual Differences in Behaviour. *Current Directions in Psychological Science* 2009;18(3):127-131.
2. Meaney MJ. Epigenetics and the biological definition of gene x environment interactions. *Child Development* 2010;81(1):41-79.
3. Waddington CH. Genetic assimilation. *Advances in Genetics* 1961;10:257-290.
4. Quatrefages A. Débats du 16 juillet 1863 de la Société d'Anthropologie de Paris. *Bulletins et mémoires de la Société d'Anthropologie de Paris* 1863;4:378-383.
5. Waddington CH. Canalization of development and the inheritance of acquired characters. *Nature* 1942;150(3811):563-565.
6. Boyce WT, Robinson GE, Sokolowski MB. Toward a new biology of social adversity. *Proceedings of the National Academy of Sciences* 2012;109(Suppl 2):17143-17148.
7. Wu H, Zhang Y. Reversing DNA methylation: mechanisms, genomics, and biological functions. *Cell* 2014;156(1-2):45-68.
8. Strahl BD, Allis CD. The language of covalent histone modifications. *Nature* 2000;403(6765):41-45.
9. Bridi M, Abel T. Histone modifications in the nervous system and neuropsychiatric disorders. In: Sweatt JD, Meaney M, Nestler EJ, Akbarian S, eds. *Epigenetic regulation in the nervous system: Basic mechanisms and clinical impact*. London: Elsevier; 2013:35-67.
10. Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *Journal of Neuroscience* 2002;22(8):3251-3261.
11. Mattick JS. RNA as the substrate for epigenome– environment interactions: RNA guidance of epigenetic processes and the expansion of RNA editing in animals underpins development, phenotypic plasticity, learning, and cognition. *Bioessays* 2010;32(7):548-552.

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12. Klengel T, Pape J, Binder EB, Mehta D. The role of DNA methylation in stress-related psychiatric disorders. *Neuropharmacology* 2014;80:115-132.

13. Smith ZD, Meissner A. DNA methylation: roles in mammalian development. *Nature Reviews Genetics* 2013;4(3):204-220.

14. Strachan T, Read A. *Human molecular genetics*. New York: Garland; 2011.

15. Lister R, Mukameld EA, Nery JR, Urich M, Puddifoot CA, et al. Global epigenomic reconfiguration during mammalian brain development. *Science* 2013;341(6146):1237905.

16. Shulha HP, Cheung I, Guo Y, Akbarian S, Weng Z. Coordinated cell type-specific epigenetic remodeling in prefrontal cortex begins before birth and continues into early adulthood. *PLoS Genetics* 2013;9(4):e1003433.

17. Champagne FA. Early adversity and developmental outcomes: interaction between genetics, epigenetics, and social experiences across the life span. *Perspectives on Psychological Science* 2010;5(5):564-574.

18. Toyokawa S, Uddin M, Koenen KC, Galea S. How does the social environment 'get into the mind'? Epigenetics at the intersection of social and psychiatric epidemiology. *Social Science & Medicine* 2012;74(1):67-74.

19. Kofink D, Boks MP, Timmers HT, Kas MJ. Epigenetic dynamics in psychiatric disorders: environmental programming of neurodevelopmental processes. *Neuroscience and Biobehavioral Reviews* 2013;37:831-845.

20. Qureshi IA, Mehler MF. Genetic and epigenetic underpinnings of sex differences in the brain and in neurological and psychiatric disease susceptibility. *Progress in Brain Research* 2010;s186:77-95.

21. Hodes GE. Sex, stress, and epigenetics: regulation of behavior in animal models of mood disorders. *Biology of Sex Differences* 2013;4(1):1.

22. Shulha HP, Cheung I, Whittle C, Wang J, Virgil D, et al. Epigenetic signatures of autism: trimethylated H3K4 landscapes in prefrontal neurons. *Archives of General Psychiatry* 2012;69(3):314-324.

23. Berko ER, Suzuki M, Beren F, Lemetre C, Alaimo CM, et al. Mosaic epigenetic dysregulation of ectodermal cells in autism spectrum disorder. PLoS Genetics 2014; 10(5):e1004402.

24. Bojang P Jr, Ramos KS. The promise and failures of epigenetic therapies for cancer treatment. *Cancer Treatment Reviews* 2014;40(1):153-169.

