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Central Nervous System Development

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Abstract

Brain development results from the realization of successive genetic programs at different ontogenic stages. The main stages of brain development include the production of neurons, their migration, the programmed death of a significant proportion of neurons, the production of axons and dendrites, the elimination of excess neurites, synaptogenesis, elimination and selective stabilization of synapses where microglia play a central role, the production of astrocytes and oligodendrocytes, myelination, and angiogenesis. These different stages of brain development and maturation are controlled by intrinsic factors (genetically determined) and modulated by extrinsic environmental factors. This modulation by environmental factors can bring into play epigenetic mechanisms.

Keywords

Critical periods, synapses, neuronal networks, microglia, neuroinflammation

Key points

- The brain of the preterm and term newborn infant is actively developing, with several key steps occurring during the third trimester, such as the end of neuronal migration, programmed cell death, the generation of axons and dendrites, and the first wave of synaptogenesis.
- These processes are controlled by genetic programs, but are also very sensitive to environmental factors.
- Epigenetic mechanisms appear to play a central role in these processes, with long-term and potentially trans-generational consequences.

Brain development results from the accomplishment of successive genetic programs during the different ontogenic stages. It starts with the individualization of the neural plate at the beginning of the 3rd week post-conception and is mostly complete by adolescence. However, some neuronal production persists lifelong. This late neurogenesis has been well described at the level of the olfactory bulbs and the dentate gyrus of the hippocampus, but its importance to the associative neocortex remains to be shown.

The principal stages of brain development can be summarized as follows: induction of the neuroectoderm, formation of the neural tube followed by the telencephalon, neurogenesis (production of neuronal progenitors and then of mature neurons), neuronal migration, programmed neuronal death, generation of neurites (axons and dendrites), elimination of superfluous neurites, synaptogenesis, elimination and selective stabilization of synapses, angiogenesis, gliogenesis (production of astrocytes and oligodendrocytes), and myelination (Fig 1). These different stages of the development and maturation of the brain are controlled by intrinsic factors (determined genetically) and modulated by extrinsic environmental factors. This modulation by environmental factors could bring epigenetic mechanisms into play. The perturbation of the unfolding of any of these different stages of brain development leads to a deficit in brain growth and/or brain malformations. The functional consequences to the child depend on the developmental stage in question. This raises the notion of ‘critical periods’ which we will touch on throughout this chapter; a critical period is a maturational stage in the lifespan of an organism during which the nervous system is especially sensitive to certain environmental stimuli.

Neuronal production and migration

The expansion of the cortex occurs through two processes that take place in parallel: a lateral expansion process that allows the surface of the cortex to grow, and a radial expansion process that leads to an increase in its thickness. The total number of neurons in a mature human brain is estimated at between three and a hundred billion. The cortex is initially generated from a radially oriented monolayer of proliferative neuroepithelial cells lining the walls of the lateral ventricles – the ventricular zone (VZ). Around the 7th gestational week in humans a second proliferative zone, the inner subventricular zone (SVZ), appears, derived from precursors in the VZ ¹. The cells of the inner SVZ do not adopt a radial conformation. More recently, a third proliferative zone has been identified in the developing neocortex: the outer SVZ, which appears in humans around gestational week 11. In humans, this outer SVZ displays prolonged proliferation. This difference in the behavior of neuronal precursors has been hypothesized to explain the impressive evolutionary expansion and folding observed in the surface of the neocortex.

These proliferative zones, situated on the dorsal side of the lateral ventricles, give rise to the excitatory (glutamatergic) neurons of the different cortical layers (the cortex in mammals consists of six layers), as well as potentially (as this is still controversial and seems to be species / cell subtype-dependent) a portion of inhibitory neurons (GABAergic interneurons). The other inhibitory neurons derive from another proliferative structure located on the lateral wall of the lateral ventricles, the ganglionic eminence (which is also the source of thalamic neurons) and one located in the preoptic area. Migrating neurons can adopt a radial trajectory by migrating in contact with specialized glial cells, the radial glia, which serve to guide them ^{2,3}.

