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Developmental programming of early brain and behaviour development and mental health: a conceptual framework

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ABBREVIATIONS

DOBHaD	Developmental Origins of Behaviour, Health, and Disease
DOHaD	Developmental Origins of Health and Disease

The Developmental Origins of Health and Disease (DOHaD) hypothesis studies the short- and long-term consequences of the conditions of the developmental environment for phenotypic variations in health and disease. Central to this hypothesis is the idea of interdependence of developmental influences, genes, and environment. Developmental programming effects are mediated by alterations in fundamental life functions, and the most enduring effects seem to occur if the main regulatory instances of the organ – the (epi)genome and the brain – are affected. Some new insights in the role of chromatin, in cellular development and differentiation, and neural plasticity from the field of epigenetics are introduced, followed by a section on epigenetics and brain development. It is proposed to extend the DOHaD hypothesis into the 'Developmental Origins of Behaviour, Health, and Disease' (DOBHaD) concept. Pregnancy and the early postnatal period are times of both great opportunity and considerable risk, and their influence can extend over a lifetime. The DOBHaD hypothesis opens fundamental new perspectives on preventing diseases and disorders.

Development is an active process that occurs as a function of the continuous dialogue between the individual and its environment.[1] The idea of developmental plasticity has a long history. Recently also the Developmental Origins of Health and Disease (DOHaD) research field has adopted this idea. The DOHaD hypothesis encompasses the short- and long-term consequences of the conditions of the developmental environment for health and disease risk.[2–6] Evidence from preclinical, clinical, and epidemiological research shows that exposure to an insult during a sensitive period in utero or early postnatal development may lead to altered programming (reprogramming) of tissue structure and function, predisposing the individual to later behavioural problems, learning difficulties, atypical or delayed cognitive development, cognitive decline, psychopathology, cancer, cardiometabolic, neuroendocrine, and other diseases.[2–6]

The main aims of this paper are to link new insights from the field of epigenetics to the DOHaD hypothesis. Some new insights in the role of chromatin, in cellular development and differentiation, and neural plasticity from the field of epigenetics are introduced, followed by a section on epigenetics and brain development. An extended concept, the 'Developmental Origins of Behaviour, Health, and Disease' (DOBHaD) hypothesis, is then proposed. This hypothesis, integrating early brain and behavioural development in a more elaborate way than the existing DOHaD hypothesis, allows better deduction of innovative, preventative, and interventional strategies.

EPIGENETICS: SOME GENERAL PRINCIPLES

Chromatin is a critical component of gene regulatory activities

The etymological meaning of epigenetics is 'outside conventional genetics', going beyond the genes.[7] In conventional genetics a gene was defined as a DNA sequence, and seen as a physical structure, 'a unit of heridity'. In this way genes were taken out of a larger context and individuated from other entities.[8] The genome was seen as containing the basic instruction of the living, and as being more or less immutable.[8] However, molecular genetics started to uncover more organizational layers as well as other mechanisms controlling heredity. The genome is now seen as a complex regulatory system that actively responds to internal and external fluctuations.[8]

In eukaryotes, the large genome is packaged in chromatin; this structure affords compaction of the genome, making it easier to fit in the small volume of the nucleus. The basic component of chromatin is a nucleosome, which consists of approximately 147bp of DNA wrapped twice around an octamer of core histone proteins (containing two copies of each of the core histones H2A, H2B, H3, H4, and linker H1). The amino (N)-terminal 'tails' of histone proteins project out of the nucleosome core and are 'decorated' with many post-translational modifications including methylation, acetylation, phosphorylation, ubiquitination, and others.[9,10]

Changes in the structure of chromatin are sufficient to cause heritable, phenotypic changes. These changes are termed epigenetic; they occur without alterations in the DNA

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sequence, i.e. they are outside conventional genetics. The mechanisms of epigenetic regulation are (1) changes in chromatin structure (by DNA methylation, histone modifications, and ATP-dependent chromatin remodelling) and (2) RNA interference.[11] DNA methylation, by which a methyl group is attached to the cytosine nucleotide in CG islands (or CpG islands: the 'p' refers to the phosphodiester bond between the cytosine and the guanine), is the most widely studied mechanism for underlying epigenetic changes. In most cases, increased DNA methylation is associated with gene silencing, and decreased methylation is related to gene activation. DNA methylation is dependent on folate, vitamin B_{12}, and vitamin B_6; these are cofactors in the enzymatic reaction. Thus, nutrition can induce epigenetic changes.[11] Epigenetic modification processes are very complex. For instance, there are hundreds of potentially methylated cytosines in a gene as well as dozens of known post-translational modifications of chromatin.[11] (More detailed information can be found in references,[9–14] for example on chromatin remodelling and RNA interference.)

