Chapter 2:

ONTOGENY OF THE HUMAN CENTRAL NERVOUS SYSTEM:

WHAT IS HAPPENING WHEN?[a]

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Abstract

The present paper reviews current data on the structural development of the human nervous system. Focus is on the timing of ontogenetic events in the telencephalon. Neuronal proliferation and migration especially occur during the first half of gestation; the second half of gestation is the period of the existence of the functionally important transient structure ‘subplate’ and the major period of glial cell proliferation and programmed cell death. Axon and dendrite sprouting and synapse formation bloom during the last trimester of gestation and the first postnatal year. Major part of telencephalic myelination occurs during the first year after birth. Many developmental processes, such as myelination, synapse formation and synapse elimination continue throughout childhood and adolescence. Evidence is emerging that the peak of synapse elimination occurs between puberty and the onset of adulthood. Neurotransmitter systems are present from early foetal life onwards and their pre- and perinatal development is characterized by periods of transient overexpression. The latter is for instance true for the acetylcholinergic, catecholaminergic and glutamate systems. Thus, the development of the human brain is characterized by a protracted, neatly orchestrated chain of specific ontogenetic events. The

continuous changes of the nervous system have consequences for vulnerability to adverse conditions, for diagnostics and for physiotherapeutical intervention.

Keywords: brain development, human development, transient circuitries, preterm, stress

Introduction

The development of the central nervous system (CNS) is a complex and long-lasting process – this can be read in many textbook chapters (e.g., Volpe 2001, Lagercrantz et al 2002). The aim of the present review is to assess as accurately as possible when specific events take place during ontogeny of the human nervous system. Knowledge on the exact timing of ontogenetic events during human brain development will shed light on the mechanisms playing a role in the determination of sequelae after adversities occurring at a specific point in time during brain development (excellently reviewed in Volpe 2001). Knowledge on the timing of developmental processes in the human nervous system is also pertinent for the development of appropriate neurological assessment techniques and for the interpretation of neurological findings at early age. It might also facilitate our understanding of the timing of intervention in infants at high risk for or with developmental disorders. For the timing of early intervention it is generally assumed that 'earlier is better' (Guralnick 2000), but a recent review on the effect of early intervention in 'high-risk' infants indicated that this is not necessarily the case (Blauw-Hospers and Hadders-Algra 2005).

In the present review we based ourselves predominantly on human data. For the missing links we preferably used non-human primate data; when such data were not available, rodent data were used. We zoomed in

on ontogenetic events in the telencephalon, i.e., the major neural determinant of human behaviour. In order to facilitate the understanding of the timing of the various events we included a schematic timetable of the various developmental processes (Fig 1).

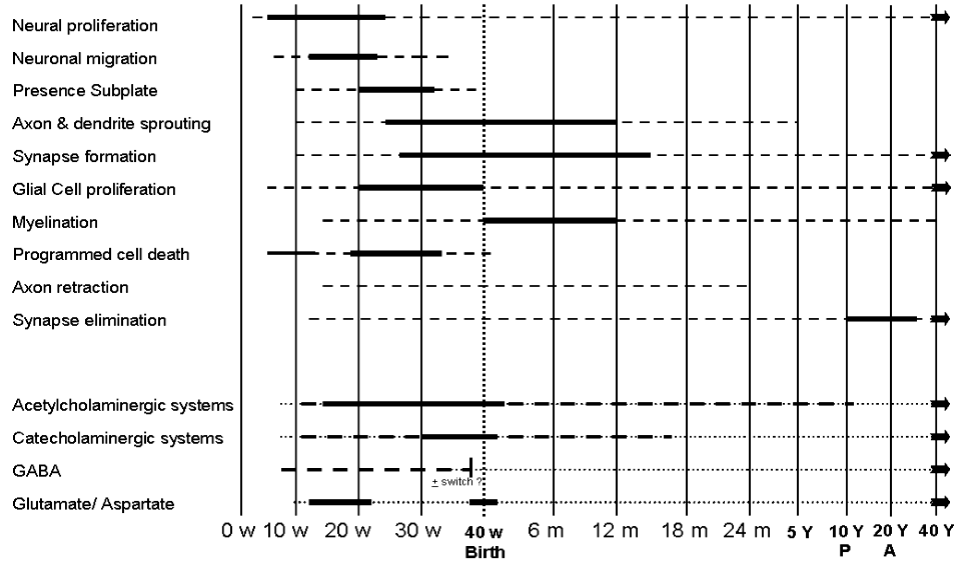

Figure 1: Summary of timing of neurobiological processes in the telecephalon during human ontogeny