After exiting the mitotic cycle, neurons migrate from the proliferative zones towards the future cortex ^{1, 4-8}. The first wave of migratory neurons forms the primitive cortical plate or preplate (Fig. 2). The second wave of migratory neurons then splits this primitive plate into two, around gestational week 7, giving rise to a three-layered structure: layer I, which contains the Cajal-Retzius neurons, is located just below the meninges, layer VI, which contains neurons that have already completed their migration, and finally the subplate – a transient structure located below the future neocortex. Consecutive waves of migratory neurons subsequently cross the subplate and the cortical layers already in place, but stop below layer I, thus successively forming layers V, VI, III and II along what is known as an "inside-out" gradient ⁹. Until recently, it was thought that the migration of neurons to the neocortex was complete by around gestational week 24 ¹⁰. However, recent studies suggest that GABAergic interneurons continue to be added to the neocortex practically until term ¹¹. In animal models of encephalopathy of prematurity and in human post-mortem tissues of preterm neonates, a rarefaction of some subclasses of cortical interneurons has been demonstrated ¹²⁻¹⁴.

Several molecules involved in controlling neuronal migration and their navigation to the appropriate destinations have been identified. These molecules can be schematically divided into four categories ^{15, 16}.

(i) Cytoskeletal molecules, which play an important role in the initiation and progression of neuronal movement (extension of the apical process and nucleokinesis). Molecules controlling initiation include Filamin-A (an actin-binding protein that is implicated in periventricular nodular heterotopias) and Arfgef2 (a molecule that plays a role in vesicular trafficking and is involved in periventricular nodular heterotopias associated with microcephaly). Among the molecules controlling progression are Doublecortin (a

microtubule-associated protein – MAP – implicated in double cortex syndrome), Lis1 (a MAP implicated in Type 1 lissencephaly and Miller Diecker syndrome) and Alpha-1 Tubulin (involved in the formation of tubulin heterodimers).

(ii) Signaling molecules that play a role in lamination, such as Reelin (a glycoprotein implicated in a human disorder combining lissencephaly with cerebellar hypoplasia).

(iii) Molecules modulating glycosylation that provide a stop signal to migrating neurons, such as POMPT1 (protein *O*-mannosyltransferase, associated with Walker-Warburg syndrome), POMGnT1 (protein *O*-mannose beta-1,2-N-acetylglucosaminyltransferase, implicated in muscle-eye-brain disease) and Fukutin (a glycosyltransferase implicated in Fukuyama congenital muscular dystrophy). These three human disorders display Type 2 lissencephaly.

(iv) In addition to these three principal groups of molecules, neuronal migration can be modulated by other factors such as certain neurotransmitters (glutamate and GABA), molecules derived from peroxisomal metabolism and certain environmental factors (inflammation, ethanol, and cocaine).

Programmed neuronal death

Depending on the brain region under consideration, 15 to 50% of the neurons initially produced die through a physiological process termed programmed cell death or apoptosis. Approximately 70% of the neurons that disappear seem to die between gestational weeks 28 and 41 in humans ¹⁷.

Programmed cell death is a complex mechanism governed by a balance between cell death- and survival-inducing signals, genetic programs involved in cell death or survival, effectors of cell death and inhibitors of these effectors ¹⁸. Cells that have initiated programmed cell death eventually go on to be phagocytosed by neighboring glial cells (microglia) without

inducing inflammatory phenomena or scar formation. This process is facilitated by changes in the composition of the apoptotic cell membrane ('eat me signals') which are sensed by the microglia which occurs very early in the apoptotic process. Within the cell death process, the activation of caspases (proteolytic enzymes) in the form of a cascade is a key stage that culminates in DNA fragmentation and the death of the neuron. In addition, it is reported that direct interaction between healthy neurons and microglia can initiate cell death programs or even engulfment of the live cell which is then 'digested' by the microglia in a process called phagoptosis ¹⁹.

