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Time Table of Normal Foetal Brain Development

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Abstract: The foetal brain develops within few weeks from a thin cell layer to a gigantic and complex network with billions of neurons and trillions of connections. This process is influenced by environmental factors (e.g. maternal stress) from the beginning. Understanding of the developmental processes is the basis of prenatal medicine and psychology. Five steps can be related to fairly defined time periods: (1) From 7 to 22 weeks of gestation 20 billion neurons are produced and migrate to their final locations in the brain. (2) From 20 to 35 weeks the transient subplate structure lays the foundation of the cortex. (3) The organization of the neural network (nerve fibre and synapse formation) starts at 24 weeks gestation and continues throughout life. (4) Individual adjustment of the neural network by elimination of more than 50% of the neurons and circuits also starts at 24 weeks, and shapes the brain in three waves. (5) Myelination of axons begins during the last weeks of gestation and continues for decades.

Keywords: cortex, gestational age, neuron, prenatal, subplate, synapse

Introduction

During the last twenty years, foetal brain development has become an essential topic of neuroscience as a result of modern non-invasive and computational techniques and animal models. The results allow quantitative description of the structure and development of individual nerve cells and entire networks within specific brain areas, and to relate the structures to the functions at both the single neuron and network levels (Berzhanskaya and Ascoli 2008). Recent results support the hypotheses of publications on prenatal psychology emphasizing the importance of environment and experience for the normal psychological development of the foetus (Fedor-Freybergh and Vogel 1988; Janus 2001, 2007; Janus and Linder 2006; Ridgeway and House 2006).

Several reviews on foetal brain development appeared during the last years (De Graaf-Peters and Hadders-Algra 2006; Eliot 2000; Gilbert 2001; Hüther and Krens 2006; Lagercrantz et al. 2002; Linderkamp 2005; Ridley 2003; Rutter 2006; Turkewitz 2007). Our present review is designed to summarize the present knowledge of foetal brain development with emphasis on the time-table of the events shaping the brain. Our paper provides the basis of understanding experience-dependent brain development and effects of maternal anxiety and stress on the brain and long-term outcome. Subsequent papers of our group will focus on these topics (Linderkamp et al. 2010a, b).

Early Human Brain Development

The brain development begins at approximately three weeks after conception (5 weeks of gestation) with the formation of the neural plate at the back of the embryo. A few days later the plate folds to form the neural tube around a canal. In the brain the canal later widens to the ventricles, in the spinal cord it forms the central canal. At the time of neural tube closure the neural wall consists of one or two layers of epithelial cells (neuroepithelium) which are the precursors of an enormous variety of neurons and the macroglia.

The development of the cerebral cortex occurs in precisely-timed stages (Table 1, Fig. 1). Each developmental process is also a vulnerable period which is sensitive to environmental insults rendering the brain susceptible to structural malformations and functional impairments.

