Prenatal Development of the Human Fetal Telencephalon

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Contents

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Abstract

› Human corticogenesis is perhaps the most complex process in the realm of biology, and also displays some unique (species-specific) features. There are major and clinically relevant differences in cortical development between rodents and humans, and they are reflected in the structure and function of the brain at every hierarchical level, from genes and cells to large neuronal assemblies and functional systems. For example, in comparison to rodents, the human cortex displays dramatically expanded fetal subplate zone, more complex and hugely expanded subventricular zone, significantly different process of initial cortical formation, more complex and diverse radial glial cells, Cajal–Retzius cells, and the subpial granular layer, as well as other unique transient fetal structures and/or features. These phylogenetic novelties contribute to the introduction of species-specific cell types (especially cortical interneurons), new cytoarchitectonic areas, and new patterns of connectivity and transmitter/receptor composition. Therefore, human-specific features of human brain are highly relevant for understanding the etiology of developmental brain disorders and for advancing their diagnostics and treatment. Fortunately, new noninvasive methods from neurohistology, neuroimaging, and genomics are making the human brain accessible for direct and detailed study as never before, and the number of these new and powerful methods for analyzing human brain development is rapidly increasing.

1 Introduction

It is common knowledge that structure and function of the human fetal telencephalon display a number of transient features. However, what is exactly transient in the developing brain? The first and the simplest answer, of course, is that everything is transient, because the brain continuously changes and reorganizes as its developmental program enfolds in the interaction with other organ systems, the pregnant mother and the environment. However, from the viewpoint of a practicing clinician, it is important to note that the concept of transient has two different meanings.

> First, there are transient appearances: any growing cell, architectonic/modular structure or organ changes as it grows, so that at each developmental age its appearance is transient (in the sense that what was seen before is no longer recognized as such). But, appearances are deceiving – if something changes its appearance, it does not cease to exist. For example, both ventricular and subventricular zones disappear (as cytoarchitectonically observable entities) but all neurons and glia generated in these zones simply move to another place and happily continue to exist.
>
> Second, there are cells (and by extension, architectonic entities) that really cease to exist after a while, because they die by apoptosis, that is, normal and developmentally programmed cell death. Such cells or structures deserve to be named transient sensu stricto – but, in fact, there are quite a few such cells or structures in the developing human brain.

Thus, so-called transient embryonic or fetal cells, structures, neuronal circuits (and, by extension, transient electrophysiological and behavioral phenomena) simply represent a fleeting and protean reflections of the basic fact of life: that the human embryo or fetus is a living organism, which cleverly and adaptively uses and re-shuffles all available resources during its long and autopoietic (self-assembling) journey to the maturity. Therefore, although the term transient is deeply entrenched in the current literature, it would be appropriate to use more neutral (and accurate) terms, such as age- or stage-specific, or characteristic for a specified developmental window. For example, the so-called transient subplate zone, when fully formed, is indeed recognizable as a distinct architectonic entity during the developmental window extending approximately from 13 postconceptional weeks (PCW) until birth. However, its first constituent neurons actually appeared much earlier (at 7 or 8 PCW), and the majority of them will continue to exist throughout the postnatal lifespan as so-called interstitial white matter neurons.

With this in mind, let us embark on a quick journey through the complex and ever-changing landscape of human brain development. Due to the limits of space, we will obviously unveil just the tip of the iceberg of the underlying bewildering variety of molecular and

cellular interactions and histogenetic processes. If the reader nevertheless finds this chapter (and especially its reference list) too long and crowded with expert details, but endures to its end, he or she will hopefully realize that the integration of the wealth of descriptive data provided by classical human neuroanatomy with data pouring from recent molecular biological, genetic, genomic and neuroimaging studies is, in fact, the order of the day. Namely, although the large majority of recent breakthroughs in the field of developmental neurobiology have originated from studies of experimental models (especially genetically modified mice), it becomes increasingly evident that "the proper study of mankind is man" – to use the famous dictum of the nineteenth-century English poet. Finally, it should be noted that this chapter is focused on prenatal development, but human brain continues to develop long after birth (Fig. 1).

2 Brain Development in the Embryonic Period Proper: Carnegie Stages 8–23 (Embryonic Days E23–E56)

As pointed out by leading authorities (O'Rahilly and Müller 1999), prenatal age is always postfertilizational by definition (or, as an acceptable alternative, postovulatory, postconceptional). Menstrual weeks are convenient in obstetrics but are not age; the ambiguous term gestational age should never be used, because three different starting points are possible: the last menstrual period, ovulation and/or fertilization, and implantation. Unfortunately, the term gestational age/gestational weeks continues to plague many current publications. In this chapter, as in all of our studies, I use the term postconceptional weeks, PCW to encompass both proper terms (postfertilizational and postovulatory). When appropriate or unavoidable, I also use embryonic days (E – e.g., E43) or postnatal days (P – e.g., P7), because it is the only way age is measured in prenatal and postnatal development of experimental animals, such as rhesus monkeys (in which the gestation period is 165 days). Finally, the most useful measurement in both embryonic and fetal development is the greatest length (GL, taken as a caliper length without inclusion of the flexed lower limbs; it is replaced after birth by the sitting height), while the crown–rump length (CRL) is frequently similar and commonly cited but less reliable measurement (O'Rahilly and Müller 1984). At 4.5 PCW, the GL is about 5 mm, and at the end of the embryonic period proper (at 8 PCW) it is approximately 30 mm, while body weight is about 2–3 g (O'Rahilly and Müller 1999).

The staging used for describing the development of the human embryonic brain is the internationally accepted Carnegie system (for comprehensive summary, see O'Rahilly and Müller 1999, 2006). In the Carnegie system the embryonic period proper occupies the first 8 PCW and is subdivided into 23 morphological Carnegie stages based on both external and internal morphological criteria. At present, morphological staging is limited to the embryonic period proper, because no fully satisfactory staging system has yet been devised for the fetal period (O'Rahilly and Müller 1999; but, see Sect. 3.2 for alternative approaches).

The human prenatal life is usually divided into embryonic (first 8 PCW) and fetal periods (9 PCW to birth). The duration of prenatal life is generally about 38 PCW, the mean being 264 days. The range 35–40 PCW is considered to indicate an infant at term. Commonly used figures at birth are about 335 mm for the GL (exclusive of the lower limbs) and about 500 mm for the crown-heel length (O'Rahilly and Müller 1999). The biparietal diameter is approximately 95 mm, the head circumference is of the order of 350 mm, the body weight at birth varies from 2,500 to 4,000 g or more (with an average of about 3,350 g), and the brain weight ranges from about 300–400 g (O'Rahilly and Müller 1999).

Another convenient way to consider prenatal life is in terms of trimesters: (1) the first trimester (including the embryonic period proper – up to about 30 mm GL) extends to some 90 or 100 mm GL; (2) the second trimester (mid-fetal period) proceeds to about 250 mm GL; and (3) the third trimester continues until birth (very approximately 335 mm GL). While the work of O'Rahilly and Müller has been predominantly restricted to the embryonic period, they offered the following classification of the postembryonic (fetal) phase (O'Rahilly and Müller 1999):

1. In the first trimester (after the embryonic period), an early postembryonic phase (approximately 30–50 mm in GL, 8–9 PCW);
2. The later postembryonic phase of the first trimester (approximately 50–100 mm in GL, 9–13 PCW);
3. The second trimester (approximately 100–250 mm in GL, 13–26 PCW); and
4. The third trimester and the newborn (approximately 250–335 mm in GL, 26 PCW to birth).

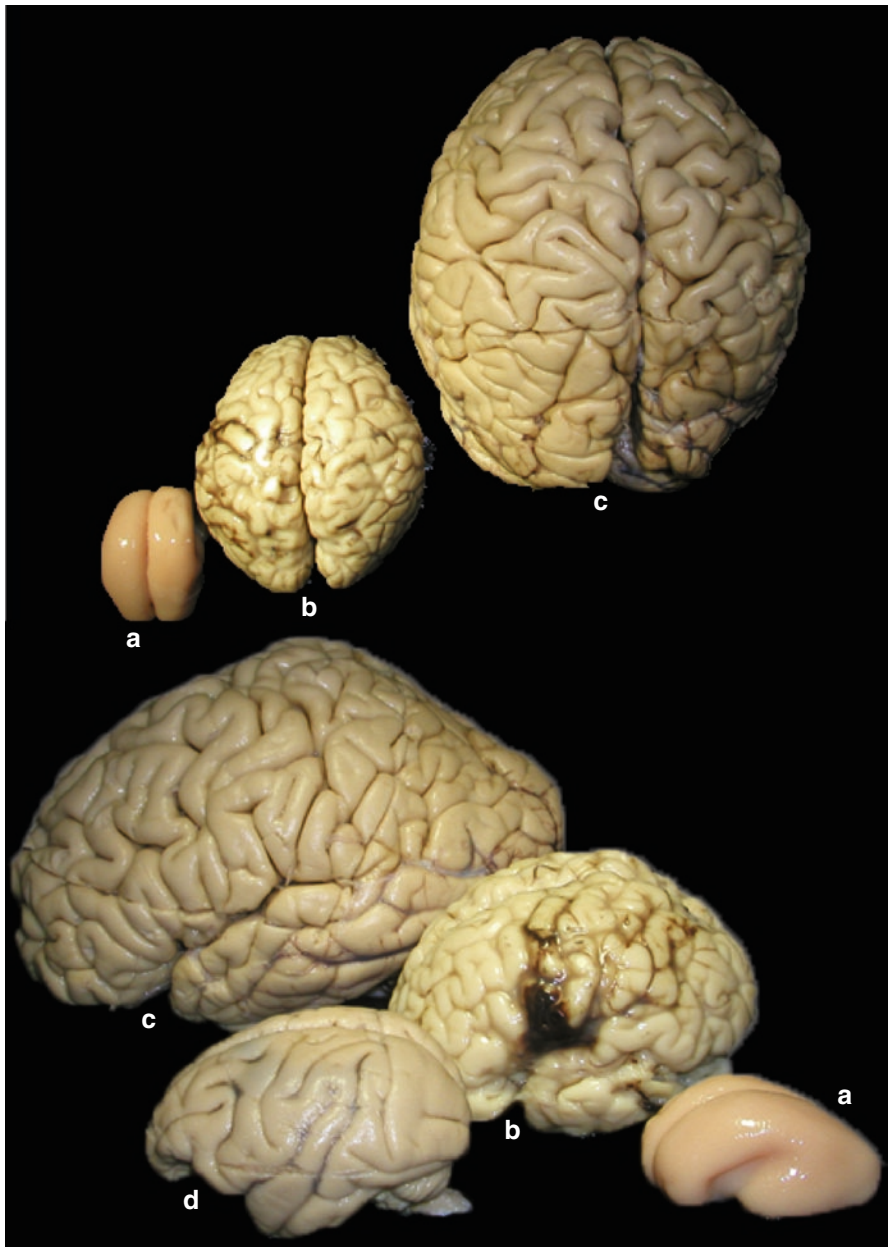


Fig. 1 Comparison of morphological and volumetric development of human brain in an 18-week-old fetus (**a**), newborn (**b**), and adult (**c**) in dorsal (*upper row*) and lateral view (*lower row*). Note that the brain of the adult rhesus monkey (**d**, *Macaca rhesus*) is intermediate in size between mid-term and newborn human brain. Note also that a huge part of human brain growth occurs postnatally (from cca. 380 g of brain mass in newborn to cca. 1,350 g in adult)

As we will see in the subsequent section, this classification has largely been superseded by more advanced ones (Sidman and Rakic 1973, 1982; Kostović 1990a, b; Kostović and Judaš 1994, 1995, 2009; Kostović et al. 2008).

In the following paragraphs, we provide synopsis of key events in the development of human embryonic brain, as described in the original publications of Ronan O'Rahilly and Fabiola Müller and, when needed, corrected in the second and third edition of their atlas (O'Rahilly and Müller 1999, 2006).

Carnegie stage 8: *approximately 1–1.5 mm in GL, 3 PCW, E23* (O'Rahilly and Müller 1981): at least in some specimens, the neural groove can be detected in

the neural plate as a very shallow sulcus bounded by faint neural folds. This is the first visible sign of the future nervous system, and it is of interest that the primordium of the brain appears before the heart or any other organs become visible.

Carnegie stage 9: *approximately 1.5–2.5 mm in GL, E26* (Müller and O'Rahilly 1983): the three major divisions of the brain (prosencephalon, mesencephalon, and rhombencephalon) are distinguishable in the folds of the completely open neural groove; no neural tube has yet formed, and "brain vesicles" are not present; the otic discs are first visible at this stage as the first indication of the (internal) ears.

Carnegie stage 10: *approximately 2–3.5 mm in GL, E29* (Müller and O'Rahilly 1985): a portion of neural tube is formed; the diencephalon consists of the future thalamic region and an optic portion; optic primordia are visible for the first time and connected by the chiasmatic plate; the lateral parts of the forebrain beyond the chiasmatic plate belong to the telencephalon medium or impar which is the first part of the telencephalon to appear at this stage.