Electrical activity appears to be a critical factor for neuronal survival. During the peak period of brain growth in rodents, the administration of substances that block electrical activity induces a serious aggravation of developmental neuronal death in various brain regions. These substances include NMDA receptor inhibitors (MK-801 or ketamine), GABA-A receptor agonists such as antiepileptics (phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin and valproic acid) and anesthetics (a combination of midazolam, nitric oxide and isoflurane) ²⁰.

Organization of the central nervous system

Subplate neurons

Subplate neurons constitute a transient structure during brain development ²¹. They are generated around gestational week 7, and the subplate itself appears around gestational week 10. This structure, located under the neocortical plate, reaches its maximum thickness between gestational weeks 22 and 36.

Subplate neurons express various neurotransmitters, neuropeptides and growth factors. They receive synapses and form connections with cortical and subcortical structures. These neurons play an important role during brain development: (i) they produce axons that project to the internal capsule, which act as guides for neurons from layers V and VI; (ii) between gestational weeks 25 and 32, they produce axons for the corpus callosum; and (iii) they constitute a "waiting zone" for thalamocortical axons (with which they establish transient? synapses) before the latter invade the neocortical plate to reach layer IV. This waiting area is necessary for the adequate targeting of thalamocortical afferents.

Subplate neurons may be destroyed in preterm newborns presenting with lesions of the periventricular white matter ²², findings which have been confirmed in animal models of periventricular white matter injury ^{23, 24}. This damage to the subplate could participate in the thalamocortical connection anomalies demonstrated by MRI in preterm infants ²⁵, as well as in the associated cognitive and/or motor disorders.

Axonal and dendritic growth

The final morphology of the mature neuron and the formation of connections between neurons depend on complex cellular dendrite-axons interactions ^{26, 27}. Maturing neurons develop axons and dendrites that extend as a result reorganization of the cytoskeleton, based on intrinsic and extrinsic cues. Many of the extrinsic cues include secreted chemoattractant or chemorepulsive factors, and adhesion molecules on target neurons that facilitate synapses formation. The interaction between these different ligands and their receptors leads to modifications in calcium levels at the growth cone/dendritic tip, which play a key role in motility and orientation. This ontogenic stage occurs largely, but not exclusively, during the second half of pregnancy, and extends into the postnatal period.

The formation of corticospinal projections occurs at early stages from the subplate, and then from neurons that populate the deep cortical layers (V and VI). Corticothalamic projections also appear, from both the subplate and the deep cortical layers. Corticocortical projections appear later.

A number of transcription factors (e.g. Ctip2, Satb2, Fezf2) regulate the commissural, corticothalamic and corticospinal projections of the cortex.

Dendritic arborisation progresses at slightly different rates for each neuronal subtype, though the stereotypical early branch formation is generally established in the third trimester. Even though genetic programs control the molecular mechanisms of axonal and dendritic growth and determine the initial pattern of these connections, experience and the environment then sculpt this global pattern to generate the final set of connections (through brain plasticity).

The processes underlying cortical expansion are still not fully understood ^{28, 29}, but recent advances have strengthened a link to differences in neurite density in addition to neuronal production ³⁰.

Synaptogenesis

In the occipital neocortex of the monkey, five successive waves of synaptogenesis have been described ³¹. Based on data obtained from the human occipital cortex ³², the following chronology has been proposed for the human cortex: (i) a first phase starting at gestational week 6-8 and limited to the deep layers, such as the subplate; (ii) a second phase starting at gestational week 12-17, with relatively few synapses produced in the cortex; (iii) a third phase starting at around the middle of pregnancy and finishing at around the 8th month after birth (this phase is characterized by a rate of production of new synapses estimated at around

40,000 per second in the monkey); (iv) a fourth phase that extends up to puberty and is also characterized by a high rate of synapse formation; and (v) a last phase that extends up to adulthood but is somewhat masked by the significant loss of synapses with age. Experimentally, the two first phases are not influenced by the deprivation of sensory stimuli. The third phase is partly dependent on sensory input whereas the fourth phase is strongly controlled by sensory stimuli and experience.