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Gene-Environment Interplay and Epigenetic Processes

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Introduction

By uncovering how genes and the environment affect each other at the molecular level, epigenetics promises to unveil how individual susceptibility and social conditions work together to affect individual differences in development, behaviour and child well-being. There is increasing evidence demonstrating that interactions between genetic predispositions and early life adversity are related to the emergence of neurodevelopmental health issues.

This report describes different domains of gene-environment interplay and reviews recent research findings from observational and population studies in humans, and experimental studies in monkeys.

Subject

There are at least three categories of processes where interactions between genes/gene expression and the environment lead to differences in development trajectories that affect mental health and well-being. First, there is a correlation between genes and the environment, where a child has a genetic predisposition (an increased chance) of selecting, altering or generating categories of experience, for example, a child with behavioural inhibitions has a tendency to choose less challenging or less intensive social environments. Second, genes and the environment can affect each other bidirectionally. For example, there are cases where genetic variations only become apparent in the presence of specific environmental conditions, and alternatively, there are examples where environmental influences are revealed only among individuals carrying a particular genetic variant (genotype). The third category of interaction involves epigenetic processes where environmental signals mark or tag DNA and in some cases this can alter gene transcription and expression. These processes are discussed in greater detail in the first article of this chapter.[2]

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The exploration of these three domains of gene-environment interplay has become a prolific and engaging area of biomedical and social science research that promises to illuminate one of the deepest mysteries of human experience — how individual susceptibility and social conditions work together at the behavioural, physiologic, neural, cellular and molecular levels to initiate and sustain individual differences in development, behaviour and health, in some cases lead to disorders.

Problem

Many molecular mechanisms control gene expression. Groundbreaking research seeks to reveal how epigenetics is involved in the interplay between genes/gene expression and the environment and the consequences for brain development, behaviour and well-being.

Research Context

Though suspected for a long time, it was only about a decade ago that reports appeared showing that epigenetic processes are associated with long-term human developmental and health outcomes. Studies in 2002 and 2003 revealed statistical links between early environmental conditions such as child maltreatment and stressful life events and the genetic variant one carries to predict antisocial behaviour and depression and the risk of suicide.[3,4]

As the body of research has grown in size and data from a number of studies have been reviewed together in meta-analyses, researchers have found strong evidence for these interactions. For example, a 2010 review of more than 40 studies about gene-environment interactions involving the serotonin transporter gene revealed strong links to sensitivity towards negative and stressful environments,[5] and a 2011 review of 54 studies found strong evidence that the serotonin transporter gene 5HTTLPR is involved in moderating the association between stress and depression.[6]

Recent Research Results

New evidence continues to build, demonstrating that environmental interactions with genes have an impact on early human neurodevelopment.

Observational Research

One group of researchers recently reported an interaction between mothers' dopamine receptor gene, DRD4, and reports of prenatal stress with predicting their children's risk for developing antisocial outcomes such as conduct disorder or oppositional defiant disorder in early adolescence.[7] In another study, researchers with the Bucharest Early Intervention Project (http://www.bucharestearlyinterventionproject.org/) identified a gene-environment interaction in children who remained institutionalized and were carriers of gene variants responsible for maintaining appropriate levels of two brain transmitters, dopamine and norepinephrine. Depletion of these neurotransmitters has been implicated in the risk for major depression. In another study, the early adversity of mothers as measured using a childhood trauma questionnaire interacted with the genetic variant they carried in the PRKG1 gene to affect maternal sensitivity to her infant. One variant buffered these mothers from earlier adversity while the other did not. This gene by environment interaction was replicated in two cohorts.[8] Finally, researchers examined data from twins in the Early Childhood Longitudinal Study (https://nces.ed.gov/ecls/) and found that genetic variation contributed in cognitive ability but was dependent on reciprocal, developmentally moderated interactions between children and their environment, and that children who were being raised in higher socioeconomic status homes were showing significantly higher scores by the age of 2 years.

In studies involving rhesus macaques, researchers demonstrated that early rearing conditions with either mother or peer-related groups interacted with the serotonin transporter gene. That interaction had an observable, predictable impact on the manufacture of stress hormones during times of separation stress.[9] Further, the interaction appeared to apply even among normal monkeys, where social dominance status during development worked together with the serotonin transporter gene and could predict the timing of sexual maturation: subordinate female monkeys who carried at least one copy of the altered promoter gene had significant delays in sexual maturation.[10]

Epigenetic processes at the population level

One of the most intriguing recent discoveries is that epigenetic processes can influence the development of specific populations of people. For example, the maltreatment of children has been linked to faulty regulation of the hypothalamic-pituitary-adrenal (HPA) axis,[11] a complex set of interactions between endocrine glands that produce hormones to regulate many body processes including stress, mood, sexuality, digestion, the immune system and energy storage, to increased inflammatory signaling[12] and long-term changes in stress-responsive neural structures.