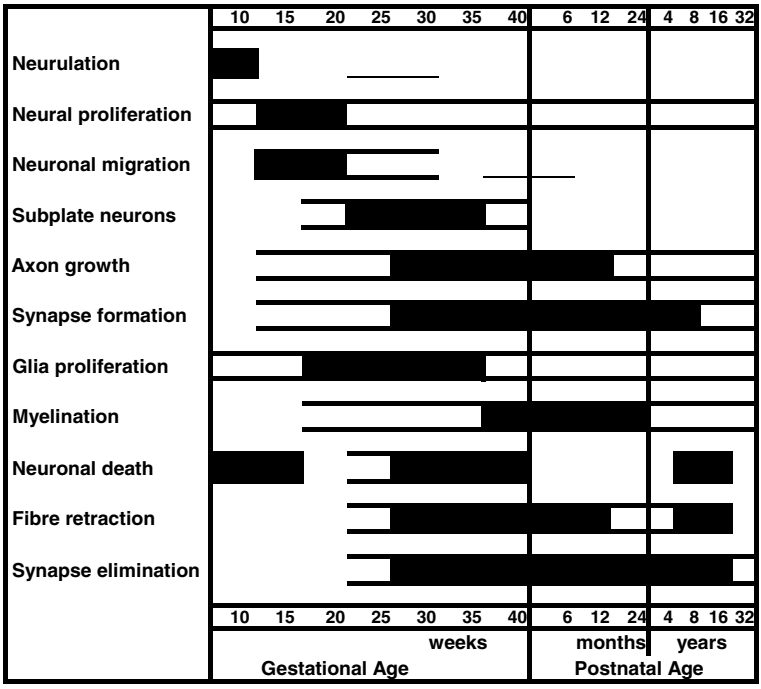

Fig. 1. Time table of developmental events of the human brain during foetal and postnatal life. Black shaded areas indicate peak activities, open lined areas indicate low or medium activity.

Neurogenesis: "Raw Material" for the Brain

Billions of nerve cells (neurons) are produced during the development of the central nervous system. Neurogenesis mainly occurs at the inner edge of the neural tube wall, the later ventricles (brain) and central canal (spinal cord), respectively (Fig. 2). In preterm infants the reproduction zone is still visible on ultrasound scans ("subependymal germinal matrix"). Cell division begins once the neural

Table 1. Major events in foetal cortical development.

Peak occurrence*	Major developmental events	Abnormal development
5-9 wk	Primary neurulation (neural tube formation) Prosencephalon formation (precursor of haemispheres)	Anencephaly Encephalocele** Meningomyelocele Spina bifida**
12-18 wk (6 wk to life long)	Neuronal proliferation (neurogenesis)	Encephalocele, microbrain** Schizophrenia**
12-20 wk (8-30 wk)	Neuronal migration Formation of cortical cell layers	Heterotopias (wrong place); reduced or no gyration: reduced attention and cognition, depressive signs**
22-34 wk (15-38 wk)	Subplate neurons (guidance of axons between thalamus, cortex and subcortical structures; final migration of neurons)	Impaired development of thalamus and cortex and connecting circuits: disorders of frontal, temporal and parietal centers**
24 wk to 15 mo (10 wk to life-long)	Outgrowth of axons Outgrowth of dendrites Synaptogenesis	White matter reduction Cortical dysplasias: Down, fragile-X syndrome sensory, behavioural, cognitive disorders**
24-38 wk (20-44 wk) 24 wk to life-long	Selective death of neurons Elimination of synapses	Excessive loss of neurons and connecting circuits: cognitive, sensory, behavioural, psychiatric disorders**
15 wk to 18 mo (6 wk to life-long)	Glial cells proliferate und differentiate (structural support, neuronal migration, myelin, “clean up”)	Impaired neuronal migration Loss of dendrites and synapses in frontal cortex, hippocampus, amygdale
35 wk to 24 mo (15 wk to adulthood)	Myelination	Dysfunction of axons: psychiatric, cognitive disorders**

Abbreviatons: IQ, intelligence quotient; p.n., mo, months postnatal; wk, weeks gestation
*Gestational (postmenstrual) age; in parentheses, occurrence prolonged at slower pace.
**Increased risk due to maternal stress has been shown in human foetuses or animal models (from Linderkamp et al. 2010b).

tube has closed at 4 to 5 weeks after conception (6 to 7 weeks of gestation). The majority of neurons are formed at 12 to 18 weeks of gestation. Approximately 100 000 neurons are produced during each second to provide a number of at least 200 billion (2×10^{11}) neurons in the human brain and 40 billion in the neocortex alone. Approximately 50% of the neurons are eliminated during the later maturation process, resulting in a final number of 100 billion neurons at 40 weeks (full-term).

Proliferation of neurons during the first 22 weeks of gestation is mainly determined by genetic factors (Bourgois 2002). However, severe maternal stress during the first trimester (i.e. neurulation and early neurogenesis) has been linked to an increased risk of encephalocele (Hansen et al. 2000) and schizophrenia (Khashan et al. 2008), suggesting that the expression of genes in early foetal life is influenced by external factors. Stress-induced reduction of neurons in late foetal life is probably the result of increased damage of neurons (Fabricius et al. 2008).