The concept of synaptic stabilization (by the elimination of non-stabilized synapses) was first proposed by Changeux and Edelman ³³. During brain development, there is a systematic overproduction of labile synapses in successive phases that lead to redundant connections in a fairly random manner. This stage is mainly controlled by genetic factors. Each wave of overproduction is followed by a period of stabilization of synapses that are of functional value and the elimination of redundant or useless ones by glial cells. This period of stabilization and elimination is strongly influenced by environmental stimuli and experience. In this model, the moderate increase in the number of genes involved in synaptogenesis during the course of evolution has resulted in a richer substrate upon which the environment and experience act to generate a more complex network.

Glial proliferation, differentiation, and myelination

Astrocytes

Neocortical astrocytes are of two origins ³⁴. At the end of neuronal migration, radial glial cells (which are both neural stem cells and play a role in guiding migrating neurons) are transformed into astrocytes, which then reside in the deep cortical layers and the white matter. In contrast, the astrocytes of the superficial cortical layers are primarily derived from glial precursors that multiply in the SVZ and then migrate into the cortex.

In the human neocortex, astrocytic proliferation begins around gestational week 24, with a peak around gestational week 26-28. The exact date at which the production of astrocytes ends is not known, but it could be supposed that the major part of astrocytic production is over by the end of a normal pregnancy. This peak in the production of astrocytes around gestational week 26-28 could be of particular importance for preterm newborns. Indeed, astrocytes play several important roles, including in axonal guidance, the stimulation of neuronal growth, synapse formation, the transfer of metabolites between blood vessels and neurons, the establishment of the pattern of certain brain structures, the production of extracellular matrix components, the production of trophic factors, neuronal survival, myelination, and maintenance of the blood-brain barrier. For example, experimentally blocking astrocyte production temporarily in the neocortex of rodents induces an increase in programmed cell death in neurons and long-term changes in neocortical synaptic equipment ³⁵. In addition, recent studies show that astrocytes can acquire different phenotypes which depend upon the physiological or pathological conditions they are exposed to ³⁶. These different phenotypes can have beneficial or toxic effects on neighboring cells.

Oligodendrocytes and myelination

Oligodendrocytes can be divided into four types depending on their degree of maturation ³⁷:

- (i) Oligodendrocyte precursors that arise from the SVZ are bipolar and mitotically active; their differentiation into preoligodendrocytes occurs during their migration into the future/putative white matter.
- (ii) Preoligodendrocytes that are multipolar cells that retain their proliferative capacity. This second cell type is predominant in the periventricular white matter during the second half of pregnancy.

(iii) Immature oligodendrocytes that are multipolar cells that appear during the third trimester and wrap axons in preparation for their myelination. (iv) The last stage is their differentiation into myelinating and extremely multipolar mature oligodendrocytes.

The oligodendrocyte precursors and preoligodendrocytes, the predominant varieties in the brain of preterm newborns, are extremely vulnerable to injury caused by inflammatory mediators including oxidative stress, the excitotoxic cascade, and hypoxic-ischemic insults ³⁸. This death of preoligodendrocytes has been implicated in cystic periventricular leukomalacia. This type of severe lesion has progressively decreased in incidence, and has replaced by more diffuse lesions ³⁹. In this diffuse white matter lesion in preterm infants, the primary phenomenon is a blockade of oligodendrocyte maturation ^{12, 40, 41}, in which the HIF ⁴² and the Wnt ⁴³ pathways play a role.