[13]

A study of over 200 newborns in Singapore found that there were over 1,400 genomic regions with wide variation in the state of epigenetic tagging across individuals, and that 75% of the measured variability in DNA methylation arose from genetic variants in interaction with environmental factor which included for example, maternal smoking, maternal depression, maternal BMI, infant birth weight and gestational age. Genetic variation alone accounted for 25% of the variation in methylation. Thus, there is a complex relationship between variation in methylation, the DNA sequence and environmental exposures.[14]

Finally, researchers have recently demonstrated that epigenetic profiles in human populations are highly divergent, involving differences in frequencies of underlying genetic codes and complex gene-environment interactions. One series of studies examined over 14,000 genes in 180 different cell lines from European and African samples. Researchers found population-level differences in DNA methylation in over one-third of the genes and that most of these differences were attributable to differences in underlying numbers of gene variants.[15] Other researchers have found similar epigenetic differences between populations.[16,17,18]

Research Gaps

To date, causal evidence about the relationship between genes and the environment is lacking in human populations. The sheer number of genes and environmental variables and their interactions poses a significant challenge for experimental research design in humans. Causal relationships between candidate DNA variants and their interactions with epigenetic modifications under adverse environmental conditions can be tested using animal models.

In the future, the use of computers to perform higher-level mathematical modeling techniques to search for gene-environment interactions is expected to overcome this challenge and advance the field. Risk scores associated with developmental phenotypes,[19] the observable characteristics and traits in development, and mathematical models of genome-wide association studies could one-day offer more answers than single searches can provide today.[20] The way forward will examine how many genes work together as a network to add or multiply the effects that lead to developmental disorders.[21]

Conclusions

Gene-environment interplay has emerged as a promising point of origin in studies of divergent developmental trajectories and the emergence of maladaptive outcomes including mental disorders. While there are many molecular mechanisms that control gene expression, research examining epigenetic processes is providing a groundbreaking look at how and under what conditions the intersection of genes/gene expression and the environment arise.

Implications

Early life adversity or enrichment has far reaching effects across the lifespan. Gene-environment interactions between specific gene variants and risk-engendering early social environments may be linked to differences in epigenetic processes, explaining variation among individuals in the expression of genes linked to neurodevelopmental disorders. In the future, changes in epigenetic marks in response to an intervention could also provide useful biomarkers for evaluation of the effectiveness of the intervention.

References

1. Boyce WT, Kobor MS. Development and the epigenome: the 'synapse' of gene-environment interplay. *Developmental Science* 2014;18:1:1-23.
2. Sokolowski MB, Boyce WT. Biology of the Epigenome. In: Tremblay RE, Boivin M, Peters RDeV, eds. Sokolowski MB, Boyce WT, topic eds. *Encyclopedia on Early Childhood Development* [online]. http://www.child-encyclopedia.com/epigenetics/according-experts/biology-epigenome. Published October 2017. Accessed November 17, 2017.
3. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. Role of genotype in the cycle of violence in maltreated children. *Science* 2002;297(5582):851-854.
4. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301(5631):386-389.
5. 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. *American Journal of Psychiatry* 2010;167:509-527.
6. 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. *Archives in General Psychiatry* 2011;68(5):444-454.
7. Zohsel K, Buchmann AF, Blomeyer D, Hohm E, Schmidt MH, Esser G, Brandeis D, Banaschewski T, Laucht M. Mothers' prenatal stress and their children's antisocial outcomes – a moderating role for the Dopamine D4 Receptor (DRD4) gene. *Journal of Child Psychology and Psychiatry* 2014;55(1):69-76.
8. Sokolowski HM, Vasquez OE, Unternaehrer E, Sokolowski DJ, Biergans SD, Atkinson L, Gonzalez A, Silveira PP, Levitan R, O'Donnell KJ, Steiner M, Kennedy J, Meaney MJ, Fleming AS, Sokolowski MB, On behalf of the MAVAN and Toronto Longitudinal Cohort research teams. The Drosophila foraging gene human orthologue PRKG1 predicts individual differences in the effects of early adversity on maternal sensitivity. *Cognitive Development* 2017;42:62-73.