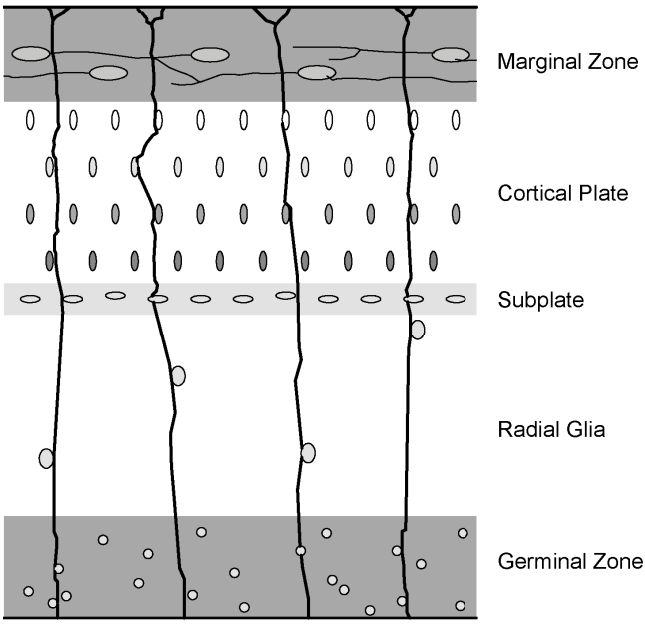

Fig. 2. Section through the cortex at approximately 24 weeks of gestation. Note that the germinal zone adjoins to the ventricle at the inner edge of the cortex. Newly formed neurons migrate along the radial glia through the subplate and previously formed neuronal layers to the upper layer of the cortical plate.

If the brain is sufficiently used and trained, new neurons are generated throughout life. Neural stem cells and pluripotent radial glia cells are able to differentiate into neurons in the adult brain (Mo et al. 2007). In mice, neurogenesis increased the efficiency of learning, but did not affect long-term memory (Zhang et al. 2008). The formation of new synapses and the prevention of neuronal damage are far more important mechanisms for life-long learning than the formation of new neurons (Uylings et al. 2005).

Migration of Neurons: Finding the Right Place

After several divisions neuroblasts lose their ability to divide and they begin to move away from the inner multiplication zone to the outer edges of the growing neural tube wall. Once a neuron has reached its final destination within the correct cortical layer, it will stay there for life. The first neurons start migration with the beginning of multiplication, the majority of cells move to their layer between 12 and 20 weeks of gestation (Gressens 2005).

Both passive pushing by subsequently migrating neurons and active movement of neurons are mechanisms of migration. In the cortex, neurons move radially outwards to the surface along specialized radial glial fibres (Fig. 2), which span the entire thickness of the hemisphere from the ventricular surface to the external pial surface (Rakic 2003). This “ladder” facilitates the journey through the earlier arriving cell layers. At the brain surface, the neurons leave the ladder and move

Table 2. Maturation of nerve cells in the cortex.

Step	Events
Neurogenesis	Subventricular stem cells divide symmetrically. The last division results in larger neurons before they migrate.
Radial glia	Generated from same stem cells a neurons. Form long processes through the entire cortex (fig. 2).
Migration	Neurons climb on radial glia to cortical surface.
Contact to subplate neurons	Migration through subplate neurons (fig. 2) and contact to thalamo-cortical and cortico-cortical fibres may accelerate their maturation.
Formation of six cortical layers	Neurons migrate through previously formed layers to the surface. Thus, the early-migrating cells form the superficial layer, the latest the deepest until six cortical layers have been established. Neurons assemble in columns above the stem cells and are therefore clonally related.
Astrocyte formation	Astrocytes are generated from radial glia.
Life-long neurogenesis	New neurons are generated from remaining subventricular stem cells and locally from radial glia.

laterally to give way to the subsequently arriving neurons and to form a layer at the surface of the cortex. Then the next group of migrating cells passes through this layer and forms a new layer at the surface. This process continues until six layers have been formed. Thus, the earlier generated neurons form the deepest cortical layer, and the latest cells settle in the most superficial layer (inside-out order). The radial migration of neurons originating from the same reproduction site results in columns of clonally related cells. This may be important for their specialized functions in their final cortical destination.