Note that the time axis at the bottom of the figure is an arbitrary one. W = weeks PMA, M = postnatal months, Y = years, P = onset of puberty, A = onset of adulthood, S = switch.
In the upper part of the figure a broken line means that the process is active, a bold line indicates that the process is very active. In the lower part development in various neurotransmitter systems is represented. A thin broken line means that the transmitter is present; a continuous bold line represents a period of overexpression of the transmitter. The increasing dot density at the catacholaminergic systems denotes the gradual increase in dopaminergic activity. The bold broken line at the GABAergic systems reflects that GABA in early life exerts an excitatory function and later on switches (S) to its adult inhibitory function.

Ontogeny of the human brain

Cell proliferation and neuronal migration

In the fifth week postmenstrual age (PMA) the neural tube starts to develop. Neural tissue differentiates along several axes: a) a longitudinal axis, where the major subdivisions of the Central Nervous System (CNS), namely the forebrain, midbrain and spinal cord, develop, b) a vertical axis that establishes dorsal and ventral sides and c) a horizontal axis that establishes medial and lateral structural growth. The axes of the neural tube are associated with gradients of genetic expression during programming, with many genes often expressed more strongly in some regions and progressively decreasing expression in more distal regions (Sarnat and Flores-Sarnat 2004).

Shortly after closure of the neural tube specific proliferation areas are formed in the ventricular and subventricular zones. The latter – possibly phylogenetically younger – zone gives rise to neurons and glial cells, the former zone produces mainly neurons (Mrzljak et al 1992). The majority of neuroblasts is formed in week 5 to 25 PMA, and the bulk of gliacells is produced between week 20 and 40 PMA (Mrzljak et al 1992). Exceptions to the rule that the majority of neurons are generated during the first half of gestation are the granule cells of the olfactory bulb, cerebellum and hippocampus, which continue their genesis after birth (Rakic 2002). The first postmitotic cells migrate in a radial fashion out of the neuroepithelium and form the first recognizable cortical layer, i.e. the preplate. In the human the preplate is present from about 7 till 10-11 weeks PMA. Subsequently, within the preplate the cortical plate is formed with on its superficial side the marginal zone and on the inner side the subplate (Super et al 1998).

Once neurons have been generated they move from their place of origin to their final place of destination. Two forms of migration occur, passive cell displacement and active cell migration (Rakic 2002). In passive cell displacement newborn cells push earlier generated cells to the surface of the brain. Active cell migration is found in particular in the cerebral cortex, where the sites of destination can lie at substantial distance from the sites of origin due to the age related increase in thickness and layering of the cortex. Most cortical neurons migrate to their destinations along specialized radial glial fibres, which span the entire thickness of the hemisphere from the ventricular surface to the external pial surface (Rakic 2002). These glial guides, which are grouped in fascicles of 3-10 radial fibres (Gressens 2000) , are induced by the pioneering Cajal-Retzius cells of the marginal zone (Super et al 1998). Neuronal migration along the radial glial scaffold most likely is regulated by complex molecular interactions between neuronal and glial cells (Hatten 1999). Various substances play a role in these cell-cell interactions, such as glycoproteins, membrane lipids containing long-chain fatty acids, GABA and glutamate (Gressens 2000). The radial scaffolding guarantees a columnar distribution of clonally related neurons derived from the ventricular ´protomap´ (Rakic 1988). The settling of the neurons occurs in an inside-out order with the earlier generated neurons travelling to the deepest cortical layers, and the later generated neurons finding their destiny in more superficial layers of the cortex. In the human cerebral cortex migration takes place from the early phases of brain development. It peaks between the third and fifth month of gestation (Rakic 1994, Gressens 2000). The point of time when migration stops is still a matter of debate, but recent data indicate that this might well be around 30 weeks PMA (Gupta et al 2005). Less than 10% of cortical neurons migrate in a non-radial fashion (Rakic 2003). The latter is true in particular for

GABAergic local circuit neurons which migrate tangentially from their origin in the subcortical ganglionic eminence (Letinic et al 2002). This telencephalic-diencephalic migration occurs between 18 and 36 weeks PMA (Letinic et al 1997, Letinic and Rakic 2001).