Carnegie stage 11: *approximately 2.5–4.5 mm in GL, E30* (Müller and O'Rahilly 1986): the rostral (cephalic) neuropore closes during this stage; the floor of the telencephalon medium becomes distinct as the future lamina terminalis and commissural plate; the optic vesicle is being formed; notochordal and neural axial structures are still closely related.

Carnegie stage 12: *approximately 3–5 mm in GL, E31* (Müller and O'Rahilly 1987): the caudal neuropore closes and its final site is at the level of somitic pair 31; the beginning of secondary neurulation; the mesencephalon consists of two neuromeres (M1 and M2) and the rhombomeres have important relations to the cranial ganglia; the first nerve fibers are differentiating.

Carnegie stage 13: *approximately 4–6 mm in GL, E32, 4–5 PCW* (Müller and O'Rahilly 1988a): both neuropores are closed, so that the closed neural tube finally appears; the retinal and lens discs are beginning to develop; the adenohypophysial pouch is distinct; three diencephalic neuromeres (D1, parencephalon, synencephalon) are present; the isthmus rhombencephali is visible; a marginal zone is distinguishable in the wall of the mesencephalon and rhombencephalon; the first indication of the cerebellum appears in rhombomere Rh.1.

Carnegie stage 14: *approximately 5–7 mm in GL, E33, 5 PCW* (Müller and O'Rahilly 1988b): the future cerebral hemispheres become identifiable during this stage and are delimited from the telencephalon medium by the torus hemisphericus internally and by the ditelencephalic sulcus externally; the pontine flexure appears; the cerebellum is formed by the alar plate of the isthmus as well as by that of rhombomere 1; blood vessels now penetrate the wall of the brain.

Carnegie stage 15: *approximately 7–9 mm in GL, E35, 5 PCW* (Müller and O'Rahilly 1988c): the medial ganglionic eminence has appeared in the previous stage and it is diencephalic; the lateral ganglionic eminence, which now appears, is telencephalic; the wall of the diencephalon presents five longitudinal zones (epithalamus, dorsal thalamus, ventral thalamus, subthalamus, and hypothalamus); the primordium of the epiphysis cerebri is beginning; the hippocampal thickening is distinct on each side of the lamina terminalis; most cranial nerves are present; axodendritic synapses have been detected in the cervical region of the spinal cord (Okado 1981).

Carnegie stage 16: *approximately 8–11 mm in GL, E37* (Müller and O'Rahilly 1989a): the presence of the hippocampal thickening and other histological features makes possible a distinction among archipallium, paleopallium, and neopallium; the primordial plexiform layer can be discerned at the periphery of the amygdaloid area; olfactory fibers enter the wall of the brain at the site of the future olfactory bulb, and the future olfactory tubercle is detectable; the evagination of the neurohypophysis is now becoming distinct. Up to and including stage 16 the neocortical part of the cerebral hemispheres is avascular, although it is already surrounded by a prominent perineural vascular process (Marin-Padilla 1988b).

Carnegie stage 17: *approximately 11–14 mm in GL, E40, 6 PCW* (Müller and O'Rahilly 1989b): due to the rostral and caudodorsal growth of the cerebral hemispheres the longitudinal fissure deepens, and the vessels of the future choroid plexus develop in it; the olfactory bulb and tubercle become outlined; the amygdaloid area contains one or two nuclei; the first indication of a septal nucleus is recognizable; the hemispheric stalk unites the cerebral hemispheres with the ventral thalamus and the medial ganglionic eminence; the telencephalon begins to overlap the diencephalon; the interventricular foramina begin to develop.

Carnegie stage 18: *approximately 13–17 mm in GL, E42, 6 PCW* (Müller and O'Rahilly 1990a): the cerebral hemispheres are slightly flattened in the future insular region; the C-shaped hippocampus, accompanied by the

area dentata, reaches the olfactory region; the lateral ganglionic eminence is distinct; the red nucleus is present and the substantia nigra is beginning to develop; choroid plexuses develop in the lateral as well as in the fourth ventricle, so that the production of cerebrospinal fluid sensu stricto can now begin. The primordial plexiform layer extends over most of the cerebral hemispheres (see later sections). Tracts present at stage 18 include the stria medullaris thalami, mamillothalamic tract, medial and lateral tectobulbar, dentatorubral, and the tractus solitarius.

Carnegie stage 19: *approximately 16–18 mm in GL, E44, 6–7 PCW* (Müller and O'Rahilly 1990a): the embryo now has a recognizably human face; the olfactory nerve, bulb, and tubercle are well developed; the nucleus accumbens appears; the cerebral hemispheres have grown rostrally; optic fibers arrive in the chiasmatic plate; many bundles are identifiable, including the thalamostriatal tract (Stammbündel of His or lateral prosencephalic fasciculus) and the stria medullaris thalami.

Carnegie stage 20: *approximately 18–22 mm in GL, E47, 7 PCW* (Müller and O'Rahilly 1990a, b): the choroid plexuses of the lateral ventricles are at the "club-shaped" phase; optic and habenular commissures develop; the medial septal nucleus and the nucleus of the diagonal band are differentiating; important fiber connections of the olfactory system are now identifiable; the intrinsic vascularization of the neocortex begins.

Carnegie stage 21: *approximately 22–24 mm in GL, E50, 7–8 PCW* (Müller and O'Rahilly 1990b): very important stage, characterized by *the first appearance of the cortical plate*, adjacent to the lateral ganglionic eminence; the transition from the hemisphere to the diencephalon is the hemispheric stalk (Hemisphärenstiel of Hochstetter) which contains a thick bundle of fibers, the lateral prosencephalic fasciculus (Stammbündel of His); the internal capsule, however, is not yet present in the absence of the appropriate neocortical connections; the subthalamic nucleus and the globus pallidus are distinguishable; the circulus arteriosus of Willis is now complete.

Carnegie stage 22: *approximately 23–28 mm in GL, E52, 7.5–8 PCW* (Müller and O'Rahilly 1990b): the internal capsule and its connections to the neopallium are now present; the primordium of the claustrum develops as a condensed stream of neurons that extends from the area caudal to the olfactory bulb and along the lateral ganglionic eminence to the future insular region; the cortical plate extends over half the surface of the neopallium; the inferior horn of the lateral ventricle is evident; the sulcus terminalis is the internal boundary between telencephalon and diencephalon.

Carnegie stage 23: *approximately 27–31 mm in GL, E56, 8 PCW* (Müller and O'Rahilly 1980, 1990a, 1990b; O'Rahilly and Müller 1990): this stage is also very important because it is the close of the embryonic period proper. The cortical plate covers almost the whole neopallial surface; the hippocampus has reached the temporal pole; the insula appears as an indented area; the primordia of the caudate nucleus and the putamen are recognizable, and the globus pallidus externus has moved from its diencephalic into a telencephalic position; the anterior commissure begins to develop in the commissural plate; the telencephalon and the diencephalon are not fused; the optic tract reaches the ventral portion of the lateral geniculate body; the inferior and the superior cerebellar peduncles are distinguishable; the presence of the pyramidal decussation is noted for the first time; the choroid plexus at this time has become lobular.

3 Spatiotemporal (Architectonic) Framework for Analyzing Corticogenesis: Transient Embryonic and Fetal Zones and Developmental Staging Systems

The aim of this section is to provide a general spatiotemporal framework for analyzing histogenetic processes in the developing human telencephalon and for correlating these events with features observed in images obtained by in vivo in utero or in vitro fetal MRI.

There are few atlases which provide systematic illustrations of Nissl-stained and serially sectioned human fetal brains (Feess-Higgins and Larroche 1987). Recently published atlases based on the Carnegie, Minot and Yakovlev Collection contain hundreds of microphotographs of the best quality, but unfortunately these illustrations are provided with descriptions and terminology that are appropriate for the developing rodent, but not human brain (Bayer and Altman 2002,

2004, 2005, 2006, 2008). However, there are also presently largely neglected but very important and excellently illustrated classical monographs (Retzius 1896; His 1904; Hochstetter 1919, 1923, 1929, 1934, 1939; Barbé 1938; Bartelmez and Dekaban 1962; Richter 1965; Kahle 1969; Windle 1970) including the series of monographs published by LeRoy Conel on the early postnatal development (birth to 6 years) of the human cerebral cortex (Conel 1939, 1941, 1947, 1951, 1955, 1959, 1963, 1967).

3.1 Boulder Committee System and Its Revisions

During embryonic and fetal periods, the telencephalic wall consists of several architectonic zones that do not exist in the mature brain. Upon the recommendation of the Boulder Committee (appointed by the American Association of Anatomists), these zones have been generally adopted as a generic description for basic histogenetic processes and developmental events for the entire vertebrate central nervous system (Boulder Committee 1970; Rakic 1982; Bystron et al. 2008; Rakic et al. 2009). However, between the initial proposal (Boulder Committee 1970) and the latest revision (Bystron et al. 2008), a number of important developments occurred which prompted subsequent revisions of the basic scheme. One such major development was the discovery of the subplate zone in the human fetal brain (Kostović and Molliver 1974). A separate line of criticism was initiated by Miguel Marin-Padilla who introduced the concept of the primordial plexiform layer (PPL) initially based on his studies of fetal cat cortex (Marin-Padilla 1971, 1972, 1978) and subsequently extended to the initial development of the human cerebral cortex (Marin-Padilla 1983; Marin-Padilla and Marin-Padilla 1982; for review, see Marin-Padilla 1984, 1988a, 1992, 1998). This concept was soon extended to rodents (Rickmann et al. 1977; Bayer and Altman 1990) and in fact remains the dominant concept in studies on cortical development in rodents and carnivora (e.g., Bayer and Altman 1991; Allendoerfer and Shatz 1994; Kanold and Luhmann 2010). However, it should be noted that significant revisions of the initial Boulder scheme were primarily driven by subsequent discoveries made in brains of humans and nonhuman primates and not in rodents (see below). For example, recent studies have revealed new types of transient neurons and proliferative cells outside the classical neurepithelium, new routes of cellular migration, and additional cellular compartments (Smart et al. 2002; Zecevic et al. 2005; Bystron et al. 2005, 2006; Carney et al. 2007; Rakic et al. 2009).

3.2 The System of Poliakov as Revised by Sidman and Rakic and Further Developed by Kostović

With respect to the development of the human fetal brain, there is another approach to developmental staging which combines the legacy of the Boulder Committee with older tradition stemming from the Russian architectonic school. The Russian neuroanatomist G.I. Poliakov (Poliakov 1949, 1959, 1961, 1965, 1979) developed a staging system which was adopted and slightly modified by Richard L. Sidman and Pasko Rakic in their highly influential reviews (Sidman and Rakic 1973, 1982; Rakic 1982). Poliakov divided the entire human prenatal cortical development into three major periods: (1) an early period of migration and consolidation (2nd to 4th fetal month), (2) a middle or transitional period of pre-differentiation of cortical layers (4th to 6th fetal month), and (3) a late period of final differentiation of cortical layers (6th month to birth). He furthermore divided his early period into four stages of cortical plate development, which he described as: (a) initial formation, (b) primary consolidation, (c) migratory-consolidating differentiation, and (d) secondary consolidation. Sidman and Rakic (1973, 1982) adopted that scheme and supplemented it with additional data from their own material. The latest version of their description of Poljakov's four stages, with inclusion of equivalent embryonic days in rhesus monkeys (Rakic et al. 2009: pp 20), is as follows:

Stage I: Initial formation of the cortical plate (6–10 PCW; E40–E54 in monkey)
Stage II: Primary condensation of the cortical plate (10–11 PCW; E55–E59 in monkey)
Stage III: Bilaminate cortical plate (11–13 PCW; E59–E64 in monkey)
Stage IV: Secondary condensation (13–15 PCW; E64–E75 in monkey)

However, after the discovery of the subplate zone (Kostovic and Molliver 1974), it soon became obvious that stage III in fact corresponds to the subplate formation stage or stage of the "second" cortical plate (Kostovic and Rakic 1990). See Fig. 2.