Insufficient movement or migrations to wrong places result in heterotopias which may be associated with serious malformations as lissencephaly (reduced gyration, “flat brain”), epilepsy and mental retardation (Gressens 2005; Nicolic and Reynolds 2008). Although normal migration of neurons to the right location is probably determined by genes (Rutter 2006), abnormal migration is mostly the result of environmental factors. Maternal stress during the gestational age of maximal neuronal migration has been shown to predispose the offspring to a variety of impairments including reduced attention span, cognitive problems and depressive symptoms (van den Bergh et al. 2008).

Organisation of the Neural Network

The first two steps, multiplication and migration of primitive nerve cells, are mostly completed at 22 weeks of gestation. At the beginning of migration neurons are not yet specialized, but they lose their pluripotency once they have reached their final position in a specialized region of the central nervous system.

Organization of an individual neuron refers to the establishment of connections with other cells and the specialization to distinct functions within the neural network. Organization of the total central nervous system refers to the formation of the entire neuronal network and its capacity to operate as an integrated whole.

Table 3. Major steps of neural organisation of the cortex (modified from Volpe 2008).

Goal:
Establishment of a functioning neural network
Major period:
20 weeks of gestation to years after birth
Steps:
• Formation of subplate neurons with initial fibre and synapse formation.
• Formation of the cortical plate with six layers of aligned neurons.
• Outgrowth of nerve fibres (axons, dendrites) and their ramifications.
• Synptogenesis.
• Selective elimination of neurons (apoptosis), nerve fibres and synapses.
• Proliferation and differentiation of neuroglia.

The process of organization starts at approximately 22 weeks of gestation and includes actions of subplate neurons, outgrowth of neural fibres, synaptogenesis and myelination.

Subplate Neurons: Pioneers Paving the Wire Tracks

Subplate neurons play a major role in the development of the gigantic network connecting billions of neurons and are probably responsible for the evolution of the neocortex. The subplate zone is situated between the intermediate zone (precursor of white matter) and the cortical plate with the six layers of neurons (Fig. 2). In magnetic resonance images, the subplate is visible as a continuous band in the entire cortex at 20–27 weeks of gestation, starts to disappear in the parietal lobe at 28 weeks, but remains prominent in the frontal lobe up to 35 weeks (Perkins et al. 2008). At 38 weeks, 90% of the subplate neurons have disappeared.

The subplate neurons excrete neurotransmitters that attract axons ascending from the thalamus and dendrites descending from cortical neurons for transient connections with the subplate neurons. When the subplate neurons die, the thalamic and cortical neurons become directly connected (thalamo-cortical tracts). Moreover, subplate neurons help cortical neurons to establish connections with other cortical neurons in both hemispheres and to guide the final migration of cortical neurons within the six layers. They help to balance excitation and inhibition in cortical layers, which is important for the "plasticity" of brain functions (Kanold and Shatz 2006). The transient connections among various brain centres via subplate neurons are the basis for early foetal (and preterm's) behaviour (Kostovics and Jovanov-Milosevic 2006).

Maternal stress during the peak actions of subplate neurons from 22 to 34 weeks gestation has been linked to developmental delays, lower IQ, behavioural problems and schizophrenia in offsprings (Bergman et al. 2007). It is likely that the stress exposure of preterm infants during intensive care can alter subplate neurons, thereby contributing to the high risk of preterm infants to long-term cognitive and behavioural problems.