The subplate: an important transient structure

Already during migration neurons start to differentiate. But major part of axon and dendrite sprouting occurs when the cells have reached their final position. The guidance of axon sprouting largely depends on the recognition of cell surface molecules, extracellular matrix cues derived from the cells along the pathway and chemical signals, such as the nerve growth factor from target and intermediate cells (Letinic et al 2002, Rakic 2003). In the axonal routing to and from the cortex the subplate plays a pivotal role. The subplate emerges during early foetal life and is thickest around 29 weeks PMA (Kostovic et al 2002). It functions as a 'waiting room' and temporary goal of afferent fibres originating from the thalamus, basal forebrain, monoaminergic brainstem nuclei and the contra- and ipsilateral hemispheres, which head for a cortical destination. Probably the subplate also plays a role in the guidance of some corticofugal pathways (Super et al 1998, Kostovic and Judas 2002, Judas et al 2003). It is important to realize that the 'waiting room' phase is not a period of functional arrest as the temporary afferents contribute to the early and transient cortical neuronal circuits involved in the generation of foetal behaviour (Kostovic and Judas 2002). The subplate is regressing after 31 weeks PMA and disappears in the period till about 38 weeks PMA. The dissolution is mainly brought about by a relocation of thalamocortical, callosal and associative fibres to the cortical plate (Judas et al 2003) and coincides with the rapid expansion of cortical gyration (Van der Knaap et al 1996).

Neuronal differentiation and synapse formation

Young neurons produce axons. The axons can be short, for instance in case of interneurons, but they also can have considerable length. This is true for the early emerging monoaminergic systems, callosal fibres and the corticospinal tract. The growth cones of the developing axon pathways navigate to their intermediate and final targets by responding to a variety of substrate bound or diffusible molecular targets at near or long distance. The axon guidance cues, which mainly belong to the families of netrins, semaphorins, slits and ephrins, can act as chemoattractor or chemorepellent (Judas et al 2003). From the major descending fibre systems, the corticospinal tract is the last to enter the spinal cord. Eyre et al. (2000) demonstrated that corticospinal axons reach the lower cervical spinal cord by 26 weeks PMA at the latest, where after they progressively and extensively innervate the spinal neurons, including the motor neurons (Eyre et al. 2000).

Dendritic development starts early during foetal life. The complex patterns of dendritic growth and branching are the result of a complex molecular orchestration of intrinsic and extrinsic cues (Jan and Jan 2003). The dendritic development of cortical neurons proceeds relatively slowly during the first two trimesters of gestation. Dendritic trees of neurons in the subplate and the deepest cortical layers, which are part of the mid-gestational transient neural circuits, mature earlier than those of more superficial cortical layers (Kostovic and Judas 2002). Dendritic development accelerates from the third trimester of gestation onwards to remain very active till the end of the first postnatal year (Super et al 1998, Eyre et al. 2000). Thereafter dendritic growth of cortical neurons continues till about the age of 5 years (Koenderink and Uylings 1995).

The length of axons and dendrites increases five to ten times during the first six postnatal months. Also the most striking development of dendrite elaboration occurs in this period (Becker et al 1984, Webb et al 2001, Rakic 2002, Nimchinsky et al 2002).

In parallel to dendritic development the number of synaptic connections increases. The very first synapses are found in the spinal cord at 8 weeks PMA (Okado and Kojima 1984) and in the cerebral cortex at 9-10 weeks PMA (Molliver et al 1973, Zecevic 1998). After the formation of the cortical plate synaptic density steadily increases with a rate of about 4% per week till 24-26 weeks PMA in virtually all cortical regions (Zecevic 1998). Next cortical synapse formation starts to boom, resulting in a six-fold increase in synaptic density from 28 weeks PMA till the age at which the peak in synaptic density occurs (Huttenlocher and Dabholkar 1997). Maximum synaptic density is reached in the primary sensory areas such as the auditory and visual cortex at the age of 3 months post-term (Huttenlocher 1984, Huttenlocher and Dabholkar 1997). This is considerably earlier than in the prefrontal cortex where maximum density first occurs at the age of 15 months (Huttenlocher and Dabholkar 1997).