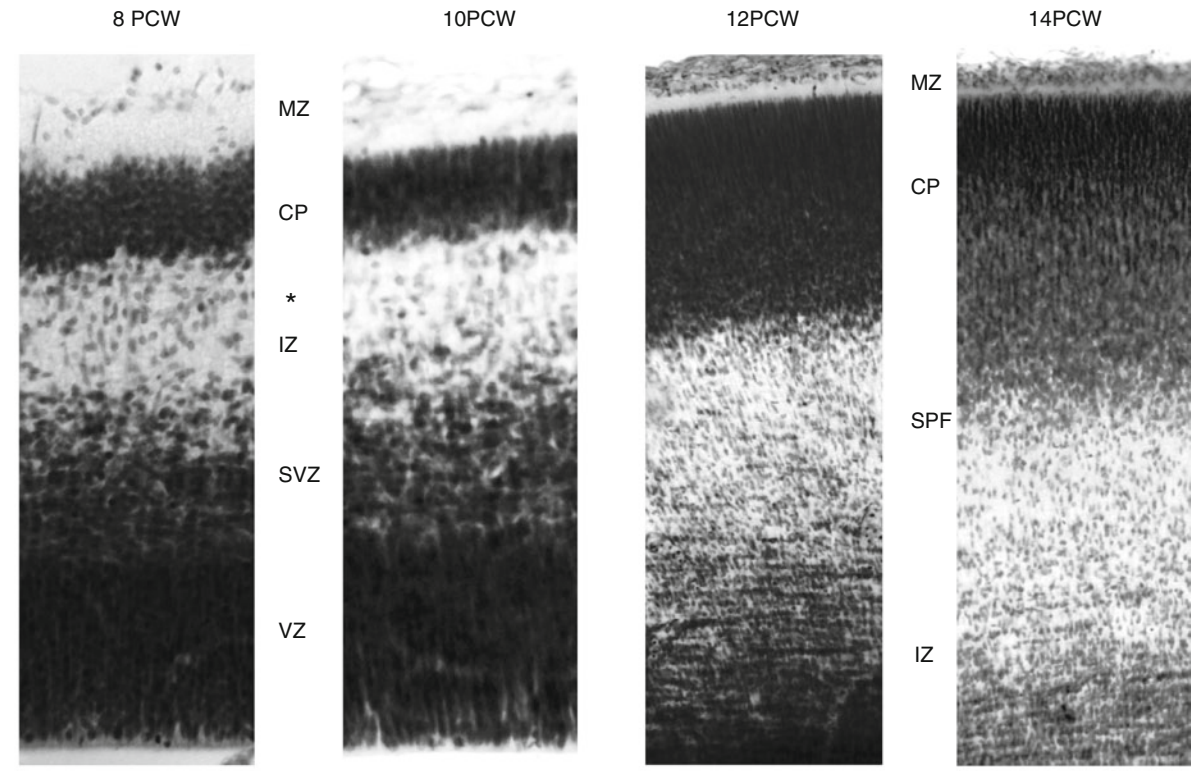
The radial columnar arrangement of cells (so-called ontogenetic columns; Rakic 1988, 1995) is a prominent feature of the early fetal cortical plate (Kostović-Knežević et al. 1978; Krmpotić-Nemanić et al. 1984; Kostovic and Rakic 1990). In the prospective somatosensory cortex of human fetuses aged 9–11 PCW (31–65 mm CRL) the cortical plate appeared as the condensed, darkly stained and clearly delineated zone with pronounced radial (columnar) orientation of its cells (Kostović-Knežević et al. 1978). However, as the fetus develops from 9 to 11 PCW, there are increasingly distinct differences between the superficial and the deep part of the cortical plate (Fig. 2): while the superficial CP remains characterized by predominantly radial orientation of both cell somata and processes, the cells and their processes in the deep CP become more loosely packed due to the enlarged intercellular space and the presence of numerous processes without radial orientation (Kostović-Knežević et al. 1978; Kostovic and Rakic 1990). This decrease in cell density and variability of cell arrangement and orientations becomes more pronounced during the formation of the subplate zone at 13–15 PCW (Krmpotić-Nemanić et al. 1984; Kostovic and Rakic 1990).

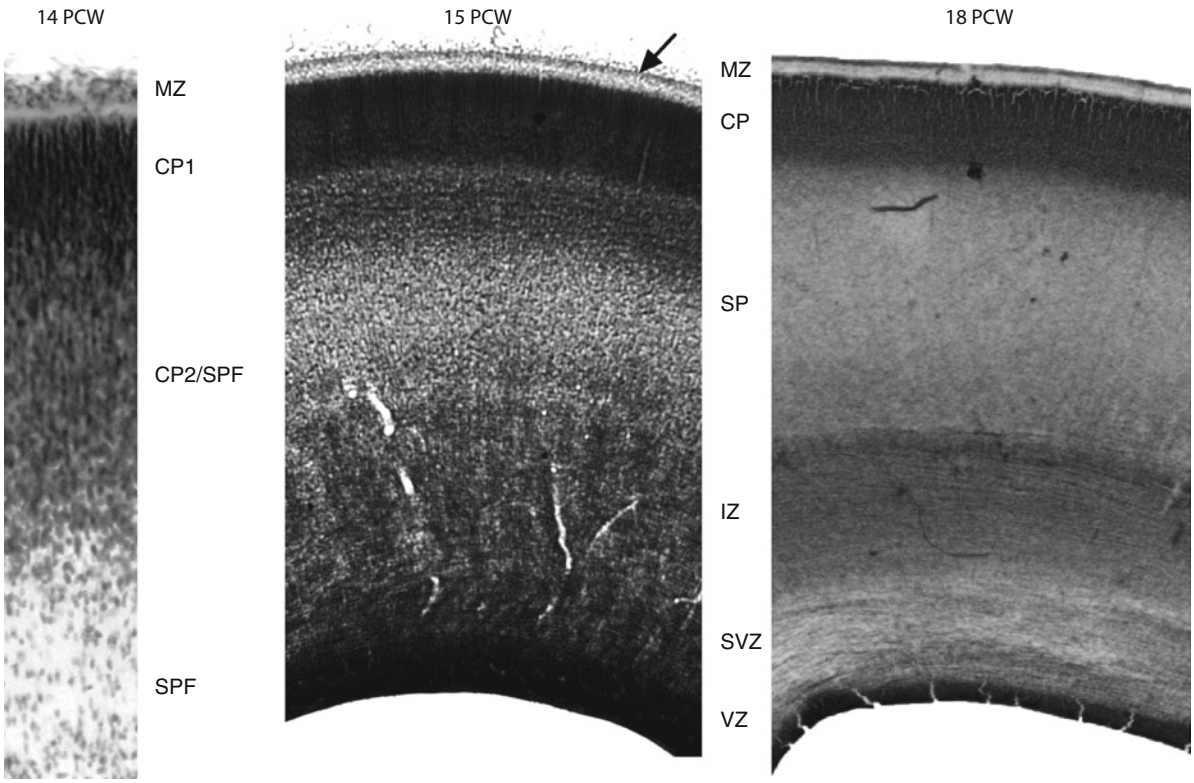
Starting from the above described Poliakov-Sidman-Rakic-Kostovic classification, and thanks to the availability of a unique resource – the Zagreb Collection of human brains located at the Croatian Institute of Brain Research (Kostović et al. 1991a; Judaš et al. 2010c) – our research group gradually developed the most detailed classification of human fetal cortical development, as described in a number of previous reviews (Kostović 1990a, b; Kostović and Judaš 1994, 1995, 2009; Kostović et al. 2008). The reader may wish to consult these reviews for a detailed description and numerous illustrations; the aim of this section is just to point out essential facts relevant for the understanding of subsequent sections.

Embryonic and fetal zones of the telencephalic wall are concentric architectonic compartments that represent a spatial framework for temporal analysis of specific histogenetic events, such as neuronal proliferation, migration, axonal pathfinding, synaptogenesis, dendritic differentiation and establishment of transient and permanent cortical neuronal circuitry and input–output connections (Fig. 2). In the human fetal telencephalon, their development peaks during the midgestation (15–24 PCW), that is, the period of the so-called typical fetal lamination pattern (Fig. 3) when all zones are present and well developed. From ventricular to the pial surface, these zones are: the ventricular zone (VZ) and the subventricular zone (SVZ), the intermediate zone (IZ), the subplate zone (SP), the cortical plate (CP), and the marginal zone (MZ).

The proliferation of cortical progenitors occurs in VZ and SVZ, initially by symmetric mitotic divisions (when one cortical progenitor cell divides to give rise to two other cortical progenitor cells). However, at 7 PCW, some progenitors begin to enter asymmetric mitotic divisions (when one progenitor cell divides to give rise to another progenitor cell and one young postmitotic neuron which will divide never again). This marks the beginning of cortical neurogenesis. Young postmitotic neurons migrate from VZ (along radial glial guides; see below) toward the pia, and their accumulation below the MZ leads to the initial formation of the CP at 7–8 PCW. While principal cortical output neurons (pyramidal neurons) are generated

Fig. 2 Sequential development of transient embryonic and fetal zones in the neocortical (pallial) wall of the human fetal telencephalon, from 8 to 18 PCW. Note that the cortical plate (CP) displays two periods of sharp delineation: the stage of primary consolidation of the CP (at 8–10 PCW) and the stage of secondary consolidation of the CP (from 15 PCW onward). These two periods are separated by the subplate formation (SPF) stage (12–15 PCW). The formation of the subplate zone is a protracted process, which begins with the formation of the presubplate (asterisk at 10 PCW), and continues during 12, 13, and 14 PCW through merging and reorganization of the deep part of the initial cortical plate (CP2/SPF) and numerous additional subplate neurons accumulating below it (SPF at 14 PCW). Note that during this period the upper part of the CP (CP1) remains compact and with strictly radially oriented cells, while its deeper part becomes rarified and looses its radial arrangement of cells (CP2). As the SP develops at the interface of CP and IZ, during the subplate formation stage it can be also subdivided into its upper part (SPU, i.e., CP2) and lower part (SPL). At 18 PCW, the typical fetal lamination pattern is fully established, and the SP becomes the thickest part of neocortical anlage as well as of the entire telencephalic wall. Note also the well-developed subpial granular layer (*arrow*) at 15 PCW. For further details, see text


8 PCW
10PCW
12PCW
14PCW
MZ
CP
*
IZ
SVZ
VZ
MZ
CP
SPF
IZ


14 PCW
15 PCW
18 PCW
MZ
CP1
CP2/SPF
SPF
MZ
CP
SP
IZ
SVZ
VZ

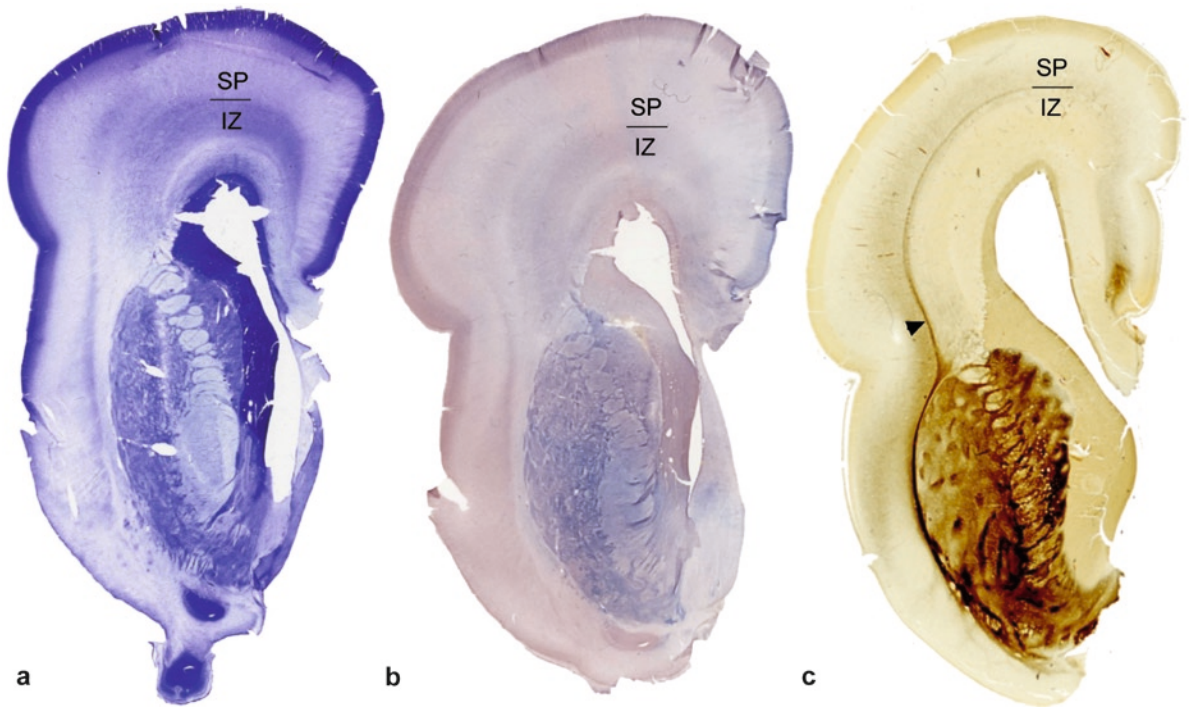


Fig. 3 Typical fetal lamination pattern at 18/19 PCW, as illustrated by Nissl staining (**a**), NADPH-diaphorase histochemistry (**b**), and AChE-histochemistry (**c**). Note that the external capsule (*arrowhead* in **c**) represents the outermost part of the fetal white matter (i.e., intermediate zone, IZ) and serves as an excellent marker for the border between the IZ and the subplate (SP), because its position is clearly recognizable in all three types of staining (and directly visualized by AChE-histochemistry). Note also the huge ganglionic eminence capping the developing caudate nucleus

within the VZ and reach the CP by radial migration, cortical interneurons are generated in both pallial SVZ and subpallial ganglionic eminence (together with neurons of basal ganglia) and reach the CP by tangential migration (for details, see Sect. 6.2.2).