Wiring the Neural Network: Axons, Dendrites and Synapses

The set-up of a functioning neural network connecting all parts of the central nervous system and other target organs requires trillions of connections among neurons via axons, dendrites and synapses. The migrating cells have no functioning axons and dendrites. Having migrated to the appropriate position, axons and dendrites begin to grow out of the young neurons.

Usually one *axon* only arises from each cell (Fig. 3). Axons are the long nerve fibres connecting distant parts within the central nervous system and with peripheral organs (e.g. muscles and glands). Their final length can be more than a meter in adults, but also just a few μm, if they connect adjacent neurons. Axons develop many branches at the tip and each final branch can form a synapse with a final branch of a dendrite or sometimes another axon or a nerve cell body. *Dendrites* emerge from many points along the cell body and appear very much like branches on a tree. Axons and dendrites find their target cells principally by growing in the direction of the targets. This growth is guided by molecules bound to cells (for short-range chemoattraction) or diffused in the environment (long-range chemoattraction, e.g. nerve growth factor). Target cells also present and secrete chemorepellents that inhibit the growth of connecting nerve fibres to these cells. The search of outgrowing fibres for target neurons can be highly specific or more or less arbitrary. Specific connections are formed between neurons that express specific marker molecules, thereby giving the connecting cells no choice (cell specificity). Other neurons are attracted to send fibres to neurons in a defined region (topographic specificity).

Synapses are formed by proteins acting as molecular switches between two nerve fibres. Chemoattractants determine when and where synapses are formed and their specificity and stability. Moreover, formation, specificity and stability of a synapse depend on the quality and quantity of impulses travelling through the connecting fibres. Synaptic activity provides critical information about the usefulness of synaptic connections, thereby influencing synapse stability and maintenance (Waites et al. 2005). Synaptic activity promotes the formation of new synapses and strengthens existing synapses in the neighbourhood. Thus, synapse formation and stabilization are dynamic processes, requiring bi-directional communication between connected partners. Subtle alterations in synaptic connections are the means by which learning wires the pathways to memory (Ge et al. 2007).

Although the first synapses are produced already at 8 weeks of gestation, synapse formation is slow until 24 weeks of gestation resulting in a total number of synapses that is not much higher than the total number of neurons. From 24 weeks gestation to 12 months of postnatal age, a myriad of connections is formed among billions of neurons. At full-term each cortical neuron is linked with approximately 2500 other neurons, at 12 months of postnatal age with 15 000 (Petanjek et al. 2008). Synaptogenesis begins in a relatively short time period in all cortical regions, but the maximum synaptic density is reached at different times after full-term, ranging from 3 months in the auditory and visual cortex to 15 months in the prefrontal cortex (Bourgeois 2002).

After the first year of postnatal life the total synapse number slowly increases and reaches the maximum at five years when the child's brain weighs almost as much as in adults. Then the number of synapses plateaus until about 10 years and