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9. Barr CS, Newman TK, Shannon C, Parker C, Dvoskin RL, Becker ML, Schwandt M, Champoux M, Lesch KP, Goldman D, Suomi SJ, Higley JD. Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. *Biological Psychiatry* 2004;55(7):733-738.
10. Wilson ME, Kinkead B. Gene–environment interactions, not neonatal growth hormone deficiency, time puberty in female rhesus monkeys. *Biology of Reproduction* 2008;78(4):736-743.
11. Tarullo AR, Gunnar MR. Child maltreatment and the developing HPA axis. *Hormones and Behavior* 2006;50(4):632-639.
12. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proceedings of the National Academy of Sciences, USA* 2007;104(4):1319-1324.
13. 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.
14. Teh AL, Pan H, Chen L, Ong ML, Dogra S, et al. The effect of genotype and in utero environment on inter-individual variation in neonate DNA methylomes. *Genome Research* 2014;24(7):1064-1074.
15. Fraser HB, Lam LL, Neumann SM, Kobor MS. Population-specificity of human DNA methylation. *Genome Biology* 2012;13(2):R8.
16. Adkins RM, Krushkal J, Tylavsky FA, Thomas F. Racial differences in gene-specific DNA methylation levels are present at birth. *Birth Defects Research: Part A, Clinical and Molecular Teratology* 2011;91(8):728-736.
17. Heyn H, Moran S, Hernando-Herraez I, Sayols S, Gomez A, Sandoval J, Monk D, Hata K, Marques-Bonet T, Wang L, Esteller M. DNA methylation contributes to natural human variation. *Genome Research* 2013;23(9):1363-1372.
18. Moen EL, Zhang X, Mu W, Delaney SM, Wing C, McQuade J, Myers J, Godley LA, Dolan ME, Zhang W. Genome-wide variation of cytosine modifications between European and African populations and the implications for complex traits. *Genetics* 2013;194(4):987-996.
19. Rietveld CA, Medland SE, Derringer J, Yang J, Esko T, et al. GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science* 2013;340(6139):1467-1471.
20. Marigorta UM, Gibson G. A simulation study of gene-by-environment interactions in GWAS implies ample hidden effects. *Frontiers in Genetics* 2014;5:225.
21. Gratten J, Wray NR, Keller MC, Visscher PM. Large-scale genomics unveils the genetic architecture of psychiatric disorders. *Nature Neuroscience* 2014;17(6):782-790.

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Epigenetic Embedding of Early Adversity and Developmental Risk

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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

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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.

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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.

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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.

Epigenetics and the Role of Developmental Time

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Introduction

The effects of experience change dynamically across the lifespan, especially in the early years, as critical and sensitive periods open and close. The effects of experience also pass on to subsequent generations. This report explains how changes caused by adverse physical and psychological exposures in parents can be passed down to future generations, altering children's risks for mental disorders and maladaptive behaviour.[1]

Subject

In developmental psychology, critical periods are defined as those in which the presence or absence of important experiences or exposures results in irreversible changes in brain circuitry. Critical periods are thought to be sharply timed and can be thought of as a window of opportunity open to particular experiences that opens and after a set period of time shuts. While sensitive periods are developmental intervals when the brain is especially responsive to such experiences and the sensitive period is thought to gradually open and gradually close.[2] Both involve experience-dependent brain plasticity during defined windows of early life.[3]

Problem

Human adaptation to environmental conditions can take place at a variety of timescales ranging from physiological changes that can occur over seconds or minutes to developmental plasticity that occurs over months or years, to genetic changes that occur on evolutionary timescales. The timing and sequencing of important neurodevelopmental processes determine the critical window of growth and development. These processes include the movement of cells to precise locations during embryonic development, the proliferation and pruning of connections between neurons in the brain, changes in the number of receptors and construction of the insulating myelin sheath around nerve cells.

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Research Context

There is evidence that the developing brain is especially vulnerable to the negative effects of chemical and social environmental exposures during early developmental periods. For example, in a random-assignment study of foster care placements for children in Romanian orphanages, neurobiological and developmental outcomes were dramatically improved when children were placed in foster care before two years of age.[4]

Recent Research Results

Scientists are demonstrating the openings and closings of critical periods in animal experiments. One group of researchers has shown that molecular 'triggers' and 'brakes' can start and slow down brain plasticity over time, and that the onset of a critical period appears to be guided and timed by the maturation of the excitatory-inhibitory circuit balance.[3] These findings, together with others,[5,6] have led to a fundamental shift in thinking about brain plasticity — rather than arising during sharply defined critical periods, a newer understanding indicates that the brain is intrinsically plastic and that normal development actually requires a timed, molecular suppression of that plasticity.