However, two other important fetal zones are interposed between VZ/SVZ and the CP: the intermediate zone (IZ) and the subplate zone (SP). The IZ has a dual role: (a) it is a compartment through which all cortical neurons have to migrate (either radially or tangentially) in order to reach their final destination in the CP (or the SP), and (b) it is the major compartment through which all cortical efferent and afferent (output–input) axonal pathways have to grow and navigate in order to reach their target region/area. The subplate (SP) is the most prominent transient compartment of the fetal neocortical anlage, which contains numerous early differentiated projection (glutamatergic) neurons and local (GABAergic and peptidergic) interneurons and serves as a waiting compartment for growing cortical afferents (Rakic 1977; Kostovic and Rakic 1990). Thus, it is the major site of synaptogenesis in the midfetal brain and contains diverse and transient neuronal circuits which represent a neurobiological basis for transient electrophysiological and behavioral phenomena in fetuses and early preterm infants (for review, see Kostović and Judaš 2002a, b, 2006, 2007, 2010). The SP circuits are also connected with another early population of well differentiated cells – Cajal–Retzius cells situated in the MZ. It also contains an abundant hydrophilic extracellular matrix which enables its easy visualization on fetal MRI (Kostović et al. 2002a; see Fig. 4).

Thus, an important take-home message is that, during midgestation (and, at least in future associative cortical regions, until birth) the human fetal telencephalic wall can be divided in three major regions: (a) the neocortical anlage which consists of the marginal zone (MZ), the cortical plate (CP) and the subplate (SP); (b) the intermediate zone (IZ) which represents the fetal white matter, and (c) proliferative ventricular/subventricular zones (VZ/SVZ), including the ganglionic eminence (which is greatly enlarged part of the VZ).

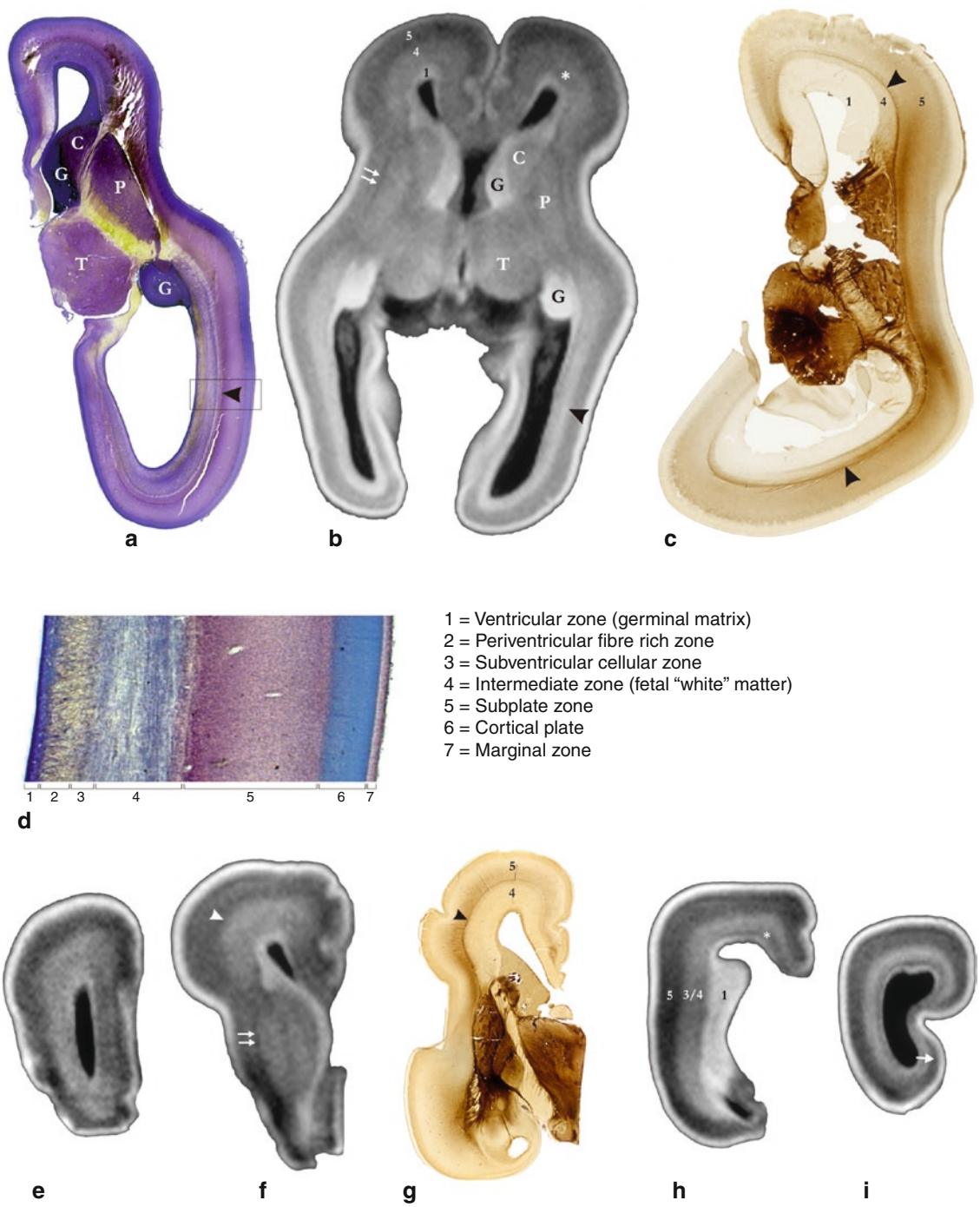


Fig. 4 At 18 PCW, the histological, histochemical, and MRI sections reveal a transient pattern of lamination in the cerebral wall. Low-power views of brains sectioned (**a**–**c**) horizontally and (**e**–**i**) coronally and stained with (**a**, **d**) cresyl violet Nissl staining, (**c**, **g**) AChE-histochemistry or (**b**, **e**, **f**, **h**, **i**) displayed on 3-D GRE T1-weighted MRI sections. For the horizontal sections anterior is to the top and for the coronal sections medial is to the right and dorsal is to the top. The box in (**a**) corresponds to the higher power view in (**d**) (*C*, caudate nucleus; *G*, ganglionic eminence; *P*, putamen; *T*, thalamus). The asterisk in (**b**, **h**) indicates the periventricular fiber-rich zone as seen on T1-weighted images, the *arrowheads* in (**a**–**c**, **f**, **g**) indicate the external capsule or its position, the *arrow* in (**i**) indicates the wedge-shaped narrowing of the subplate zone in the prospective primary visual cortex, and the *double arrows* in (**b**, **f**) indicate the position of the external capsule in the MRI sections (From (Kostovic et al. 2002a). With permission)

The MZ represents a future cortical layer I, while CP will differentiate into future cortical layers II–VI. While the SP will subsequently disappear as an architectonic compartment, the majority of subplate neurons will survive as interstitial neurons of the gyral white matter in the adult brain (or become partly incorporated in the deepest part of the layer VI; see Sect. 7.2). As the SP at its developmental peak (25–30 PCW) is four to five times thicker than the CP, the neocortical anlage occupies the entire outer half of the fetal telencephalic wall, while the fetal white matter (IZ) occupies deep periventricular regions (Figs. 3 and 4).

4 Histologically Defined Fetal Zones Can Be Successfully Traced by MRI in Vitro and in Vivo

Recent advances in MRI technology have opened new vistas for both in vivo and in vitro studies of human brain development (Chung et al. 2009; Ment et al. 2009; Kostovic and Vasung 2009; Lodygensky et al. 2010). Fetal MRI provides a precise insight into brain structure and thus allows the correlation with functional maturation and facilitates early detection of brain damage (Rutherford et al. 2005; Ment et al. 2009). The MRI is also important in the postnatal follow-up of neurodevelopmental outcome in preterm infants at risk (Counsell and Boardman 2005; Ment et al. 2009). Thus, a close correlation of in vivo MR images with histological images of the fetal brain has became a necessity for a proper neurobiological interpretation of normal and disturbed human brain development. An in vitro MRI analysis of postmortem human fetal brain specimens represents a convenient first step in bridging the gap between histogenesis and in vivo MRI (Kostović and Vasung 2009). The layered appearance of the fetal cerebral wall was already observed in early MRI studies (Girard and Raybaud 1992; Girard et al. 1995; Chong et al. 1996; Brisse et al. 1997; Childs et al. 1998, 2001; Sbarbati et al. 1998; Hüppi et al. 1998; Felderhoff-Mueser et al. 1999; Lan et al. 2000; Hüppi et al. 2001; Garel et al. 2001). In a pioneering study, we demonstrated the full correspondence between fetal architectonic zones and corresponding MR images between 15 and 36 PCW (Kostović et al. 2002a; Judaš et al. 2005; Radoš et al. 2006). We demonstrated that changes in the MRI lamination pattern of the human fetal cerebral wall are predominantly caused by changes in the subplate zone (Fig. 4) and that SP can be easily visualized in MR images due to its abundance of the hydrophilic extracellular matrix (Kostović et al. 2002a; for review, see Judaš et al. 2003a). These findings were subsequently confirmed and extended in both in vitro and in vivo MRI studies of the human fetal brain, including those which used a more advanced diffusion tensor imaging (McKinstry et al. 2002; Maas et al. 2004; Gupta et al. 2005; Prayer et al. 2006; Perkins et al. 2008; Dubois et al. 2008a, b; Trivedi et al. 2009; Widjaja et al. 2010; Kasprian et al. 2010).

5 There Are Major and Clinically Relevant Differences in Cortical Development Between Rodents and Humans

Rats and mice cannot speak, write or read or suffer from schizophrenia, but we can. While everybody wants to know what distinguishes the human brain from that of other animals, most neuroscientists study nonhuman species and leave the human and comparative neuroanatomy to a small group of devotees. Thus, neuroscientists rely on studies of nonhuman species for understanding human brain organization. This emphasis on studies of model animals, which comes to us from the biomedical research tradition and from experimental psychology, has become the accepted approach to biomedicine (Preuss 2009). The underlying assumption has been that there are basic features of brain organization that are widely shared across animals and that eventual differences are minor and unimportant (Preuss 2009). As a paragon for that approach may serve a long ago disproved but still widely cited study claiming that there is the "basic uniformity in the structure of neocortex" (Rockel et al. 1980). As pointed out in a recent review (Preuss 2009: pp 61): "The science we have built, centered on the model-animal paradigm and supported by biomedical funding agencies, is in important respects the wrong kind of science for elucidating the structure, functions, and diseases of the human brain…. I am not suggesting that we abandon our model species, but rather that those species are not enough."

There are a myriad of significant differences between rodents and humans (or, for that matter, even between humans and chimpanzees) in the structure and function of the brain at every hierarchical level, from genes and cells to large neuronal assemblies and functional systems (for a comprehensive review, see Kaas and Preuss 2007). There are large differences in number and varieties of cortical interneurons and specializations of the cortical microstructure of humans (DeFelipe et al. 2002, 2007; Hof and Sherwood 2007; Sherwood and Hof 2007). There are pronounced specializations of the neocortical pyramidal cell during primate evolution (Elston 2003, 2007) including pyramidal neurons which express calretinin (Hof et al. 2001); significant cortical area and species differences in dendritic spine morphology (Benavides-Piccione et al. 2002); primate-specific patterns of cortical commissural connections (Doty 2007); uniquely human patterns of organization within the primary visual cortex (Preuss et al. 1999; Preuss and Coleman 2002) and lateralization of minicolumns in the planum temporale (Buxhoeveden et al. 2001); special types of large, spindle-shaped layer V pyramidal neurons (Von Economo neurons) in the anterior cingulate and frontoinsular human cortex (Von Economo and Koskinas 1925; Von Economo 1926; Nimchinsky et al. 1995, 1999; Allman et al. 2002, 2005); and even hominoid specializations of the density and morphologies of cholinergic (Raghanti et al. 2008a) and serotonergic (Raghanti et al. 2008b) fibers in frontal cortex or a human-specific gene in microglia (Hayakawa et al. 2005).

The bourgeoning field of comparative genomics has convincingly demonstrated that the genetic specializations of human beings turn out to be far more extensive than expected, and include not only changes in gene sequences and gene expression, but also rearrangements, duplications, and losses of blocks of DNA (Eichler et al. 2001; Johnson et al. 2001; Gagneux and Varki 2001; Enard et al. 2002a, b; Cáceres 2003; Clark et al. 2003; Gu and Gu 2003; Hsieh et al. 2003; Preuss et al. 2004; Uddin et al. 2004; Bustamante et al. 2005; Cheng et al. 2005; Evans et al. 2005; Mekel-Bobrov et al. 2005; Khaitovich et al. 2005; Varki and Altheide 2005; Arbiza et al. 2006; Bailey and Eichler 2006; Berezikov et al. 2006; Donaldson and Gottgens 2006; Harris and Meyer 2006; Oldham et al. 2006; Popesco et al. 2006; Sikela 2006; Varki 2006; Cáceres et al. 2007; Calarco et al. 2007; Spiteri et al. 2007; Vernes et al. 2007; Zhang et al. 2007; for review see Varki et al. 2008; Preuss 2009).