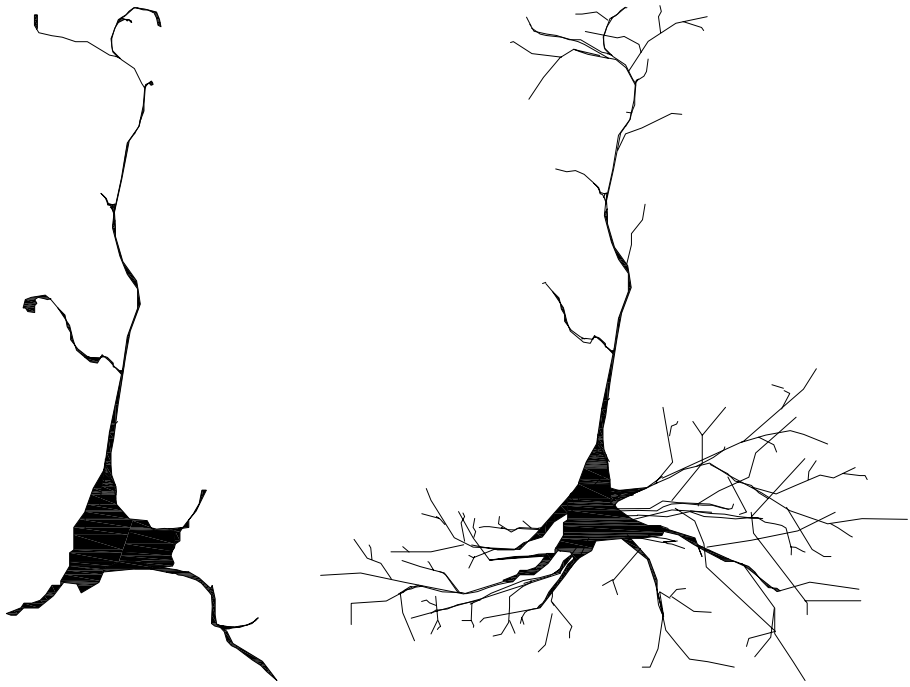

Fig. 3. Neurons with one axon and several dendrites arising from the neuronal cell body. The left neuron represents the development in the sensory cortex at approximately 24–28 weeks, the right neuron at 32–40 weeks. Note the marked differences in ramifications between the two neurons.

begins to decrease by approximately 40% with the onset of puberty. Thus, during the first 5–10 years of life, the child achieves the highest number of synapses, thereby enabling the child to acquire enormous behavioural, social, environmental, linguistic and cultural information. After the age of five years, synaptogenesis continues as a local event (Bourgeois 2002) in dependence on the activity of neighbouring synapses. Formation of new synapses and changes of specificity and stability of synapses are fundamental to life-long learning, memory and cognition in the mature brain (Waites et al. 2005).

Outgrowth of fibres and formation of synapses are largely influenced by environmental factors, including sensory experience. Both decreased sensory input of the foetus and maternal stress may cause a marked reduction of axons, dendrites and synapses in the prefrontal cortex, the hippocampus and other brain centres (Linderkamp et al. 2010b).

Glial Cells and Myelination

Glial cells (also called neuroglia) are non-neuronal cells that outnumber neurons by about 10 to 1, but constitute only half of the brain volume, since they are smaller than neurons. Glial cells surround neurons and hold them in place, play an important role in neuronal and axonal guidance, supply nutrients and oxygen to neurons, produce and remove chemical transmitters, insulate axons by myelin,

destroy pathogens, dead neurons and other debris, and contribute to formation of new neurons. Glial cells are crucial in the development of the nervous system and in processes such as synaptic plasticity and synaptogenesis. Various types of glial cells are defined by origin, appearance and functions (Table 4).

Macroglial cells comprise radial glia, astrocytes and oligodendrocytes and develop from the same stem cells in the ventricular zone of the neural tube as the neurons. Radial glia cells are the progenitors of astrocytes, some oligodendrocytes and neurons. In the developing brain, radial glia functions as a "ladder" upon which neurons migrate to the surface of the cortex. Microglia are specialized immune cells capable of phagocytosis. They are derived from haemopoietic precursors as other immune cells.

Oligodendrocytes produce myelin that forms insulating sheaths around axons. *Schwann cells* provide myelination to axons in the peripheral nervous system. *Myelin* is a white fatty material wrapped around most neural axons. It prevents the leakage of ions and thus of electrical current from the axon, thereby increasing the speed of nerve conduction by ten to one hundred times. Moreover, myelin prevents erratic activation of adjacent axons. Without myelin, electric activity would be aimlessly distributed throughout the brain, and information would become chaotic. Myelination also inhibits plasticity, since a myelinated axon has less ability to branch out and connect with other neurons. Myelin is involved in cognitive functions and learning (Fields 2008).