Epigenetic changes and critical periods

Epigenetic changes drive much of the molecular machinery that determines critical period onset and offset.[7] For example, epigenetic modification of gene expression guides the differentiation of neurons into unique neuronal subsets, axon growth and the radial organization of brain development.[8] Brain circuitry responds to environmental events by epigenetic processes, DNA methylation and histone modifications.[3] Epigenetic processes control closure of the critical period for acquiring ocular dominance. Epigenetic factors also regulate the expression of a gene that codes for an inhibitory neurotransmitter and drugs have been shown to shift the timing of critical periods; for example, the drug valproate has been shown to reopen the critical window for the acquisition of absolute pitch.[9] Excitatory-inhibitory circuitry imbalance and critical period timing errors have been found in mouse models of autism spectrum disorder.[10]

Inheritance of epigenetic marks across multiple generations

There is now substantial evidence in both humans and animals that adverse physical and psychological exposures in one generation can be replicated among or passed down to following

generations, altering risks for mental disorders and maladaptive behaviour in offspring.[11] Prenatal exposure to stressors in both animal and human mothers has been associated with differences seen in the autonomic nervous system and adrenal cortex responses of their offspring.[12] The autonomic nervous system influences the function of internal organs and the adrenal cortex oversees the production of sex hormones and cortisol. Human population studies have found elevated risks of psychiatric disorders in offspring in the absence of actual exposures.[13]

In mice, scientists have demonstrated that epigenetic marks related to the appearance of these disorders were transmitted to offspring, and the same process is presumed to occur in humans.[14] One way that epigenetic marks are believed to cross generations is through behavioural and social transfers of those marks to offspring. In the paper on epigenetic embedding of early deprivation, adversity and developmental risk,[15] we described the groundbreaking rat experiments where varying levels of maternal grooming and licking changed epigenetic marks throughout their pups' genome. These epigenetic changes changed the pups' stress responses, but also predisposed them to treat their own pups with similar maternal care when they became mothers.[16] An other way that intergenerational inheritance can occur is through in utero exposure of the fetus to stress of the mother as occurred in some children who were in utero during the Dutch Winter Hunger of 1944-45 (as discussed in the third paper of this chapter[15]). In humans, a recent observational study demonstrated that adult offspring of Holocaust survivors have epigenetic marks on the promoter of the glucocorticoid receptor (GR) gene, an important gene involved with development, metabolism and immune response, and that those marks are correlated with the PTSD status of the mother and the father.[17] Finally, the transmission of epigenetic marks may occur is through changes in egg or more likely sperm cells, which is far more difficult to prove. The epigenome is reset through a widespread DNA demethylation process during the early formation of an embryo, as described in more detail in the first article of this chapter, The Biology of the Epigenome,[18] but some recent exceptions have been reported where some epigenetic marks escaped this process and were passed on.[19,20]

Research Gaps

There may be other ways in which epigenetic marks pass on from parents who experience adversity to their offspring (intergenerational transmission). Scientists are examining modifications to stress response pathways passed to children from developing placenta,[21,22] the transmission of epigenetic marks in the sperm of a traumatized male mouse[23] and the transfer of

fear-conditioning from parent mice to offspring via an olfactory signal.[24] Whether and how epigenetics plays a role in inheritance through the generations (transgenerational inheritance) is a challenging topic for future studies.

Conclusions

Development depends on the interaction between environmental influences and critical periods in development when neurobiological circuitry is especially responsive to experience and plasticity is most accessible. The opening and closing of critical and sensitive periods are regulated by epigenetic events that guide the maturation of excitatory-inhibitory neural circuitry and the expression of molecular 'brakes' that reverse the brain's inherent plasticity.

Epigenetic processes are also thought to transmit risk and disorder from one generation to the next. This transmission can occur when behavioural risk and protective factors are passed down from parents to offspring via behavioural or social factors, or through the possibility of germ line transfers of epigenetic marks which is under investigation.