Glial cells and the formation of myelin

While neurons are the most characteristic cells of the nervous system and are primarily responsible for information transfer, they are dependent on, interact with and are surrounded by glial cells. Two basic forms of glial cell can be distinguished: macroglia and microglia. Microglia, which are the CNS resident macrophages, are immigrants from the haematopoietic system during very early development. Macroglial cells are present in various forms, oligodendrocytes and astrocytes being the most prominent ones. Oligodendrocytes are responsible for the formation of myelin in the

CNS. The functions of astrocytes are more diverse and include regulation of the composition of the extracellular environment, clearance of excess of neurotransmitters and modulation of formation and efficiency of synaptic connections (Miller 2002). Macroglia, i.e., the astrocytes and oligodendrocytes, are derived from the same tissue as the neurons themselves, i.e. they arise from precursor cells in the germinal matrix (Miller 2002, Liu and Rao 2004). In any particular region of the CNS cell types arise in a distinct sequence: first the neurons arise, followed by the astrocytes, and finally the oligodendrocytes are produced (Altman and Bayer 1984). The earliest oligodendrocyte precursors arise in the ventral regions of the neural tube and – more rostrally - in the ventricular and subventricular zone (Pringle and Richardson 1993, Ono et al 1995). Other sources of telencephalic oligodendrocytes are the medial and lateral ganglionic eminence (Rakic and Zecevic 2003). Immature oligodendrocytes migrate along considerable distances to their final destination (Miller 2002). Migration in the cerebral cortex takes place via radial routes – which is the case for cells originating in the ventricular region - and via tangential routes, which is the pathway for cells originating in the subcortical ganglionic eminences (Kakita and Goldman 1999). The mechanisms governing oligodendrocyte migration are not well understood. Factors that have been proposed to play a role are pre-existing axons, adhesion molecules and extracellular matrix receptors (Miller 2002). The final step in oligodendrocyte development is the formation of a mature myelinating phenotype. Myelin is a fatty insulating sheath. It surrounds axons and promotes a rapid and efficient impulse conduction (Brostoff et al 1977). Myelination starts in the human spinal cord at 12 weeks PMA (Weidenheim et al 1996), in the telencephalon around week 14 PMA (Zecevic et al 1998). Iai et al (1997), who used the expression of the major myelin protein

proteolipid protein as a marker of myelination, revealed that myelin can be detected in the globus pallidus and pallidothalamic fibers at 20 weeks, in the striatum at 28 weeks, in the pre- and postcentral gyri and the optic radiation at 35 weeks and in the acoustic radiation at 40 weeks PMA (Iai et al 1997). These data are in line with those of Back et al (2001) who reported that oligodendrocyte progenitor cells in the periventricular white matter are abundantly present till 27 weeks PMA, where after they gradually turn into more mature myelin producing cells (Back et al 2001). It is noteworthy that the progenitor and immature oligodendrocytes are much more vulnerable to hypoxic-ischaemic injury than the mature myelin producing oligodendrocytes (Fern and Moller 2000). Data from recent diffusion-weighted magnetic resonance imaging are in line with the above-described timetables of early myelination (Prayer and Prayer 2003, Miller et al 2003).

During the first year after term age myelination becomes a vigorously active process (Yakovlev and Lecours 1967, Brody et al 1987). Thereafter myelination continues at a slower pace (Yakovlev and Lecours 1967). Volumetric imaging studies indicated that it takes at least four decades before myelination is completed, with the intracortical connections being amongst the last ones to become myelinated (Paus et al 1999, Bartzokis et al 2001, Sowell et al 2002).