Myelination starts in the spinal cord (at about 12 weeks gestation), then in brain stem (14 weeks) and thalamic axons (20 weeks), and finally in the cortex (35 weeks) and continues for decades in the human brain (Miller et al. 2003). Axons connecting the frontal-limbic system (responsible for complex cognitive functions) start to myelinate after birth. Late myelination explains that the brains of infants and young children are slow compared with adult brains. Myelination is modifiable by experience and severe maternal or postnatal stress may inhibit myelination, thereby contributing to psychiatric disorders, including schizophrenia and depression, and cognitive impairment (Fields 2008).

Shaping the Brain by Elimination of Excess Neurons and Circuits

At least twice as many neurons as necessary are produced during the time period of active neuronal multiplication, and most of the excess neurons are eliminated during maturation of the neuronal network ("programmed cell death" or apoptosis). Three peak periods of neuronal death can be distinguished (Fig. 1): 1) at the beginning of neurogenesis; 2) from 24 to 38 weeks gestation; and 3) between the onset of puberty and adulthood (Lossi and Merighi 2003).

The second and third periods are linked to selective elimination of axons, dendrites and synapses. Production of neurons and growth of axons and dendrites in the direction of target cells are not very selective and result in overproduction of connections. The initial wiring is diffuse, with a lot of overlap making communication inaccurate and disorganized. Elimination of fibres, synapses and entire neurons allows quantitative adjustments of connections between neurons and to compensate for errors of cell migration (mislocation) and projection of axons and dendrites (misprojection). Elimination of neurons, fibres and synapses parallels

Table 4. Glial cells.

Cell type Structure	**Functions**
Radial glia Long radial processes spanning the thickness of the cortical wall	Progenitors of neurons and astrocytes Guidance of neurons and nerve fibers Regulation of synaptic plasticity
Astrocytes Support cells with short, thick processes for neurons ("protoplasmic" astrocytes) or long, thin processes for nerve fibers ("fibrous" astrocytes)	Structural support of nerve fibers and cell bodies Secretion and elimination of neurotransmitters Chemical homeostasis Oxygen and nutrient supply for neurons Blood-brain barrier Regulation of local blood flow
Oligodendrocytes **Schwann cells** Small cells with few processes	Myelin production; functions of myelin: • increases the speed of nerve conduction by ten to one hundred times; • prevents loss of activation by ion diffusion and erratic activation of adjacent axons • Inhibition of the formation of new fibres for new connection (reduction of plasticity); • involved in learning and cognition.
Microglia Resemble blood monocytes	Immune cells (phagocytosis of pathogens, cell debris)

the formation of new connections to match the number of outgrowing fibres to the capacity of target cells (Lossi and Merighi 2003; Saxena and Caroni 2007).

The fittest neurons survive in competition for limited resources in the brain as electrical impulses, neurotransmitters (e.g. nerve growth factor) and nutrients within the neural network. Active cells with many connections to target cells receive more of these life-savers than less active neurons. Thus, overproduction and subsequent elimination of excess neurons and connections are not a waste of resources, but necessary to allow optimal locations and interconnections of neurons.

Synapses are newly formed and eliminated throughout life. This allows continuous reorganization of the neural network in accordance with the requirements of the environment and is thus the basis of life-long neural development and plasticity (Goda and Davis 2003). Between the onset of puberty and adult age approximately 40% of synapses and nerve fibres (Bourgeois 2002) and a substantial portion of neurons are eliminated, particularly in the prefrontal cortex, the brain region involved in major cognitive abilities. In accordance with the "use it or lose it" principle, cells with apparently redundant connections for unused (not useless!) skills are discarded to enhance abilities that have been extensively utilized (Lopez et al. 2008).

Adjustment of neurons and connections to the demands of the individual environment usually makes sense, but can result in severe impairments of sensory, behavioural and cognitive functions, if the foetus or young infant is deprived from normal sensory input or exposed to severe stress (Fabricius 2008). The hippocampus (stores memory!) is particularly sensitive to the apoptotic actions of

corticosteroids transmitted to the foetus as a result of maternal stress (Fenoglio et al. 2006).

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