Myelination occurs during a prolonged period, persisting into childhood. The chronology and the degree of myelination vary according to the brain structure studied. There is no detectable myelination in the prosencephalon before the 7th month of pregnancy. Myelination in the telencephalon is most intense during the third trimester and postnatally and is mostly complete by the age of 2 to 3 years. The olfactory and auditory pathways and the sensorimotor cortex are the first to be myelinated, while projection and association pathways (in particular the prefrontal cortex) are the last ⁴⁴.

It is also worth noting that preoligodendrocytes are currently indistinguishable from another glial population – the polydendrocytes, or NG2 glia. Polydendrocytes give rise to oligodendrocytes, but these proliferative, lineage plastic, motile cells also play independent roles in response to injury and form uni-directional synapses with neurons ^{45, 46}. However, very

little is known about the function of these cells due to the current lack of specific tools with which to study them: an issue that should be a research priority for understanding brain development and health.

Microglia

Microglia constitute 5-15% of the total number of brain cells. Microglia are derived from a pool of embryonic myeloid precursors that arise from the yolk sac and infiltrate the developing brain, distinct from tissue resident macrophage⁴⁷. They have distinct maturational stages, are self-renewing and can live for up to 4 years in the human brain⁴⁸. During the first trimester of pregnancy in humans, microglia have an amoeboid morphology that evolves progressively towards an intermediate and then a mature phenotype with a small cell body and long processes. Around mid-pregnancy, microglial populations are principally detected in white matter fascicles such as the internal and external capsules, the corpus callosum, and axonal fascicle crossings⁴⁹. Experimental data support the hypothesis that these microglia play an important role in the origin of injury to these developing white matter tracts in preterm infants^{12, 50, 51}.

Microglia play a suite of key roles in brain development⁵², including regulating synaptic and neurite pruning and thus connectivity, regulating programmed cell death including the formation of cortical layers, and the initiation of oligodendrocyte maturation impacting myelin production. Like astrocytes, microglia can acquire various phenotypes in response to injury or insult. Depending on brain regions and pathological conditions the microglia can be directly deleterious or can attempt to repair the brain. These diverse roles for microglia mean that during brain development they can directly injure the brain via their inflammatory responses, and by not being capable of participating in brain building due to ‘distracted’ by

inflammatory activation. This is particularly relevant for preterm born infants, as the systemic inflammation commonly seen in these premature babies spreads to the brain and leads to the immune activation of microglia. This "double jeopardy" for the developing brain is an important contributor to the subsequent onset of cognitive and behavioral deficits seen in many formerly very premature babies^{53, 54}.

The environment and epigenetics

The different stages of brain development are finely controlled by diverse genetic programs. Nevertheless, experience, the environment, or stimulation can modulate, adapt or refine the initial pattern to allow the brain to adjust to its environment. These adaptive processes are the expression of the great plasticity of the developing brain and allow the acquisition of new skills throughout childhood and adolescence. This is true even regarding developmental stages that were initially thought to be almost completely controlled by genetic programming, such as the proliferation of neuronal precursors. Experimental studies have shown that a maternal factor (vasoactive intestinal peptide or VIP) can change the proliferative capacity of these precursors by up to 20%⁵⁵. However, the environment can also have deleterious effects on brain maturation. Preterm newborns are exposed to numerous stimuli that exist only sparingly or not at all with a fetus of the same age, such as excessive or repeated sensory stimulation, painful stimuli, stress, several neuroactive drugs, as well as the withdrawal of maternal and placental factors. Any environmental factor or drug that affects the brain is capable of altering a few or several stages of brain development.

The major mechanisms by which these environmental factors (positive or deleterious) act on brain maturation depend on the epigenetic events that control the organization and compaction of the genome, and thus the expression of genes. Chromosomes in eukaryotes

result from a complex between DNA and a protein sheath called "chromatin", whose basic unit is the nucleosome, around which the DNA is wrapped. Each nucleosome is composed of an octamer of histones (H2A, H2B, H3 and H4). The compaction of DNA - and thus the accessibility of genetic information to the transcriptional machinery – is regulated on the one hand by covalent modifications of the DNA (including DNA methylation), and on the other by post-translational modifications that decorate the N-terminal regions (tails) of histones (acetylation, phosphorylation and methylation). The combination of these two types of events governs the opening or closing of chromatin, and the transcription or repression of the gene in question.