Regressive phenomena

Programmed cell death is a highly phylogenetically conserved mechanism by which cells die following a stereotyped series of molecular and cellular events commonly referred to as apoptosis. It plays a fundamental role in the control of the final number of neurons and glial cells (Lossi and Merighi 2003). Various techniques, such as the TUNEL method

which enables the detection of genomic DNA fragmentation, offered new insight into apoptosis in the human brain. Two subsequent periods of cell death can be distinguished. The first occurs at the onset of neurogenesis and is not related to synapse formation (Lossi and Merighi 2003). This type of apoptosis has been observed in the proliferative zones of the human telencephalon already at 7 weeks PMA. It continues during the first trimester of gestation (Rakic and Zecevic 2000). The second process is linked to cell differentiation and synaptogenesis and therefore may be related to the wiring of young neurons (Lossi and Merighi 2003). In the cerebral cortex this type of cell death peaks at 19 to 23 weeks PMA (Rakic and Zecevic 2000), in the striatum between 22 and 29 weeks and in the globus pallidus between 26 and 33 weeks PMA (Itoh et al 2001). Possibly, the apoptotic index in cortical regions is lower than that in the brainstem (Chan and Yew 1998). Rabinowicz and coworkers (1996), who calculated neuronal densities in various cortical regions, estimated that apoptosis in motor, prefrontal and cingulate cortices continues till term age and that in the sensory areas till about 44 weeks PMA. Even though apoptotis strongly depends on endogenous, programmed processes, rodent experiments indicated that enriched behavioral experience during the period of programmed cell death resulted in an increased level of neural cell numbers in adulthood. The increased cell number was attributed a reduction in programmed cell death and an increase in cell proliferation (Greer et al 1982, Kolb 1999, Kolb et al 2001).

Axon retraction is another prominent regressive process in the CNS (Cowan et al 1984). It starts as soon as neurons have formed axons. Very little information on the removal of axons in man is available. Extrapolation from monkey data indicates that axon retraction occurs especially during the second half of gestation and continues after term age (Darian-Smith et

al 1990, Barone et al 1996). The latter seems to be true in particular for long projection fibres such as the fibres of the corpus callosum and corticospinal tract. LaMantia & Rakic (1990) reported that in callosal development of the rhesus monkey two phases of axon elimination can be distinguished: a phase of rapid elimination occurring during the first three postnatal weeks and one of slower elimination during the next three months. They suggested that the elimination of callossal axons might help to shape local synaptic relationships between individual terminals and their targets, rather than defining the gross topography of callosal projections. Information on axon elimination in the corticospinal tract is present in the form of neuroanatomical data of macaque monkeys (Galea and darian-Smith 1995) and neurophysiological data of human infants (Eyre et al 2001, Eyre 2003). The data indicate that during the first 24 postnatal months a substantial part of corticospinal axons, in particular ipsilateral projections, is eliminated. Physiological data of children with congenital hemiplegia suggest that axon elimination in the corticospinal tract may be activity-dependent, as in these children major parts of the ipsilateral corticospinal projections are conserved (Eyre et al 2001).

Throughout life synapse formation is paired with synapse elimination. The resulting continuous synaptic reorganisation forms the basis of neural development and plasticity (Purves 1994, Goda and Davis 2003). During prenatal and early postnatal life the net effect of synaptic development in the cerebral cortex is a rapid increase in synaptic density. Human data indicate that cortical synaptic density peaks during infancy (visual and auditory cortex: at 3 months (Huttenlocher and Decourten 1987, Huttenlocher and Dabholkar 1997) prefrontal cortex: at 15 months (Huttenlocher and Dabholkar 1997), and decreases gradually thereafter till adult levels are reached around puberty (Huttenlocher and Dabholkar

1997). The first monkey studies on cortical synapse elimination provided data that generally were in line with this developmental course (Rakic et al 1986). But later monkey studies, which were more detailed, suggested that the time course of synapse elimination is different. These studies indicated that after the phase of rapid synaptogenesis, first a plateau phase follows during which synaptic density remains relatively constant. The plateau phase ends around the time of puberty, at which point in time synaptic density in all cortical regions starts to decrease (Zecevic et al 1989, Bourgeois et al 1989, Bourgeois and Rakic 1993). The process of synapse elimination results in a decrease in synaptic density of 40% between the onset of puberty and adult age (Bourgeois and Rakic 1993). The discrepancy between the more recent monkey data and the available human data can be explained by the lack of human data in the age period of 5 to 12 years (Huttenlocher and Dabholkar 1997). The onset of substantial cortical synapse elimination occurring first at puberty would fit well with the clinical notion that with the emergence of physical signs of puberty the prevalence of minor neurological dysfunction shows a marked decrease (Lunsing et al 1992).