Implications

Research reveals that there is a complex, critical time period in development — both adaptive and maladaptive — that is likely initiated, guided and curtailed by epigenetic events that modify genes in the brain responsible for neurodevelopment. Evidence that epigenetic marks might be passed on to subsequent generations suggests that DNA sequences alone may not determine inherited traits.[17]

References

1. Boyce WT, Kobor MS. Development and the epigenome: the 'synapse' of gene-environment interplay. *Developmental Science* 2014;18(1):1-23.
2. Fox SE, Levitt P, Nelson CA. How the timing and quality of early experiences influence the development of brain architecture. *Child Development* 2010;81(1): 28-40.
3. Takesian AE, Hensch TK. Balancing plasticity/stability across brain development. *Progress in Brain Research* 2013;207:3-34.
4. Zeanah CH, Gunnar MR, McCall RB, Kreppner JM, Fox NA. Sensitive periods. *Monographs of the Society for Research in Child Development* 2011;76(4):147-162.
5. Pizzorusso T, Medini P, Landi S, Baldini S, Berardi N, et al. Structural and functional recovery from early monocular deprivation in adult rats. *Proceedings of the National Academy of Sciences, USA* 2006;103(22):8517-8522.
6. Morishita H, Miwa JM, Heintz N, Hensch TK. Lynx1, a cholinergic brake, limits plasticity in adult visual cortex. *Science* 2010;330(6008):1238-1240.

7. Fagiolini M, Jensen CL, Champagne FA. Epigenetic influences on brain development and plasticity. *Current Opinion in Neurobiology* 2009;19(2):207-212.

8. Fox SE, Levitt P, Nelson CA. How the timing and quality of early experiences influence the development of brain architecture. *Child Development* 2010;81(1):28-40.

9. Gervain J, Vines BW, Chen LM, Seo RJ, Hensch TK, Werker JF, Young AHl. Valproate reopens critical-period learning of absolute pitch. *Frontiers in Systems Neuroscience* 2013;7:102.

10. Gogolla N, Leblanc JJ, Quast KB, Sudhof TC, Fagiolini M, Hensch TK. Common circuit defect of excitatory-inhibitory balance in mouse models of autism. *Journal of Neurodevelopmental Disorders* 2009;1(2):172-181.

11. Franklin TB, Russig H, Weiss IC, Graff J, Linder N, Michalon A, Vizi S, Mansuy IM. Epigenetic transmission of the impact of early stress across generations. *Biological Psychiatry* 2010;68(5):408-415.

12. Matthews SG, Phillips DI. Transgenerational inheritance of stress pathology. *Experimental Neurology* 2012;233(1):95-101.

13. Yehuda R, Halligan SL, Bierer LM. Relationship of parental trauma exposure and PTSD to PTSD, depressive and anxiety disorders in offspring. *Journal of Psychiatric Research* 2001;35(5):261-270.

14. Saavedra-Rodriguez L, Feig LA. Chronic social instability induces anxiety and defective social interactions across generations. *Biological Psychiatry* 2013;73(1): 44-53.

15. Sokolowski MB, Boyce WT. Epigenetic Embedding of Early Adversity and Developmental Risk. In: Tremblay RE, Boivin M, Peters RDeV, eds. Sokolowski MB, Boyce WT, topic eds. *Encyclopedia on Early Childhood Development* [online]. http://www.child-encyclopedia.com/epigenetics/according-experts/epigenetic-embedding-early-adversity-and-developmental-risk. Published November 2017. Accessed October 17, 2017.

16. McGowan PO, Suderman M, Sasaki A, Huang TC, Hallett M, Meaney MJ, Szyf M. Broad epigenetic signature of maternal care in the brain of adult rats. *PLoS One* 2010;6(2):e14739.

17. Yehuda R, Daskalakis NP, Lehrner A, Desarnaud F, Bader HN, Makotkine I, Flory JD, Bierer LM, Meaney MJ. Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. *American Journal of Psychiatry* 2014;171(8):872-880.

18. Sokolowski MB, Boyce WT. Biology of the Epigenome. In: Tremblay RE, Boivin M, Peters RDeV, eds. Sokolowski MB, Boyce WT, topic eds. *Encyclopedia on Early Childhood Development* [online]. http://www.child-encyclopedia.com/epigenetics/according-experts/biology-epigenome. Published October 2017. Accessed November 17, 2017.

19. Whitelaw NC, Whitelaw E. How lifetimes shape epigenotype within and across generations. *Human Molecular Genetics* 2006;15(Spec No. 2):R131-R137.