Even the so-called essential genes (considered responsible for survival) give different phenotypes in different species, and about 20% of mouse orthologs of human-essential genes are nonessential in mice (Liao and Zhang 2008). The recent data in humans (Johnson et al. 2009) have uncovered an order of magnitude of greater transcriptional differences between neocortical areas than has been obtained in comparable studies in rodents (Kudo et al. 2007; Mühlfriedel et al. 2007). For example, the gene *contactin associated protein-like 2* (*CNTNAP2*), previously studied for its role in autism and specific language impairment (Arking et al. 2008; Alarcón et al. 2008; Bakkaloglu et al. 2008; Vernes et al. 2007, 2008), is selectively and highly enriched in the orbital prefrontal cortex, an area involved in regulation of social behavior in humans and has no comparable analogue in rodents. The mouse homologue *Cntnap2* has not been found to be expressed in any areal pattern or gradient in the mouse brain at any stage of development (Abrahams et al. 2007). This is an example of how unique structures and gene expression patterns that give rise to abilities, such as language, are also involved in disorders, such as autism, for which there is no accepted mouse model (Levitt 2005; Rakic 2009).

In the field of developmental neurobiology, the vast majority of published work has focused on rodent cortical development (Ragsdale and Grove 2001; Alvarez-Buylla et al. 2001; O'Leary and Nakagawa 2002; Kriegstein and Parnavelas 2003; Kriegstein and Noctor 2004; Rakic 2006a; O'Leary et al. 2007; Molyneaux et al. 2007; Rakic et al. 2009; Preuss 2009). Indeed, the mouse may be regarded as an unexcelled model for studying development of the cerebral cortex (Rakic 2000). While the basic principles of cortical development in all mammals are similar (Rakic et al. 2009), the modifications of developmental events during evolution produce not only quantitative but also qualitative changes (Preuss 2009; Rakic et al. 2009). Thus, it should be not surprising that the large primate cerebral cortex displays much more complex development and has some distinct features not observed in commonly used laboratory animals (Rakic 2006a). The human brain has different cell-cycle kinetics during cortical neurogenesis (Kornack 2000; Kornack and Rakic 1998) and longer developmental period, larger size, and evolutionary new areas with enlarged corticocortical layers II and III (Hill and Walsh 2005).

There are also a number of major differences between rodents and humans with respect to the brain development itself. For example, human cortex displays dramatically expanded subplate zone (Kostovic and Rakic 1990; see Sect. 7.2); more complex and hugely expanded SVZ (Smart et al. 2002; Zecevic et al. 2005; see Sect. 6.2.2); very prominent subpial granular layer (see Sect. 7.1.2) and significantly different process of initial cortical formation (Bystron et al. 2008; see Sect. 6.1); more complex and diverse Cajal–Retzius cells (Meyer 2010; see Sect. 7.1.1); particularly prominent and morphologically and functionally more diverse radial glial cells (Rakic 2003a, b; see Sect. 6.2.1); significantly different gradients of gene expression in the developing cortex (see Sect. 7.3.3); and several unique transient fetal structures and/or features (see Sect. 7.5). In terms of neurogenesis, one important difference deserves to be pointed out already in this section: humans have greatly expanded SVZ (Sidman and Rakic 1973, 1982; Kostovic and Rakic 1990; Smart et al. 2002; Zecevic et al. 2005) as well as the mitotically active subpial granular layer in the marginal zone (Zecevic and Rakic 2001). In comparison to rodents, these phylogenetic novelties contribute to the introduction of species-specific cell types (especially cortical interneurons; see Sect. 6.2.2), new cytoarchitectonic fields, and the pattern of connectivity and transmitter/receptor composition that needs to be taken into account if we are to understand the etiology of congenital malformations in humans (Rakic 2006a; Rakic et al. 2009).

For example, fewer than four extra rounds of symmetric cell divisions during the initial proliferation in the VZ can account for the ten-fold difference in size of the cortical surface between monkeys and humans (Rakic 1995, 2006a). In contrast, the 1,000-fold difference between the size of the cerebral cortex in mouse and human can be achieved by less than seven extra symmetrical divisions in the VZ before the onset of corticogenesis (Rakic 2006a). Indeed, such changes were experimentally confirmed in mice in which production of proliferative units has been increased either by reduction in programmed cell death (Kuida et al. 1996; Haydar et al. 1999) or through an increase in production (Chenn and Walsh 2003).

In conclusion, the traditional model-animal research paradigm (focused almost exclusively on rodents) does not offer a solid foundation for understanding what is human-specific in the human brain and human mind. However, new methods from histology, neuroimaging, and genomics share the common feature of being non-invasive and are thus making the human brain finally accessible for direct, detailed study and enable direct comparisons of humans with any other species (Preuss 2009). Thus, the time is ripe for bridging the gap between the treasure of data provided in classical human neuroanatomy and molecular biology and genomics, by taking advantage of these modern approaches and creating a foundation for new, integrative neuroscience of human brain development.

6 The Complexity and Unique Features of the Human Corticogenesis

Brain development is a complex and long process which involves sequential expression of genes, cascades of multiple molecular pathways, and continuous interactions among heterogeneous classes of cells (Rakic 2006a; Rakic et al. 2009; Preuss 2009). Modern and powerful methodological approaches, such as genomics and neuroimaging, offer unprecedented possibilities for getting new insights into development of the human brain, which, unlike in rodents, remains inaccessible for experimental approaches, for obvious ethical reasons. The complexity and unique features of human corticogenesis are evident at all major stages of cortical development: the initial formation of the neocortical anlage at the embryonic preplate stage; the pronounced heterogeneity of neuronal and glial progenitor pools in both VZ and SVZ (including the ganglionic eminence); the huge development and phylogenetically new features of both the SVZ and the subplate; distinct features of radial glial cells; multiple origins of Cajal–Retzius cells and the subpial granular layer; and other features mentioned in the following paragraphs.

6.1 The Embryonic (Preplate) Stage and the Initial Formation of the Neocortical Anlage

Over the past three decades, modern histological and/or molecular biological methods have been used to analyze the initial formation of the neocortical anlage (so-called preplate stage) during the human embryonic

period proper (Carnegie stages 12–22, E31–E51, 4–8 PCW) or during the initial development of the neocortical plate and the pre-subplate (8–10 PCW) in a rapidly increasing number of studies (Molliver et al. 1973; Kostović-Knežević et al. 1978; Larroche et al. 1981; Larroche 1981; Larroche and Houcine 1982; Marin-Padilla 1983; Krmpotić-Nemanić et al. 1984; Kostović 1986; Kostovic and Rakic 1990; Kostović et al. 1993; Zecevic 1993, 2004; Zecevic and Rakic 2001; Rakic and Zecevic 2003a; Zecevic et al. 1999, 2005; Meyer et al. 2000, 2002b, 2003; Bystron et al. 2005, 2006; Howard et al. 2006; Carney et al. 2007; Cabrera-Socorro et al. 2007; Bayatti et al. 2008a, b; Ip et al. 2010; Kerwin et al. 2010; Verney et al. 2010).

These studies revealed a previously unsuspected complexity of the early neocortical anlage in humans (for review, see Bystron et al. 2008) and clearly demonstrated that the concept of the primordial plexiform layer as introduced by Miguel Marin-Padilla (Marin-Padilla 1971, 1972, 1978, 1983, 1988a; Marin-Padilla and Marin-Padilla 1982) was overly simplified and that it at best can only be applied to the developing brains of rodents and carnivora. For example, at 4–7 PCW, a widespread network of precocious MAP2-immunoreactive cells, with long, nonaxonal processes, are present in the human preplate before the appearance of the cortical plate (Bystron et al. 2005). These cells seem to be generated outside the cerebral wall rather than in the local VZ and the first thalamocortical axons and axons of preplate cells extend across the striato-cortical boundary before the arrival of the first cortical plate neurons (Bystron et al. 2005). In a subsequent study, the same group described a distinctive, widespread population of neurons (predecessor cells) situated beneath the pial surface of the human embryonic forebrain even before complete closure of the neural tube (Bystron et al. 2006). These predecessor cells invade the cortical primordium by tangential migration from the subpallium and precede all other known cell types of the developing cortex, because they are neither Cajal–Retzius cells nor interneurons of basal origin (Bystron et al. 2006). Thus, in human forebrain, unlike rodent, predecessor cells migrate into the cortical primordium from the subpallium even before local neurogenesis has begun and no equivalent of predecessor cells has been described in any other species (Bystron et al. 2005, 2006; Carney et al. 2007); in addition, there are also other human-specific and tangentially migrating cell types (Bystron et al. 2008).

6.2 The Heterogeneity of Neuronal and Glial Progenitor Pools

The past decade has wittnessed a number of important discoveries which revealed a hitherto unexpected complexity and heterogeneity of neuronal and glial progenitor pools in the telencephalon of mammals, including humans: (1) it was discovered that radial glia not only serves as guide for radially migrating neurons but also represents a neural stem cell which produces both astrocytes and neurons; (2) it has been demonstrated that cortical principal (pyramidal) neurons as well as interneurons originate from multiple and separate proliferative pools; (3) newly generated neurons arrive to the cortex by multiple radial and tangential migratory routes; (4) there are major differences between rodents and primates in both the diversity of origins and migratory routes of cortical neurons; and (5) there are major differences between rodents and humans with respect to the clinically important question of adult neurogenesis. Thus, in the developing mammalian telencephalon, there are several classes of progenitors that can produce distinct neuronal subclasses with considerable species-specific differences in their relative proportions (Rakic et al. 2009). These differences are controlled by genes that act on the progenitor cells at or prior to their exit from their cell's mitotic cycle (Shirasaki and Pfaff 2002) and thus generate a different outcome, depending on the given evolutionary context (Rakic 2003a, b). In the following sections, we focus on several key topics which illustrate why data obtained in rodents in most cases simply cannot be meaningfully extrapolated to the developing human telencephalon.

6.2.1 Radial Glial Cell: Just a Radial Guide for Migratory Neurons, or Mother of Them All?

There are several excellent reviews on the long history of radial glia (Bentivoglio and Mazzarello 1999) and their developmental and evolutionary adaptations (Cameron and Rakic 1991; Rakic 2003a, b). It is important to recognize at least three separate developmental roles of these cells: (1) their role as temporary guides for radially migrating neurons; (2) their role as precursors of astrocytes; (3) their role as neural stem

cells, including their putative role as multipotent stem cells in the adult brain (see Sect. 6.2.2).

Radial Glial Fibers as Guides for Radial Migration of Neurons

In studies combining the use of Golgi impregnation and electron microscopy in the monkey developing cortex, Pasko Rakic discovered that radial glial cells serve as guides for radial migration of young postmitotic neurons on their journey from the VZ to the cortical plate (Rakic 1971, 1972). The glial nature of these radial fibers was assumed on the basis of the morphological criteria (Rakic 1971, 1972; Schmechel and Rakic 1979a) and confirmed by early immunocytochemical studies in both monkey (Levitt and Rakic 1980; Levitt et al. 1981) and human brain (Choi and Lapham 1978; Choi 1986). In the human and macaque fetal cerebrum during the course of corticogenesis, radial glial cells contain glial fibrillary acidic protein (GFAP) and are distinctly different from GFAP-negative cells (Antanitus et al. 1976; Choi and Lapham 1978; Levitt and Rakic 1980; Levitt et al. 1981, 1983; Choi 1986; Kadhim et al. 1988; DeAzevedo et al. 2003). The intermediate filament vimentin is also a helpful marker for the identification of radial glia as a separate cell line in primates, since the adjacent neuronal cells are vimentin-negative (Rakic 2003a, b). Unlike in primates, radial glial cells in rodents are not GFAP-positive until the completion of corticoneurogenesis (Cameron and Rakic 1991) and the change in their developmental phenotype is indicated by a substitution from vimentin to GFAP (for review, see Rakic 2003a, b). In primates, radial glial cells express both GFAP and vimentin throughout at least two-thirds of gestation (Antanitus et al. 1976; Choi and Lapham 1978; Levitt et al. 1981; Choi 1986; Sasaki et al. 1988; Stagaard and Mollgard 1989; Gould et al. 1990; Wilkinson et al. 1990; Sarnat 1992; Honig et al. 1996; Zecevic et al. 1999; DeAzevedo et al. 2003).