Neurotransmitters and neuromodulators

Neurotransmitters and neuromodulary substances play an important role in the development of the nervous system. They affect neural migration and differentiation (Herlenius and Lagercrantz 2001) and especially contribute to the shaping of synaptic circuitries (Bouwman et al 2004). The major neurotransmitters (catecholamines, acetylcholine, glutamate and gamma-aminobutiryc acid (GABA)) are present from very early age onwards, not only in the spinal cord and brainstem, but also in telencephalon (Kostovic 1986, Verney 2003). The way in which

neurotransmitters affect development can change with age. Here we summarize the ontogenetic changes in the major neurotransmitter systems. The summary remains somewhat incomplete as information on development of neurotransmitter systems in the human CNS is limited and scattered.

Hellström-Lindahl et al. reported that nicotine acetylcholine receptors can be detected in the spinal cord, medulla oblongata, pons, cerebellum, mesencephalon and telencephalon from 6 weeks PMA onwards (Hellstrom-Lindahl 1998). Kostovic (1986), who studied the development of acetylcholinesterase reactivity in the nucleus basalis complex, which is a major source of cholinergic innervation of the cerebral cortex, found that the nucleus basalis complex shows acetylcholinesterase reactivity from 11 weeks PMA onwards (Kostovic 1986). At 20-24 weeks PMA acetylcholinesterase reactive fibres from the complex invade the subplate of the frontal, temporal, parietal and occipital cortices. Next, acetylcholinesterase reactive fibres transiently accumulate in the superficial part of the subplate and the deep part of the cortical plate, i.e., at the location of the mid-gestational transient neural circuits (Kostovic and Judas 2002). Thereafter cholinergic innervation obtains a pattern of topographical relationships which can be compared to that of the human adult brain (Kostovic 1986). Another subcortical structure, i.e., the mediodorsal nucleus of the thalamus, which is the principle source of diencephalic afferents in prefrontal association areas, shows a transient acetylcholinesterase staining. The staining is maximal between 18 and 36 weeks PMA and becomes virtually absent around 6 months post term. This transient cholinergic activity most likely corresponds to an active outgrowth of thalamocortical axons (Kostovic and Goldman-Rakic 1983).

The catecholaminergic systems also emerge early during development. Dopaminergic cells can be found in the rostral spinal cord, medulla oblongata, pons, mesencephalon and hypothalamic region at 8 weeks PMA. At the same age noradrenergic cells can be detected in the medulla oblongata, locus coeruleus and pons (Zecevic and Verney 1995). Around 10 weeks PMA catecholaminergic, i.e. dopaminergic, noradrenergic and serotonergic fibers, reach the cortial anlage (Zecevic and Verney 1995, Verney et al 2002). At 13 weeks PMA many catecholaminergic fibres, especially dopaminergic fibres, can be found in the subplate and at 15 weeks the fibres penetrate the cortical plate (Zecevic and Verney 1995, Verney et al 2002). Between 22-26 weeks PMA, when a rudimentary cortical lamination emerges, dopaminergic and noradrenergic innervation becomes visible throughout the cerebral cortex with a regional and laminar distribution pattern which is similar to that observed in the adult (Verney et al 1993). The latter means that the dopaminergic innervation extends to the entire cerebral cortex and that the noradrenergic innervation is essentially concentrated in primary motor and sensory areas (Berger et al 1991). Extrapolation of rhesus monkey data indicates that the dopaminergic innervation of pyramidal neurons in the cerebral cortex runs a protracted course. It reaches its adult level of innervation first in puberty (Lambe et al 2000a , b). Another remarkable feature of the development of dopaminergic circuitries is the transient presence of extremely high levels of dopamine-1 receptors in the pallidum during the last trimester of gestation. The disappearance of the transient surplus in pallidal dopamine-1 receptors starts shortly after term age (Boyson and Adams 1997). As dopamine-1 receptor stimulation has been linked to gene regulation, it is conceivable that abnormal stimulation of these receptors during late foetal life can result in long-term consequences (Herlenius and Lagercrantz 2001).