20. Bohacek J, Gapp K, Saab BJ, Mansuy IM. Transgenerational epigenetic effects on brain functions. *Biological Psychiatry* 2013;73(4):313-320.

21. Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, Simerly RB, Susser ES, Nestler EJ. Early life programming and neurodevelopmental disorders. *Biological Psychiatry* 2010;68(4):314-319.

22. Bale TL. Sex differences in prenatal epigenetic programming of stress pathways. *Stress* 2011;14(4):348-356.

23. Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, Farinelli L, Miska E, Mansuy IM. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. *Nature Neuroscience* 2014;17(5):667-669.

24. Dias BG, Ressler KJ. Parental olfactory experience influences behavior and neural structure in subsequent generations. *Nature Neuroscience* 2014;17(1):89-96.

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Epigenetics: comments on Sokolowski and Boyce

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Introduction

The four linked papers by Sokolowski and Boyce review the relationship between genes, environment and behavioural, psychological and neurodevelopmental outcomes, summarised as two opposing states: ‘vulnerability’ and ‘resilience’. The focus of their chapter is epigenetics, defined as “the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.”[1] At its core are a set of small molecules that sit on top of (epi) our genes (genetics) and by doing so influence the molecular machinery that regulates gene activity. Changes in the distribution of the sum total of epigenetic molecular marks throughout the genome (the epigenome) drive early development of humans as well as all other multicellular organisms. Such developmental changes, from the single-celled zygote, through to the differentiation of hundreds of different cell types in humans was historically termed ‘epigenesis.’[2,3]

Epigenetic marks are themselves influenced by genetics and environments, both externally to, and within individuals. One of the main goals of epigenetics research has been to understand how environment influences the activity of our genes and how this can predispose states of health or disease.[4] As the first one thousand days of human life are especially sensitive to environment, much of the research in the area has focused during this time period and equivalent periods in animal models.[5,6] These four papers discuss and expands upon the above-mentioned concepts and cites milestone studies that have begun to assign the epigenetic state of specific genes to specific earlier environments and late states of resilience and vulnerability (fragility). The authors explain how the field of epigenetics is still in its infancy and point the way forward to future studies. Most importantly, they discuss the implications for medical tests and interventions, and for policy.

Research and Conclusions

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In ‘Biology of the Epigenome’, Sokolowski and Boyce introduce epigenetics, initially in lay terms, then building in more technical terms, including specific mechanisms, namely DNA methylation, histone modification and non-coding RNAs. They discuss the history of the use of the word ‘epigenesis’ that was used to describe the process of human development and its current usage as ‘epigenetics’. One minor omission is the citation of Aristotle as the originator of the term ‘epigenesis’.[2] The authors review studies that have shown that the one thousand days following conception is the time when we are most vulnerable to environment-induced epigenetic change. They rightly indicate that knowledge of disease-specific epigenetic states will lead to a better understanding of disease mechanisms and, more important for policy, to disease-specific biomarkers. They cite autism spectrum disorders as one example of a brain-related disorder that has been investigated using epigenetic methods, although they don’t mention that such research has not yet led to diagnostic biomarkers, most likely due to the methodological differences between studies. Finally and importantly, they briefly detail the challenges of epigenetic research, which include choosing the most appropriate and convenient tissue with which to analyse in relation to resilience and sensitivity; how to separate cause and effect; and the importance of analysing multiple epigenetic mechanisms to provide a more complete picture of epigenetic state.

In ‘Gene-Environment Interplay and Epigenetic Processes’ Sokolowski and Boyce discuss, in a clear and concise way, how genes and environment interact and focus on epigenetics as one proven example. However, there was probably no need to discuss DNA sequence-environment interactions, although such studies have shed light on studies of mood disorders.[7] In addition, more examples of specific studies of environment-induced epigenetic change could have been provided, although such studies are featured in the following paper by the same authors. The authors are correct to point out that epigenetic marks can be affected by genetics as well as environment, and by an interaction of both.[8] Conclusions and implications for this paper focus on understanding the effects of early life social interaction but are not as strongly phrased as the previous paper.