In addition, human and monkey radial glial cells display much more complex and diverse morphological features in comparison to rodents – such as, lamellate expansions and cone-shaped endfeet forming a continuous glia limitans component of the pial surface. In fact, radial glial cells reach the peak in size and phenotypic differentiation in the human fetal forebrain (Rakic 2003a, b). As the size of the cerebral wall expands during evolution, radial glial scaffolding also becomes more differentiated, more permanent, and functionally more significant – that is, radial glial cells have undergone substantial evolutionary transformation (Schmechel and Rakic 1979a, b; Levitt and Rakic 1980; Levitt et al. 1981, 1983; Rakic 2003a, b). There are important structural, molecular, and functional differences in radial glia between different regions within the same species as well as between the same regions of different species (Rakic 2003a, b). For example, the length of the radial glial fiber in the macaque monkey cerebrum toward the end of corticoneurogenesis may reach 3–7 mm (Rakic 1972) and at this stage in the primate forebrain, many radial glial cells stop transiently to divide while their shaft serves as scaffolding for a cohort of migrating neurons (Schmechel and Rakic 1979a, b). In the fetal human cerebral wall several generations of GFAP-negative migrating neurons can be aligned along a single GFAP-positive radial glial shaft, and the number of thus associated neurons increases with the gestational age (Rakic 2003a, b). For example, in the wide intermediate zone of the human fetus during midgestation, as many as 30 generations of migrating neurons can be simultaneously aligned along the single radial glial shaft (Sidman and Rakic 1973, 1982).

Thus, this radial glial scaffolding may be particularly important in the primate fetal cerebrum, where a large SVZ supplies a bulk of interneurons at the late developmental stages, thus contributing to evolutionary and developmental cortical expansion (Letinic et al. 2002; Smart et al. 2002; Zecevic 2004; Kriegstein et al. 2006). The fate of the radial glial cells depends on the context and functional requirements, which differ between species (Rakic 2003a, b).

Radial Glia as Precursor of Astrocytes

In most mammals the telencephalic radial glial cells are transient, and disappear or transform into astrocytes with the completion of cortical development (Schmechel and Rakic 1979a, b; Kadhim et al. 1988; Wilkinson et al. 1990; DeAzevedo et al. 2003; Rakic 2003a, b). During the early embryonic and fetal development, the pial contacts of these cells are multiple, connected by tight junctions, and each one terminates in a characteristic endfoot process covered with basal lamina material (Marin-Padilla 1995). The apposed

and basal lamina-covered endfeet of these radial cells constitute the primordium of neocortical external glial limiting membrane, which is perforated and subsequently reformed only at specific sites by entering meningeal blood vessels and olfactory axons (Marin-Padilla 1985, 1988b; Krisch 1988; Marin-Padilla and Amieva 1989).

In the fetal brains of monkeys and humans, radial glial cells become transformed into fibrous (white matter) and/or protoplasmic (gray matter) astrocytes (Choi and Lapham 1978; Schmechel and Rakic 1979a; Levitt and Rakic 1980; Eckenhoff and Rakic 1984; Choi 1986; Marin-Padilla 1995). The first fibrous astrocytes in the neocortex are those of the SVZ and the subplate and their appearance parallels the early vascularization of these zones (Marin-Padilla 1995). However, modified radial glial cells may be found in some regions of the adult nervous system – for example, Bergmann glial cells of the cerebellum, Müller cells of the retina, tanycytes of the hypothalamus (Rakic 2003a, b).

Radial Glia as Neural Stem Cells

While it has been known for a long time that the primary radial glial phenotype (as defined by Cameron and Rakic 1991) can revert to the neuroepithelial form and generate neurons, recent studies in rodents provided direct evidence that radial glia give origin to cortical neurons (Malatesta et al. 2000, 2003; Noctor et al. 2001, 2002; Tamamaki et al. 2001; Hartfuss et al. 2001; Tramontin et al. 2003; Gal et al. 2006; for review, see Barres 1999; Alvarez-Buylla et al. 2001; Parnavelas and Nadarajah 2001; Campbell and Götz 2002; Gaiano and Fishell 2002; Fishell and Kriegstein 2003; Weissman et al. 2003; Götz and Huttner 2005). Thus, the daughter cells (i.e., young postmitotic neurons) are guided by the radial fibers of their mother's cells to the appropriate location in the cortical plate (Noctor et al. 2001; Rakic 2003a, b). The protein Numb is a crucial player in maintaining the adhesiveness of radial glia in the VZ, preventing premature detachment and subsequent astrogliogenesis (Rasin et al. 2007). In contrast, Notch functions cell-autonomously to maintain the radial glial cell fate while the proneural genes antagonize Notch signaling to promote neuronal differentiation and subsequent migration (Breunig et al. 2007b). Furthermore, the daughter neuronal cell stimulates Notch signaling in the radial glial mother cell to maintain the neurogenic VZ niche and migratory scaffold (Yoon et al. 2008).

Multipotent astrocytic stem cell has also been identified in fetal and adult mouse brain (Laywell et al. 2000). More recent observations have indicated the existence of a transit-amplifying cell that populates both the VZ and SVZ. These cells are considered dedicated neuronal progenitors derived from the parent radial glial cells that do not inherit the pial fiber (Noctor et al. 2004; Gal et al. 2006; Martinez-Cerdeno et al. 2006). There are radial glial cells that span the entire neocortical cerebral wall as well as short neural precursors (SNPs) with basal processes of variable length that are retracted during mitotic division (Gal et al. 2006). While SNPs are marked by their preferential expression of the tubulin alpha-1 promoter, radial glial cells instead express the glutamate astrocyte-specific transporter (GLAST) and brain lipid-binding protein promoters (Gal et al. 2006). Thus, radial glial cells can give rise to both neuron and astrocytic progenitors that each can produce several generations of dedicated progenitors before their terminal differentiation (Rakic 2006a). Multipotential progenitors have also been recognized in the human fetal brain: human embryonic stem cells produce separate neuron- and glia-restricted precursors in vitro (Carpenter et al. 2001); molecular phenotyping of neurospheres obtained from fetal human brain revealed glial and neuronal classes of cells (Suslov et al. 2002; Kim et al. 2006); glial cells from the human fetal lateral ganglionic eminence in vitro produce either glia or neurons (Skogh et al. 2001); and in the human brain radial glia can directly produce neurons (Weissman et al. 2003; Mo et al. 2007; Hansen et al. 2010). Multipotent astrocytic stem cells have also been identified in the adult human brain (Kirschenbaum et al. 1994; Kukekov et al. 2002; Sanai et al. 2004).

In human VZ and SVZ already at 5–6 PCW (Carnegie stages 14–15), three major cell types are observed (Zecevic 2004): (a) most proliferating VZ cells are labeled with radial glial markers such as vimentin, GFAP, and GLAST antibodies; (b) a subpopulation of these cells also express the neuronal markers β III-tubulin, MAP-2, and phosphorylated neurofilament SMI-31, in addition to the stem cell marker nestin, which indicates their multipotential capacity; and (c) some VZ cells that immunoreact only with neuronal markers, which indicates the emergence of restricted neuronal progenitors. All three classes are proliferative and share common

radial morphology with attachments to the VZ and pial surface (Zecevic 2004). Thus, multipotential progenitors coexist with restricted neuronal progenitors and radial glial cells during initial human corticogenesis, demonstrating that the diversification of cells in human VZ and overlying SVZ begins earlier and is more pronounced than in rodents (Zecevic 2004; Howard et al. 2006). However, radial cells double labeled with glial and neuronal markers cease to be present in human fetuses of 10 PCW and older (DeAzevedo et al. 2003; Zecevic 2004). In a subsequent study, it was confirmed that restricted neuronal progenitor cells divide simultaneously with radial glial cells in the human embryonic VZ at the onset of cortical neurogenesis, that at midgestation radial glial cells proliferate not only in the VZ, but throughout various regions of the telencephalic wall, and that several subtypes of radial glial cells can be distinguished on the basis of their antigen content (Howard et al. 2006). In a recent in vitro study, Mo et al. (2007) provided the first direct evidence that radial glial cells in the human cerebral cortex serve as neuronal progenitors and that diverse populations of cortical progenitor cells (including multipotent radial glia and neuron-restricted progenitors) contribute differentially to cortical neurogenesis at the second trimester of gestation (Mo et al. 2007). In contrast to mouse, it seems that radial glia in human do not generate all, or even the majority, of cortical neurons during midgestation – an additional progenitor subtype (restricted neuronal progenitors) is contributing to neuronal population of the human cerebral cortex (Piper et al. 2001; Howard et al. 2006; Mo et al. 2007).

6.2.2 Pallial Versus Subpallial Origin of Cortical Neurons and the Evolutionary Expansion of the Subventricular Zone

The Rodent Story: Pyramidal Neurons from Pallial Ventricular Zone and Interneurons from the Subpallial Ganglionic Eminence

Initial studies in rodents offered a simple and attractive concept: while all cortical glutamatergic pyramidal neurons originate from the pallial VZ and reach cortical plate by radial migration, all cortical GABAergic interneurons originate from the subpallial ganglionic eminence and reach the cortex by tangential migration through deep IZ/SVZ or through the superficial MZ (DeDiego et al. 1994; Tamamaki et al. 1997; Anderson et al. 2001, 2002; Parnavelas 2000; Marin and Rubenstein 2001, 2003; Nadarajah and Parnavelas 2002; Polleux et al. 2002; Nery et al. 2002; Kriegstein and Parnavelas 2003; Kriegstein and Noctor 2004; Xu et al. 2004; Wonders and Anderson 2005; for review see Métin et al. 2006; Hernández-Miranda et al. 2010). Cortical interneurons originate from several sources and migrate via distinct and independent tangential streams to reach their final destination (Ang et al. 2003; Marin and Rubenstein 2003). In rodents, the majority of cortical interneurons originate in the medial ganglionic eminence from progenitors that express ventral (subpallial) transcription factors *Dlx2*, *Nkx2.1*, *Lhx6* and *Mash1* (Xu et al. 2004).

The Human Story: Cortical Interneurons Predominantly from Pallial VZ/SVZ

Unlike in rodents, many GABAergic cortical interneurons are generated in pallial VZ/SVZ in monkeys (Petanjek et al. 2009) and humans (Letinic et al. 2002; Rakic and Zecevic 2003a; Fertuzinhos et al. 2009; for review, see Jones 2009). In the human, most of the cortical interneurons originate in the VZ/SVZ of the dorsal telencephalon subjacent to a given area (Letinic et al. 2002). This is particularly evident in the primary visual cortex, which in monkeys and humans contains a significantly larger number of interneurons than the adjacent areas (Smart et al. 2002; Lukaszewicz et al. 2005). In humans, a distinct lineage of neocortical GABAergic neurons that express *Dlx1/2* and *Mash1* transcription factors and originate from the neocortical VZ/SVZ comprise about two-thirds of the neocortical GABAergic neurons, while the remaining third originate from the ganglionic eminence (Letinic et al. 2002; Rakic and Zecevic 2003a). The expression of Nkx2.1 mRNA and protein was also demonstrated in human neocortical VZ/SVZ from 5 PCW until midgestation (Rakic and Zecevic 2003a).

Evolutionary Expansion of the Subventricular Zone in Primates and Humans

It is now generally accepted that, in addition to multipotential radial glial cells, the telencephalic proliferative

centers (VZ, SVZ, ganglionic eminence) also contain more restricted neuronal and glial cell progenitors. Initial studies in monkeys (Levitt and Rakic 1980; Levitt et al. 1981, 1983) as well as in humans (Carpenter et al. 2001; Letinic et al. 2002; DeAzevedo et al. 2003) demonstrated the existence of at least two separate stem cell lines in the VZ and a highly expanded SVZ: one glial and the other neuronal. For example, cells isolated from the human VZ/SVZ even at early fetal stages generate separate neuron-restricted and glia-restricted precursors (Carpenter et al. 2001). There are multiple divisions of human neuronal stem cell progenitors in the VZ/SVZ before they begin radial migration to the neocortex (Letinic et al. 2002).

An expansion of cortical progenitor cell number during evolution must have contributed to the increase in size of the human brain (Rakic 1995, 2009; Molnár et al. 2006; Dehay and Kennedy 2007; Fish et al. 2008; Abdel-Mannan et al. 2008). The evolution of primate and human neocortex is associated with enormous increase in size of the SVZ and the subplate (Kostovic and Rakic 1990; Smart et al. 2002; Kriegstein et al. 2006; Martinez-Cerdeno et al. 2006).

In humans, the SVZ appears as the secondary proliferative zone at 7–8 PCW (Sidman and Rakic 1982; Zecevic 1993). The SVZ in primates, including humans, produce mostly interneurons (Letinic et al. 2002; Rakic 2003a) and late generated subplate neurons (Smart et al. 2002; Zecevic et al. 2005) and glial cells (Rakic 2003a), including oligodendrocyte progenitors (Zecevic et al. 2005) and eventually in the adult cerebrum transforms into the subependymal zone (SEZ) which produces mostly glial cells (Lewis 1968; McDermott and Lantos 1990; Sanai et al. 2004). In the adult human brain, mature ependyma serves as an important barrier between CSF and brain parenchyma (Bruni 1998), and human ependymal cells were studied by immunohistological methods and electron microscopy (Gould and Howard 1987; Gould et al. 1990) and always described as the lining of the ventricular cavity (Roessmann et al. 1980; Gould et al. 1990).