In contrast to the prolonged postnatal changes in dopaminergic innervation of the cerebral cortex, serotonergic innervation of the cortex does not change after late foetal age (Del Olmo et al 1998). Remarkably, the content of 5-HT1A receptors - a member of the seven families of serotonin receptors (Whitaker-Azmitia 2001) - remains stable after term age in all parts of the brain with exception of the cerebellum. In the cerebellum a high level of 5-HT1A receptors is present around term age. The level subsequently gradually decreases to very low levels in adulthood (Del Olmo et al 1998).

GABA is the dominating neurotransmitter in the inhibitory local circuit neurons of the cerebral cortex. The GABAergic cells originate in the ganglionic eminence. At early age they migrate to the cortical anlagen, where they can be found in relatively large numbers in the preplate at 8-9 weeks PMA (Rakic and Zecevic 2003). The inhibitory transmitter GABA acts as an excitatory transmitter during early development. The switch from excitatory to inhibitory occurs in the rat between the second and seventh postnatal day (Ben Ari et al 1997), which from a neurodevelopmental point of view corresponds to sometime during the last trimester of human gestation (Romijn et al 1991). During the time that GABA acts as an excitatory transmitter, $GABA_A$ receptors play the role conferred to glutamatergic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate) receptors later on in development, i.e., act in synergy with the glutamatergic NMDA (N-methyl-D-aspartate) receptors (Ben Ari et al 1997).

Glutamate and aspartate are the dominating excitatory amino acids in the primate cortex. Glutamate receptors (NMDA, AMPA and kainate receptors) are present in the foetal cortex as early as 10 weeks PMA (Ritter et al 2001). Possibly, cortical glutamate receptors have two transient periods of increased expression. One coinciding with the peak of neural

migration, i.e., between 13 and 21 weeks PMA (Ritter et al 2001), and the other around term age. At the beginning of the latter period cortical glutamatergic synapses involve almost exclusively NMDA receptors, which form a network that is silent at resting potential. This NMDA-based network seems to form independently of sensory information (Durand et al 1996). Next, electrical activity at the preformed 'silent' contacts can induce functionally active and stable synapses which consist of co-localized AMPA and NMDA receptors (Durand et al 1996, Wu et al 1996, Isaac et al 1997). This perinatal period of receptor upregulation probably plays a prominent role in the glutamatergic exitotoxicity induced by perinatal asphyxia (McDonald and Johnston 1990).

Possible clinical consequences of the neural ontogenetic timetable

From our summarizing figure (Fig. 1) it is clear that major part of the structural development of the telencephalon occurs during early life. But the figure also indicates that it takes about two decades before the central nervous system obtains a more or less adult configuration.

The continuous neurobiological changes during pre- and postnatal life have important clinical consequences. First, the fact that a child has an age-specific nervous system invokes the need of an age-specific neurological assessment, that is, the application of neuromotor evaluation techniques which are adapted to the age-specific characteristics of the nervous system. Second, the age-dependent characteristics affect the way in which neural dysfunction is expressed. Neurological dysfunction in adults is expressed by means of specific and localized signs, e.g., by means of the specific syndrome of a spastic hemiplegia in case of stroke. In contrast,

neurological dysfunction in young infants is expressed by means of generalized and aspecific dysfunction. For instance, a full-term infant with a left-sided cortical infarction may respond with a generalized hypotonia, a generalized hypertonia, a hypokinesia, a hyperexcitability syndrome, abnormal general movements or with no clinical abnormality (Prechtl 1977, Hadders-Algra 2004).

Third, the marked developmental changes of the brain have important implications for the prediction of developmental disorders at early age. The neurodevelopmental changes can induce a disappearance of dysfunctions present at early age. The reverse is also possible: children can be free from signs of dysfunction at early age, but grow into a functional deficit with increasing age due to the age-related increase in complexity of neural functions (Vohr and Carcia Coll 1985, Hadders-Algra 2002).