Cellular development and differentiation in the embryo

A fertilized egg does more than reproduce itself; it produces something new(Waddington 1949, cited in Van Speybroeck,[7] p. 67)

The single-celled zygote has to produce cells of various phenotypes to form the embryo. All cells in an organism carry the same genes and the same alleles; it is because not all genes are activated or repressed at the same time in the same cell that cells have a different morphology, physiology, and function.

Until the blastocyst stage, a zygote undergoes many mitotic divisions. The inner cell mass of the blastocyst contains all totipotent cells from which the embryo will be formed. This inner cell mass will reorganize and form three germ layers: ectoderm, mesoderm, and endoderm. These layers give rise to distinct tissues and organ systems. Genes that encode pluripotency markers are transcriptionally repressed and, simultaneously, genes characteristic of the chosen cell fate are maintained in a transcriptionally active or poised state. The differential chromatin state in different tissues is inherited in daughter cells during cell division (proliferation); this seems to be dictated by histone methylation, which has a relatively slow turnover.[12] There is a balanced state of proliferation and differentiation in the differentiated cell, which results in homeostatic stability.[13]

During cellular development and differentiation, the commitment of cells to their specialized phenotypic characteristics is temporally coordinated by 'a complex dynamical system comprised of large numbers of interacting genes and their products' (Huang et al.[13] p. 2). It was earlier suggested that gene networks are the result of cellular processes and not their cause. However, according to Huang et al.,[13] theoretical considerations as well as experimental evidence support the view that cell fates (or commitment) are 'high dimensional attractor states' of the underlying molecular network. This view is in accordance with the definition that Bird[14] gives of epigenetic events, namely 'structural adaptations of chromosal regions so as to register, signal or perpetuate altered activity states'[14] (p. 398).

EPIGENETICS AND BRAIN DEVELOPMENT

Neuronal development and plasticity: dynamic epigenetic regulation by enzymes, stimuli and signalling pathways

Epigenetic marks, such as modifications of chromatin, have generally been considered to be both stable and heritable. However, in post-mitotic cells such as fully differentiated neurons, epigenetic modifications might be highly dynamic and could thereby support neuronal functions and plasticity.[9] They integrate multiple extracellular signals (including synaptic activity and neurotrophic factors) and in this way generate a coordinated neuronal transcriptional response. It is now also accepted that the enzymes that bring about the modification work in multiprotein complexes. Results of earlier studies, based on biochemical (in vitro) and genetic (in vivo) approaches revealed results that apparently were contradictory to those from genome-wide studies using high-throughput technologies (such as chromatin immunoprecipitation sequencing) in which whole gene-regulatory networks are studied. For example, whereas earlier studies suggested that enzymes such as histone acetyl transferases exert a high degree of specificity in cellular processes, genome-wide approaches argue for a low specificity.[15] Anamika et al.,[15] propose a unifying model that distinguishes between two states: an early 'initiation state' (i.e. during cell differentiation when, owing to cell commitment, a high functional specificity is needed) and a later 'maintenance state' (with less specific functionality).

Both intrinsic activity and sensory-driven neural activity influence the development of brain circuits and mature connectivity

The trajectory of brain development occurs in multiple stages. The foundation of brain architecture is established early (from about day 56 postconception until about 24wks' gestation).[16] Neurons and glia cells have a developmental stage-dependent expression of electrical signals. Patterns of electrical activity are present in the visual, somatosensory, and auditory cortex already before the maturation of sensory perception and therefore do not represent responses to environmental stimuli but intrinsic neuronal activation. So, coordinated endogenous patterns of activity synchronize the cortico-subcortical networks long before environmental inputs start to influence sensory maps.[17] According to Del Rio and Feller,[18] it is clear that both spontaneous and sensory-driven neural activity influence the development of mature connectivity. An important functional magnetic resonance imaging study in preterm babies showed that, indeed, a repertoire of resting state dynamics emerges during the period of rapid neural growth in the last trimester of gestation.[19] Although the visual, auditory, somatosensory, motor, frontoparietal, and executive control networks developed at different rates, by term, complete networks were present and several were integrated with thalamic activity.[19] Epigenetics raised new questions such as how the patterns of activity may alter signalling events, which, in turn, regulate cell

function at levels from transcription to post-translational modification.[18]