In ‘Epigenetic Embedding of Early Adversity and Developmental Risk’, Sokolowski and Boyce discuss how epigenetic changes can mediate the effect of early life adversities such as poverty, neglect and trauma, on risk for disorders of mental health, educational achievements and chronic disorders in general. They focus on the question of whether, using epigenetics, we will be able to predict which children are more likely to be resilient or vulnerable. By detecting both kinds of

children, resources and interventions can be focused on the latter. The authors review a few animal studies that have linked early life adversities such as neglect, maltreatment and social dominance on neurodevelopment and on endocrine and immune systems, all of which appear to be mediated at least in part through epigenetic change. They also review human studies linking early life adversities such as famine, abuse, institutionalisation, and socioeconomic disadvantage with epigenetic change in neurodevelopmental pathways. They reiterate the challenges mentioned in their first paper. What was missing, however, was a discussion on the social implications of epigenetic tests themselves, as studied by others.[9,10] For example, would a positive test result for vulnerability stigmatise both parents and offspring and raise these children's future insurance premiums?

In their final paper, 'Epigenetics and the Role of Developmental Time', Sokolowski and Boyce discuss the issue of how developmental timing can influence epigenetic state and brain plasticity. In particular, they focus on the emerging topic of how the pre-conceptional environments of parents could be passed down to their children through epigenetic processes. They again provide key examples from animal and human studies. One pertinent example is that children of holocaust survivors who developed PTST have epigenetic alterations with a gene involved in response to stress. The authors rightly mention that most epigenetic marks are completely reset twice per generation, during early somatic and germ cell development, and that we don't currently know which genes escape this resetting.

In summary, Sokolowski and Boyce bring their readers up to speed with the history and mechanisms of epigenetics, focusing on how epigenetic state in early life environment can be influenced by social, biological and physical environments, to predispose individuals to vulnerability or resilience. They argue that epigenetics research has tremendous implications for policy at many levels.

Implications for the Development and Policy

Clearly, there is a wealth of evidence to indicate that adverse environments during pregnancy, childhood and adolescence, can confer risk for adverse mental and physical health and that many of these environments are mediated by epigenetic change. This has several policy implications. The first is that children and adolescents should be provided with optimum environments by parents and, more importantly, by society, to maximise resilience and minimise vulnerability. In doing this, instead of pointing the finger of blame at parents and children, we should target as

many resources as possible to provide both with resources to nurture resilience. Such resources will be specific, e.g. guidelines on raising resilient children, and general, such as government investments targeting families of low socioeconomic status. As studies linking epigenetic state to future states of resilience and vulnerability are replicated across multiple cohorts and countries, it will become feasible to test children of all ages to predict those who are likely to benefit from targeted interventions. However, before such tests are undertaken, all stakeholders, especially current and future parents, should be surveyed about their attitudes and concerns of such tests. In addition, discussions need to be had about a positive test result for vulnerability, which could result in stigmatisation and discrimination from other children, from schools, and from their future employers and insurers.

References

1. Riggs AD. Epigenetic mechanisms of gene regulation. In: Russo VEA, ed. *Epigenetic mechanisms of gene regulation*. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press; 1996:1.
2. Nise MS, Falaturi P, Erren TC. Epigenetics: origins and implications for cancer epidemiology. *Medical Hypotheses*. 2010;74(2):377-382.
3. Quatrefages A. Débats du 16 juillet 1863 de la Société d'Anthropologie de Paris. *Bulletins et Mémoires de la Société d'Anthropologie de Paris*. 1863;4:378-383.
4. Schiele MA, Domschke K. Epigenetics at the crossroads between genes, environment and resilience in anxiety disorders. *Genes, Brain and Behavior*. 2018;17(3):e12423.
5. Bianco-Miotto T, Craig JM, Gasser YP, van Dijk SJ, Ozanne SE. Epigenetics and DOHaD: from basics to birth and beyond. *Journal of Developmental Origins of Health and Disease*. 2017;8(5):513-519.
6. Soubry A. Epigenetics as a Driver of Developmental Origins of Health and Disease: Did We Forget the Fathers? *BioEssays*. 2018;40(1).
7. 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. *Archives of General Psychiatry*. 2011;68(5):444-454.
8. Teh AL, Pan H, Chen L, et al. The effect of genotype and in utero environment on interindividual variation in neonate DNA methylomes. *Genome Research*. 2014;24(7):1064-1074.
9. Meloni M, Testa G. Scrutinizing the epigenetics revolution. *BioSocieties*. 2014;9(4):431-456.
10. Muller R, Hanson C, Hanson M, et al. The biosocial genome? Interdisciplinary perspectives on environmental epigenetics, health and society. *EMBO Reports*. 2017;18(10):1677-1682.

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