Fourth, the presence of periods with specific neurodevelopmental events results in windows of specific vulnerability for adverse influences. A well known clinical example of the age dependent effect of an adverse condition during early life is the difference in the effect of perinatal asphyxia or hypoxic-ischemic disease in preterm and full-term infants. Perinatal asphyxia does not always result in brain damage. But when it does, the lesion in preterm infants usually is localized in the periventricular regions, whereas in full-term infants the cortical areas, thalamus, basal ganglia and brainstem show a specific vulnerability (Volpe 2001). Examples of the differential effect of age at exposure on outcome in the field of developmental neurotoxicity are the effects of prenatal exposure to radiation and alcohol. Follow-up studies on the effect of the atomic bombs in Hiroshima and Nagasaki revealed that the highest risk of mental retardation occurred in children who had been exposed to radiation

between 10 and 17 weeks PMA, i.e. during the period of abundant neuronal proliferation. Exposure prior to this period did not result in an increased risk of mental retardation and exposure during later phases of foetal life were associated with an only moderately elevated risk of low cognitive function (Otake and Schull 1984). Recent studies on the effect of prenatal alcohol exposure indicated that alcohol exposure may interfere in particular with programmed cell death. This means that especially exposure to alcohol during the second trimester of gestation is associated to adverse outcome (Olney 2002).

Fifth, the ontogenetic neural timetable might have consequences for the timing of early intervention. Rodent research showed that in case of early brain damage the period during which the processes of dendritic outgrowth and synapse formation are highly active offers better possibilities to reconnect and find functional solutions than later periods (Kolb 1999, Kolb et al 2001, Nimchinsky et al 2002). Figure 1 indicates that from this point of view the period between 28 weeks PMA and 15 months postnatally would offer the best opportunities. Intervention in rodents in general consists of being raised in an enriched environment, which induces active play behaviour of the animal. Similar active forms of intervention prior to term age, such as head balancing exercises in prone position, might however not be appropriate for the young infant and – consequently – be a source of stress[b]. Rodent research demonstrated that stress during early development, i.e. during the period which is equivalent to the second half of human gestation, can induce substantial changes in catecholaminergic content of the cortical and subcortical regions (Peters 1988, Weinstock 2001). Monkey data indicate that these changes are accompanied by long

[b] Stress is defined as a state that threatens or is perceived by the individual to threaten his physiological equilibrium.

lasting unfavourable changes in motor, social and cognitive behaviour (Schneider 1992a, Schneider et al 1992, Schneider et al 1998). In addition, it has been reported that prenatal stress can induce impaired development of the maps of body representation in the primary somatosensory cortex Cases et al (1995) and inappropriately developed ocular dominance columns in the visual cortex (Gu and Singer 1995). Possibly these effects are mediated by interference with the transient role of the serotonergic system in the fine-tuning of thalamocortical projections in the young cortical layer IV (Rebsam et al 2002). EMG-studies in preterm children suggested that disturbances in the monoaminergic systems could explain part of the motor dysfunctions of these children (Hadders-Algra et al 1997, Hadders-Algra et al 1999, Vander Fits et al 1999). Thus, it is conceivable that stress during the preterm period might be one of the explanations why many low-risk preterm infants suffer from motor, cognitive and behavioural problems in later life (Botting et al 1997, 1998, Fallang et al 2005). Not only the catecholaminergic systems are characterized by a period of transient overexpression till the age of about 40-44 weeks PMA, but also the acetylcholinergic and glutamatergic system. Therefore we suggest to restrict intervention prior to 40-44 weeks to forms of intervention which aim at mimicking the intrauterine environment, such as proposed in the Neonatal Individualized Developmental Care and Assessment Program (NIDCAP) (Als et al 1994). Recent data indicated that NIDCAP intervention may be beneficial for brain development, as NIDCAP in low risk preterm infants has a significant positive effect on electrophysiological and MRI correlates of brain development at 42 weeks PMA (Buehler et al 1995, Als et al 2004).

Concluding remarks

The development of the human central nervous system is characterized by a protracted, neatly orchestrated chain of specific ontogenetic events. The continuous changes of the nervous system have consequences for vulnerability to adverse conditions, for diagnostics and for physiotherapeutical intervention. Our review suggests that intervention prior to 40-44 weeks PMA rather should be restricted to forms of intervention which aim at mimicking the intrauterine environment, such as NIDCAP. After 40-44 weeks intervention might be switched to active stimulation of infant development.

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