The effect of prenatal and early postnatal adversity on early brain development

It is known that during the period before the epigenetic marks (i.e. changes in chromatin structure) are fully re-established in daughter cells, any cell is likely to be very sensitive to incoming signals.[12] Alteration in these marks (both in histones and DNA) can have lasting effects[9] on neural development and plasticity[9]; that is, disruption of cellular differentiation may lead to subtle aberrations in the brain that nevertheless may have an impact on later sensory–cognitive, behavioural development.[20] Early insults that retard or accelerate the developmental programme may lead to an atypical architecture of the brain. It is, for example, suggested that misplaced neuronal ensembles remain 'frozen' in an 'immature excitable state' and perturb the construction of functional units.[16] Infantile epilepsies, dyslexia, schizophrenia, autism, and in certain conditions even Huntington's and Alzheimer's diseases are seen as neurodevelopmental disorders. Even though the precise mechanisms involved still need to be delineated, a prevalent hypothesis is that infection-induced disruption of fetal neurodevelopment may predispose the organisms to long-lasting changes in subsequent neural and behavioural development. Other insults include maternal alcohol, nutrition restriction, and endocrine changes associated with maternal stress.

Much DOHaD research has focused on the role of maternal glucocorticoids during pregnancy and fetal/infant glucocorticoids. They are prime candidates for perinatal reprogramming as they are critical during development, for example for maturation of tissues and organs, cellular differentiation, and lung maturation. They can act as transcription factors and so regulate gene expression. It has been suggested that changes in epigenetic modifications of glucocorticoid receptor genes play a role in the transmission of environmental cues to rat pups[21] or infants.[22] The offspring of the high-licking and -grooming mothers had higher glucocorticoid receptor expression in the hippocampus through increased serotonergic tone. DNA methylation of the binding site for nerve-growth-factor-inducible protein A (a transcription factor involved in the regulation of glucocorticoid receptor gene expression) and histone modification in the hippocampus of high licking and grooming mothers were increased.[21] This study may indicate that epigenetic modifications of specific genomic regions in response to variations in maternal care might serve as a major source of variation in biological and behavioural phenotypes. In humans, McGowan and colleagues have reported epigenetic changes in brain samples from adults exposed to childhood abuse.[22]

DEVELOPMENTAL ORIGINS OF EARLY BRAIN AND BEHAVIOUR DEVELOPMENT AND MENTAL HEALTH: THE DOBHAD HYPOTHESIS

Developmental programming effects are mediated by alterations in fundamental life functions. The most enduring effects seem to occur if the main regulatory instances of the organ – the (epi)genome and the brain – are affected.[5] We propose to extend the DOHaD hypothesis into the 'Developmental Origins of Behaviour, Health, and Disease' (DOBHaD) hypothesis; we argue that it is important to integrate early brain and behavioural development in an elaborate way. The DOBHaD hypothesis opens fundamental new perspectives on preventing diseases and disorders, i.e. before they start to develop. For instance, specific architectural or electrical signature may announce disorders well before clinical symptoms appear.[16] So, rather than treating symptoms, an appreciation of the disturbed intrinsic and extrinsic factors and how developmental processes respond to the insult should be used to guide understanding of the nature of the illness and its future treatment.

Figure 1 attempts to integrate DOBHaD results from preclinical, clinical, neurobehavioral developmental, and epidemiological research in a general way. Evidence for altered underlying neural circuits mediating the link between early adversity and behavioural and learning impairments are mainly based on preclinical research (see Bock et al.[23]). Importantly, early brain and behaviour development are integrated and put