The methylation of DNA at CpG islands located in transcriptional regulatory regions of genes represses their transcription by blocking the binding of transcription factors to the DNA ⁵⁶. DNA methyltransferases (DNMTs) catalyze the methylation of DNA by using S-adenosyl-methionine (SAM) as a methyl group donor. In addition, the information deposited by the methylation of the DNA is "read" and "translated" by proteins that recognize methylated DNA: the methyl-CpG-binding proteins (MBPs). These MBPs recruit histone-deacetylases, HDACs (and thus constitute the link between DNA methylation and the post-translational modifications of histones), as well as other chromatin remodelers, and contribute to the establishment of transcriptionally inactive chromatin. The crucial role of histone acetylation in brain development is illustrated, for example, by the role of the histone-acetyl-transferase CBP, whose mutation in the heterozygous state is characteristic of Rubinstein-Taybi syndrome in humans, and leads to anomalies of cortical gyration, a reduction of white matter and regional hypoplasia in association with intellectual disability ⁵⁷.

The level of DNA methylation is much higher in the brain than in other tissues and is essential for brain development in mouse models.⁵⁶ DNA methylation especially affects neuronal differentiation and survival and the neurogenesis/gliogenesis "switch". In humans, several syndromes with intellectual disability have a developmental origin linked to the DNA methylation pathway. This is the case with Rett syndrome, which is associated with mutations of the MBP MeCP2, and ICF syndrome (combined immunodeficiency, instability of the pericentromeric heterochromatin and facial dysmorphism), caused by mutations in Dnmt3b^{57, 58}. The recent discovery that DNA methylation occurs in a non-CPG context, mostly in brain neurons after birth, has greatly modified our understanding of the role of this epigenetic mark in pathophysiological brain development, in particular for RETT syndrome⁵⁹. There are numerous imprinted genes (i.e. those expressed uniquely from the paternal or maternal allele), which are affected by epigenetic regulation, are expressed in the brain. The deregulation of their expression is often associated with intellectual disability. This is the case, for example, with the neurodevelopmental syndromes, Prader-Willi and Angelman syndromes⁶⁰. Interestingly, fetal stress modifies the pattern of DNA methylation of key genes involved in neurodevelopment and the integrity of the adult brain (such as BDNF, Reelin or GAD67)^{57, 61}. Thus, women suffering from depression or anxiety-related disorders during the third trimester of pregnancy give birth to newborns in whom the promoter region of the glucocorticoid receptor gene is hypermethylated. Additionally, neuronal plasticity as well as learning and memory rely on the establishment of epigenetic events, and neuronal activity modifies patterns of DNA methylation⁶².

In summary, one could speak of "neuro-epigenetics" and all that this entails in terms of future therapeutic possibilities, since an in-depth knowledge of epigenetic events and their reversibility opens the door to the search for compounds that could remodel the epigenome of

the brain and reprogram neural cells. In this context, diets poor in methionine (the precursor of SAM) and treatment with HDAC inhibitors (such as valproic acid) have been widely prescribed for psychiatric disorders such as schizophrenia or bipolar disorder⁵⁷.

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Figure legends

Figure 1. Schematic representation of the major ontogenic events taking place in the human neocortex.

Figure 2. Schematic illustration of mammalian neocortical formation and neuronal migration.

GZ, germinative zone; I, cortical layer I or molecular layer; II to VI, cortical layers II to VI;

IZ, intermediate zone (prospective white matter); PPZ, primitive plexiform zone; SP,

subplate. Arrows and green circles indicate migrating neurons.