ENCYCLOPEDIA on Early Childhood Development

EPIGENETICS

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.

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.