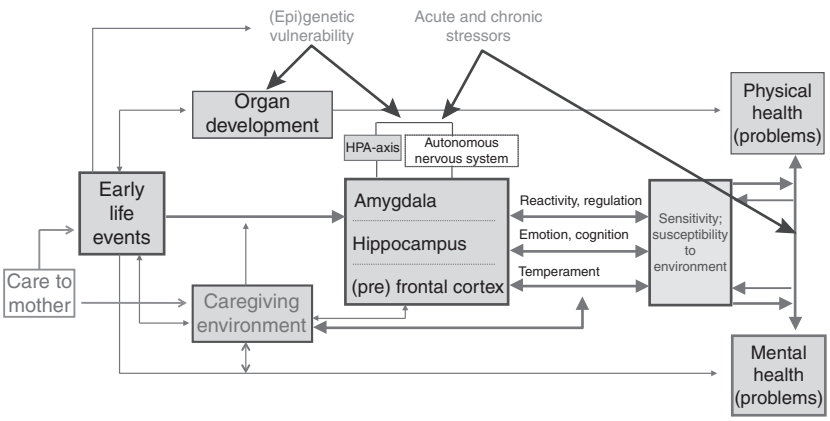

Figure 1: Developmental programming of early brain and behaviour development and mental health.

in a central place in the figure. Effective coping with stress is important throughout life[24] and is an important behavioural regulation factor. The perinatal period is seen as a unique period in ontogeny where the fine-tuning of the stress-regulating system can be permanently reprogrammed and alter the resilience; vulnerability to developing diseases may be enhanced. Research in animals has convincingly shown that developmental exposure to excess glucocorticoids or stress reprogrammes the peripheral and central nervous system involved in the two co-acting stress-regulating subsystems, i.e. the hypothalamic–pituitary–adrenal axis (with the hormones corticotrophin-releasing hormone, vasopressin, adrenocorticotrophic hormone, mineralocorticoid, and glucocorticoid) and the autonomous nervous system (with noradrenaline and adrenaline). Changes are seen in neuronal circuits – in limbic brain structures (hippocampus, amygdala) and prefrontal cortex – which are involved in stress reactivity and regulation patterns, in emotional (e.g. anxiety, anger) and cognitive (e.g. learning, memory) processing, and in temperamental variation in behaviour (e.g. novelty seeking, harm avoidance, reactive temperament).[2–6,25,26] These changes may influence how an individual 'behaves' (i.e. perceives, interprets, and reacts) to its environment, to situations of acute and chronic stress; in concert with physiological activity, these processes may underlie behavioural problems and psychopathology, or more in general, mental health problems. Importantly, recent theories hold that individuals vary in their biological sensitivity[27] or in their susceptibility[28] to environmental influences. These theories predict that some individuals are more susceptible than others to both the adverse and beneficial effects of, respectively, unsupportive and supportive environments.[27,28] The nature of the environment and this difference in sensitivity or susceptibility will influence how mental health or mental health problems are shaped; these processes covary with physical health and health problems.

Some remarks and critical questions are in order. Although the DO(B)HaD hypothesis stimulated some interdisciplinary research, more is still necessary, in which the different elements described in Figure 1 can be examined in concert. For instance, there still is a paucity of translational research, truly merging clinical data with animal models. We are convinced that more brain–behaviour research should be included in DOBHaD research, and fully agree with the following statement of Pennington et al.[29] (p. 439): 'The mapping between brain and behaviour is complex, not unidirectional and changes with development. The same is even true for mapping between genes and behaviour. Although behaviour does not change DNA sequence it does affect gene expression. Most developmental scientists understand the complexities in localizing behaviour or deficits. Their sophistication in analysing behaviour and interpreting relations with other levels of the biological analysis will be crucial as our capacity for finding genes, and brain structures that influences complex behaviours increases'.

CONCLUSION

The DO(B)HaD hypothesis has stimulated some interdisciplinary research and has led to convergence of knowledge from fundamental and applied sciences from the molecular over the behavioural to the population level. There is clear evidence that prenatal and early postnatal adversity may have a negative impact on brain architecture and circuits, and affect lifelong behaviour and both mental and physical health. Developmental plasticity, however, also allows changes for the better. The study of the prenatal environment has very substantial implications for improving behaviour and health, because maternal lifestyle and stress, which are shown to have long-term negative impacts on offspring behaviour and health, are modifiable. Both the prenatal and early postnatal periods are targets for innovative preventative and intervention strategies. The expected potential social and economic returns on investment are substantial.[30] Pregnancy and the early postnatal period are times of both great opportunity and considerable risk, and their influence can extend over a lifetime.

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