The adult human SVZ represents a niche of neural stem cells, displays unique features and its architecture and function differs significantly from that described in other mammals (Quinones-Hinojosa et al. 2006). It is composed of four layers: a monolayer of ependymal cells (layer I), a hypocellular gap (layer II), a ribbon of cells (layer III) composed of astrocytes, and a transitional (layer IV) zone into the brain parenchyma (Quinones-Hinojosa et al. 2006). It contains three distinct types of astrocytes (which differ significantly from those described in rodent brain) and a group of displaced ependymal cells. Unlike rodents and non-human primates, adult human GFAP-positive SVZ astrocytes are separated from the ependyma by the hypocellular gap, and the adult human SVZ appears to be devoid of chain migration of large numbers of newly formed young neurons (Quinones-Hinojosa et al. 2006).

Radial glial cells in the VZ generate intermediate progenitor cells that migrate into the SVZ and further proliferate to increase neuronal number (Haubensak et al. 2004; Noctor et al. 2004; Fietz et al. 2010). In the human brain, a substantial fraction of interneurons originates locally, in the pallial VZ/SVZ (Letinic et al. 2002; Rakic and Zecevic 2003a; Zecevic 2004). Furthermore, oligodendrocytes and astrocytes (Back et al. 2001; Rakic and Zecevic 2003b; Zecevic 2004; Jakovcevski and Zecevic 2005a, b; Jakovcevski et al. 2009) and stem-like cells (Flax et al. 1998; Vescovi et al. 1999; Ourednik et al. 2001) are generated and reside in the human fetal SVZ. It should be noted that hypoxic-ischemic injury in prematurely born infants frequently damages the SVZ (Judaš et al. 2005; McQuillen and Ferriero 2005; Volpe 2009).

A distinguishing feature of primate corticogenesis is the appearance of the outer SVZ (OSVZ) during midgestation (Smart et al. 2002; Kostović et al. 2002a; Zecevic et al. 2005; Fish et al. 2008; Fietz et al. 2010). Cell divisions in both the OSVZ and the VZ coincide with the major wave of cortical neurogenesis, suggesting that OSVZ cells produce neurons (Lukaszewicz et al. 2005). Unlike in rodents, cells expressing the transcription factor PAX6 are found in the OSVZ of human and primate cortex (Fish et al. 2008; Bayatti et al. 2008a; Mo et al. 2007). Neuronal proliferation in the human SVZ between 18 and 24 PCW is important for generation of upper cortical layers, because at that time the SVZ remains the only proliferative zone (Zecevic et al. 2005) while during the cortical expansion in the last trimester a threefold increase in the number of cells takes place (Badsberg Samuelsen et al. 2003).

Hansen et al. (2010) recently described classes of radial glia-like (neural stem) cells and transit-amplifying (intermediate progenitor) cells in the human OSVZ

that contribute significantly to neurogenesis. OSVZ radial glia-like cells show unusual cell cycle behaviors that further distinguish them from traditional RG cells (Hansen et al. 2010). Large numbers of radial glia-like cells and intermediate progenitor cells populate the human OSVZ; OSVZ radial glia-like cells have a long basal process but, surprisingly, are non-epithelial as they lack contact with the ventricular surface. They undergo proliferative divisions and self-renewing asymmetric divisions to generate neuronal progenitor cells that can proliferate further. The inhibition of Notch signaling in OSVZ progenitor cells induces their neuronal differentiation. This novel finding that OSVZ progenitors undergo expansive proliferative divisions contrasts with observations of the rodent SVZ – in which intermediate progenitor cells usually divide only once – and provides a new cellular basis for understanding the evolutionary expansion of surface area in human cortex (Hansen et al. 2010; Kriegstein et al. 2006; Martinez-Cerdeno et al. 2006). These results indicate a new mechanism for cortical expansion outside the VZ through the addition of radial columns arising from the OSVZ – the establishment of non-ventricular radial glia–like cells may have been a critical evolutionary advance underlying increased cortical size and complexity in the human brain (Hansen et al. 2010).

There Is No Firm Evidence for Adult Neurogenesis in the Cerebral Cortex of Monkeys and Humans

In the adult mammalian brain, neurogenesis persists in two germinal regions: the SVZ on the walls of the lateral ventricle (Lois and Alvarez-Buylla 1994; Alvarez-Buylla and Garcia-Verdugo 2002; Alvarez-Buylla and Lim 2004) and the subgranular layer of the hippocampal dentate gyrus (Kempermann 2002). In rodents, SVZ astrocytes function as primary progenitors which generate intermediate precursors that function as transit amplifying cells for the generation of large number of new neurons.

Granule cell formation has been found in small numbers in the dentate gyrus of adult monkeys (Kornack and Rakic 1999) and some studies purported to show that there is a long-lasting postnatal granule cell proliferation in the dentate gyrus of both monkey (Gould et al. 1998, 1999a) and the human hippocampus (Murell et al. 1996; Eriksson et al. 1998; Roy et al. 2000). However, only one of these studies indicated granule cell formation in the adult human dentate gyrus (Eriksson et al. 1998), while the other two reports were based on in vitro studies (Murell et al. 1996; Roy et al. 2000). Even these authors later suggested that adult-generated hippocampal and neocortical neurons in macaques have a transient existence (Gould et al. 2001). Furthermore, neurogenesis was not changed in the resected hippocampi of epileptic patients (Seress et al. 2001; Heinrich et al. 2006; Fahrner et al. 2007), and human brain after stroke and irradiation displays very limited possibilities for neuronal repair (Price 2001; Snyder and Park 2002; Arvidsson et al. 2002), in spite of isolated report that adult neurogenesis may occur after stroke (Jin et al. 2006). Adult neurogenesis was also suggested to occur in the monkey striatum (Bedard et al. 2006) and amygdala and adjoining cortex (Bernier et al. 2002). The rostral migratory stream of newly generated neurons (which differentiate into interneurons of the olfactory bulb) has been demonstrated in the brain of adult rodents (Lois and Alvarez-Buylla 1994) and adult monkeys (Kornack and Rakic 2001a; Pencea et al. 2001), but does not occur in adult human brain (Sanai et al. 2004; however, see Bédard and Parent 2004). However, SVZ astrocytes isolated from the adult human brain can function as neural stem cells and can generate new neurons in vitro (Sanai et al. 2004). Previous study observed PSA-NCAM-positive (presumably migrating) cells in the human SVZ of children less than 1 year old, but also did not see similar clusters in adult specimens (Weickert et al. 2000).

Similarly, one initial study suggested neurogenesis for the adult primate neocortex (Gould et al. 1999b), but subsequent studies clearly demonstrated that neurogenesis in the primate and human neocortex is an early prenatal phenomenon (Korr and Schmitz 1999; Kornack and Rakic 2001b; Rakic 1998, 2002a, b, 2006b; Koketsu et al. 2003; Spalding et al. 2005; Bhardwaj et al. 2006; Breunig et al. 2007a). One can safely conclude that there is no firm data to support the claim that neurogenesis would occur in the adult human brain in general, which is in accordance with classical reports on limits of neurogenesis in primates as a form of evolutionary adaptation (Rakic 1985). Pasko Rakic proposed that a stable population of cortical neurons

that lasts throughout the life span has evolved to enable storage of long-term memory and retention of learned experience (Rakic 1985, 2006a, b).

7 The Transformation of the Neocortical Anlage into the Six-Layered Neocortex and Development of the Cortical Map

The transformation of fetal neocortical anlage into the adult six-layered neocortex is a very protracted process, starting during the last trimester and extending to at least 3 or 4 years after birth. This transformation in fact consists of sequential reorganizational events (accompanied by corresponding transient electrophysiological and behavioral phenomena) and, importantly, encompasses the perinatal period in which both transient and permanent cortical circuitry elements coexist (Kostović and Judaš 2006, 2007, 2010). These reorganizational events affect all three major compartments of the fetal neocortical anlage: (1) the marginal zone (with significant changes in Cajal–Retzius neurons and other small neurons, and disappearance of the subpial granular layer); (2) the cortical plate (with gradual appearance of Brodmann's six-layered ontogenetic Grundtypus, intense morphological and chemical differentiation of cortical neurons and ever increasing intensity of synaptogenesis); and (3) the subplate zone, which after birth gradually disappears as a recognizable architectonic entity, but many of its neurons survive into adulthood as the so-called subcortical white matter interstitial neurons (for review, see Judaš et al. 2010a, b). These major reorganizational events enable the final regional and areal differentiation and specification of the cortical map and occur in parallel with increasing myelinization of the cortical white matter. In addition, during the same perinatal period a number of other transient fetal structures (some of which seem to be human-specific) disappear – such as the ganglionic eminence, the gangliothalamic body, the perireticular nucleus, certain transient populations of intracallosal and subcallosal neurons, and so forth (see Sect. 7.5). As the last trimester is also the period of prematurely born babies, which frequently suffer from hypoxic-ischemic brain damage and thus are at risk for poor neurodevelopmental outcome (Leviton and Gressens 2007; Miller and Ferriero 2009; Volpe 2009), it is obvious that the detailed knowledge of these perinatal and postnatal reorganizational events is of great clinical significance – especially if these events can be visualized and used as in vivo biomarkers in modern neuroimaging studies (Ment et al. 2009). Such knowledge is also vital for understanding and (hopefully) managing brain reorganization after pre- and perinatal brain lesions (for review, see Staudt 2010).

7.1 The Transformation of the Marginal Zone into the Neocortical Layer I

7.1.1 The Origin and Fate of Cajal–Retzius Cells

The Cajal–Retzius cells are a special population of large neurons in the fetal marginal zone and the future cortical layer I (Krmpotić-Nemanić et al. 1987; Meyer and Gonzalez-Hernandez 1993; Verney and Derer 1995; Meyer and Goffinet 1998; Meyer and Wahle 1999; Meyer et al. 2000, 2002a, 2003; Abraham et al. 2004a; Cabrera-Socorro et al. 2007; Meyer 2010). They have important functions in the initial establishment of cortical lamination and transient neuronal circuitry of the fetal cortex and they secrete an extracellular matrix glycoprotein reelin (for review see Meyer et al. 1999; Tissir and Goffinet 2003; Meyer 2010). For example, autosomal recessive lissencephaly is associated with human reelin (*RELN*) gene mutations (Hong et al. 2000). The main site of origin of Cajal–Retzius cells destined for the neocortex is the cortical hem (Grove and Tole 1999; Ragsdale and Grove 2001), a putative signaling center at the interface of the prospective hippocampus and the choroid plexus, which is most highly developed in the human brain (Abu-Khalil et al. 2004; Meyer 2010). Additional populations of Cajal–Retzius cells may derive from the thalamic eminence in the ventral thalamus and from the amygdalar hem (Meyer 2010).

The Cajal–Retzius cells may represent a rare example of truly transient fetal neurons, because recent studies indicate that they degenerate and undergo cell death when cortical migration is completed (Meyer 2010); however, this is by no means a generally shared opinion, and the debate on their supposed postnatal existence continues for almost a century (e.g., Marin-Padilla 1984, 1988a, 1992, 1998; Martin et al. 1999).

The first Cajal–Retzius cells in the human neocortical anlage have been observed already at 7 PCW (Larroche 1981; Larroche and Houcine 1982) in the early preplate; they express reelin and continue to increase in number after the appearance of the cortical plate (Meyer 2010).

Some NPY-positive Cajal–Retzius cells can be observed in the human marginal zone already at 14 PCW, but they become quite rare from 36 PCW onward (Uylings and Delalle 1997). At midgestation, most Cajal–Retzius cells in humans are reported to contain calbindin-D28k and calretinin (Verney and Derer 1995; Yan et al. 1997) while only few of them contain parvalbumin (Verney and Derer 1995; Cao et al. 1996). In the human newborn, neocortical layer I contains parvalbumin-positive Cajal–Retzius cells, and many of them display clear signs of degeneration (Ding et al. 2000). There is also a plexus of horizontal parvalbumin-positive fibers in deep layer I, and many small neurons of the layer I also contain parvalbumin (Ding et al. 2000). Finally, human Cajal–Retzius cells are unique because they specifically express the RNA gene *human accelerated regions 1F* (*HAR1F*), part of a region of the human genome that has shown a significant evolutionary acceleration since the divergence of humans and chimpanzees (Pollard et al. 2006).

7.1.2 The Origin and Fate of the Subpial Granular Layer

The subpial granular layer (SGL) is a transient layer composed of small granular cells located within the fetal marginal zone (MZ) and is usually considered specific to human or primate cortex (Brun 1965; Gadisseux et al. 1992; Sidman and Rakic 1982; Bystron et al. 2008; Rakic 2009; for review see Judaš and Pletikos 2010). While it has been frequently stated that the SGL has been recognized only in man, it should be noted that the SGL is also well developed in the fetal monkey cerebral cortex (Zecevic and Rakic 2001); has been observed in fetal brains of sheep, cow, dog, and cat (Ranke 1910; Sanides and Sas 1970); and it has recently been described even in the developing cortex of rodents (Meyer et al. 1998; Jiménez et al. 2003). Nevertheless, it remains true that the SGL is the most prominent (and present during the longest prenatal period) in the human fetal brain. In the human fetal brain, the SGL originates in the paleocortical region at the end of the first trimester of gestation, spreads over the entire cerebral surface during the following 2 months, and disappears progressively during the third trimester (Brun 1965). It seems that the SGL is formed by an extension of the olfactory SVZ (Gadisseux et al. 1992), that is, the prepiriform region of the human fetal basal forebrain (Meyer and Wahle 1999; Meyer et al. 1999), and spreads from this localized fountainhead over the entire neocortex through tangential, subpial migration (Brun 1965; Gadisseux et al. 1992). At least some small neurons of the fetal marginal zone (including probably at least some SGL cells) are generated in the olfactory placode and olfactory primordium, both in humans (Meyer and Wahle 1999) and in monkeys (Zecevic and Rakic 2001). The usual explanation for the gradual disappearance of the SGL is that its cells migrate inwardly into the cortical plate, thus supplementing the cortical contingent of interneurons (Brun 1965; Gadisseux et al. 1992). However, it is worth noting that at least some of the SGL cells degenerate (Gadisseux et al. 1992) and that after 30 PCW the naturally occurring cell death is an active mechanism contributing to the disappearance of SGL cells, but not the Cajal–Retzius cells (Spreafico et al. 1999).

The SGL is clearly not present during the early human preplate stage (4–8 PCW, that is, Carnegie stages 12–22, or embryonic days E31–E51) or during the initial formation of the neocortical plate (8–10 PCW), as demonstrated in a number of studies (Larroche 1981; Marin-Padilla 1983; Zecevic 1993; Zecevic et al. 1999; Meyer et al. 2000, 2002b, 2003; Bystron et al. 2005, 2006). However, when exactly the SGL appears in the human fetal brain remains a somewhat debatable topic. It has been suggested that the SGL appears around 11 PCW (Zecevic and Milosevic 1997; Bystron et al. 2008), or at 12 PCW (Gadisseux et al. 1992), or 14 PCW (Meyer and Goffinet 1998; Meyer et al. 1999), or 15 PCW (Marin-Padilla 1995). The SGL is said to be most prominent from 17 to 26 PCW (Brun 1965), or from 16 to 24 PCW (Meyer and Gonzalez-Hernandez 1993; Meyer and Goffinet 1998; Meyer and Wahle 1999), or fully developed by 25 PCW but already starts to disappear by 26 PCW (Marin-Padilla 1995). The SGL is supposed to disappear by 27–29 PCW (Rakic and Zecevic 2003a), by 28–30 PCW (Meyer and Gonzalez-Hernandez 1993), by 31 PCW (Spreafico et al. 1999), by 35 PCW (Gadisseux et al. 1992; Marin-Padilla 1995), or simply around the end of gestation (Brun 1965).

While some have interpreted SGL cells as glial precursors destined to layer I (Marin-Padilla 1995), a number of subsequent histochemical and immunohistochemical studies demonstrated that most, if not all, SGL cells are indeed neurons (Gadisseux et al. 1992; Meyer and Gonzalez-Hernandez 1993; Meyer and Wahle 1999; Spreafico et al. 1999). The SGL cells are positive for neuronal marker MAP2 and negative for a glial marker GFAP (Gadisseux et al. 1992).

What is the exact developmental fate and possible function of transient SGL cells? According to the traditional interpretation, the SGL in cats, monkeys and humans produces neurons that may descend to the underlying cortical plate and thus contribute to the wealth of interneurons in certain cortical areas (Brun 1965; Zecevic and Milosevic 1997; Zecevic and Rakic 2001).

Another group of researchers proposed that SGL cells basically represent a precursor pool for subsequent development of two main types of Cajal–Retzius cells (Meyer and Goffinet 1998; Meyer et al. 1999). The same group also demonstrated that human fetal SGL cells also express the gene *doublecortin – DCX* (Meyer et al. 2002a). However, it does not seem likely that Cajal–Retzius cells are derived from the SGL, since most of them are already present in the marginal zone before the transient SGL develops (Sidman and Rakic 1982; Zecevic and Rakic 2001). An autoradiographic study in rhesus monkeys (Zecevic and Rakic 2001) also demonstrated that, unlike in rodents, neurons of layer I are generated during the entire 2 month period of corticogenesis. The large Cajal–Retzius cells (which express reelin and calretinin but not GABA) are generated first (E38–E50), while smaller, GABAergic neurons are generated from E43 to E94. These late-generated layer I cells are imported from outside sources such as the olfactory primordium and ganglionic eminence and via a massive SGL that may also supply some GABAergic neurons to the subjacent cortical plate (Zecevic and Rakic 2001). This study demonstrated that in monkey the SGL appears only after the large Cajal–Retzius cells have been generated, and thus the SGL in primates contributes mostly to the later-generated layer I neurons (Zecevic and Rakic 2001). In addition, a recent study using both classical interneuron markers (calretinin, calbindin, and GABA) as well as transcription factors (*NKX2.1* and *DLX* – markers indicating subcortical, i.e., ganglionic eminence origin) demonstrated that the human SGL between 17 and 22 PCW contained a population of small interneurons that originated mainly in the lateral ganglionic eminence/olfactory region, since the majority of these cells were double-labeled with DLX/GABA and rarely with NKX2.1/GABA (Rakic and Zecevic 2003a). But some of these cells also originated from the cortical SVZ (Rakic and Zecevic 2003a), indicating that neurons in the human cortical layer I are heterogeneous, with more complex origin and migratory routes than in rodents.

According to the analysis of our own material, the subpial granular layer develops around 13 PCW, starts to disappear after 28 PCW, and is not visible at 34 PCW (Kostović et al. 2004). It should be noted that the marginal zone of the human neocortex between 18 and 28 PCW displays a very complex six-layered organization (Kostović et al. 2004) and starting from the pia to the cortical plate, the following layers can be distinguished: (1) cell-poor marginal stripe (Randstreifen), (2) the SGL, (3) marginal zone proper, (4) stratum lucidum, (5) deep granular layer, and (6) stratum radiatum.

In conclusion, both the marginal zone and the SGL in the human fetal telencephalon have a complex cell composition, which may change over time. The subpopulations of interneurons that originate in the SGL may be involved in human cortical disorders that do not occur or cannot be mimicked in mice (Rakic 2009). Thus, the developmental fate of the human SGL certainly requires further studies.

7.2 The Dissolution of the Subplate Zone and Postnatal Persistence of Subplate/Interstitial Neurons

As already mentioned, the subplate zone appears at the beginning of the early fetal period, reaches its peak during midgestation, and its dissolution begins during the last third of gestation; however, it remains present under the prefrontal association cortex up to 6 postnatal months (Kostovic and Rakic 1990; Kostovic 1990a, b, b; for an extensive review see Judaš et al. 2010a, b). However, the dissolution of the subplate does not mean that its neurons disappear after fulfilling their presumed prenatal developmental roles. In fact, a large number of these cells survive for a life-time as so-called interstitial white matter neurons (Kostovic and Rakic 1980; for review see Suárez-Solá et al. 2009;

Judaš et al. 2010a, b). In this section our primary goal is to draw attention to a pronounced diversity of morphological and molecular phenotypes of fetal subplate and postnatal interstitial neurons. Various functional roles of the subplate zone were subject of many previous reviews in both experimental animals (Allendoerfer and Shatz 1994; Friedlander and Torres-Reveron 2009; Kanold and Luhmann 2010) and in human brain (Kostović 1990b; Kostović and Judaš 2002a, 2006, 2007, 2010).

7.2.1 Morphological Phenotypes and Projections of Subplate and Interstitial Neurons

We already published a detailed description of morphological differentiation and growth of human subplate neurons, from 10.5 PCW to early postnatal period on the basis of Golgi-stained material (Mrzljak et al. 1988, 1990, 1992; Kostovic and Rakic 1980, 1990). We also used NADPH-d histochemistry which offers a Golgi-like staining of many subplate neurons (Judaš et al. 1999) and postnatal interstitial neurons (Judaš et al. 2010b).

At 10.5 PCW the primordial human subplate contains rich rootlike arborization of descending processes of deep cortical plate neurons as well as more differentiated polymorphous subplate and bipolar neurons (Mrzljak et al. 1988). These polymorphous neurons have two or three dendrites protruding from oval or irregularly shaped cell bodies and branching several times, with axons which either ascend toward the CP or (less frequently) descend toward the IZ. At 13.5–15 PCW, the subplate consists of an upper part (with horizontally spaced rows of cells) which incorporates the primordial subplate of the previous stage, and the pale lower part which displays a fibrillar organization. The subplate neurons are more differentiated, polymorphous, variably oriented, with more branched dendrites and axons which usually run toward the CP. Horizontally oriented neurons are most frequent at the interface of the CP and the upper SP (Mrzljak et al. 1988). Between 17 and 25 PCW, the subplate is the most prominent part of the neocortical anlage and appears as a wide homogeneous zone, and different types of subplate neurons appear within it for the first time: fusiform, pyramidal, inverted pyramidal, and polymorphous (Mrzljak et al. 1988, 1990). Around 20 or 21 PCW, another cell type appears – large, multipolar neurons with three to five long dendrites and axons which either ascend or descend or remain horizontally oriented. From 17 PCW onward, the most frequent Golgi-impregnated subplate neurons were inverted pyramidal neurons with axons ascending toward the CP (Mrzljak et al. 1988). Between 26 and 29 PCW, the subplate remains the widest cortical zone with a rich population of various types of neurons, the polymorphous and fusiform being impregnated most frequently at all depths of the subplate, while large multipolar neurons were usually observed in its superficial part. Between 32 and 34 PCW, subplate neurons displayed a further dendritic differentiation, although the subplate zone is already significantly diminished in size. Subplate neurons displayed varicosities and growth-cone-like terminal tips on dendrites and short, newly formed branches arising from the main dendrites, and it was not possible to demonstrate degeneration of subplate neurons that could parallel the reduction in depth of the subplate zone (Mrzljak et al. 1988). In addition, around 36 PCW another interneuron type appeared in the subplate zone – a small type of neuron with strictly local axonal arborization which probably corresponds to the neurogliaform cell of Ramón y Cajal (Mrzljak et al. 1990). Finally, in the newborn child rather numerous subplate neurons are present below the developing layer VI, although the subplate zone is largely dissolved. However, while all types of subplate neurons could be observed within the 1 mm below the layer VI in the crowns of gyri, at the bottom of sulci the fusiform and bipolar forms predominated (Kostovic and Rakic 1980; Mrzljak et al. 1988).

Thus, the intensive differentiation of subplate neurons into five neuronal types (in the human dorsolateral prefrontal cortex) between 17 and 25 PCW coincides with the ingrowth of afferent fibers into the subplate zone. However, the subplate neurons continue with further dendritic growth even after afferent fibers have relocated to the cortical plate and acquire spine-like protrusions on dendrites during the last trimester of fetal life. In fact, their dendrites continue to grow even after birth and at early postnatal age (Mrzljak et al. 1992). In a quantitative Golgi analysis of 157 subplate neurons it was found that their dendrites grow continuously and their dendritic trees increase in size from the earliest stages studied (13.5 PCW) to the second postnatal month (Mrzljak et al. 1992).

Fusiform neurons with very long dendrites were the most frequently impregnated interstitial cell type in the gyral white matter after birth, and a constant increase of spine number was observed in these neurons between 1 and 7 postnatal month (Mrzljak et al. 1990). In addition, slightly modified pyramidal neurons and multipolar nonpyramidal interstitial neurons are present in the postnatal gyral white matter. While most of them were healthy-looking, some neighboring neurons had disrupted dendrites.

So, an important finding of these studies has been the continuation of dendritic growth and differentiation of new neuronal types in the subplate in the preterm, newborn and early infant (Mrzljak et al. 1988, 1990, 1992). A rich morphological diversity of subplate neuronal types has also been documented in the monkey (Kostovic and Rakic 1980, 1990).

7.2.2 Molecular Phenotypes of Subplate and Interstial Neurons

The neurochemical diversity of subplate neurons surpasses the diversity of their morphological types. Just in the human cortex, the following neurotransmitters, neuropeptides, transmitter-related enzymes and other specific molecular markers have thus far been demonstrated in the subplate neurons and their descendants in the adult brain, the interstitial neurons: GABA (Yan et al. 1992; Zecevic and Milosevic 1997), somatostatin (Kostović et al. 1991b), neuropeptide Y (Uylings and Delalle 1997; Delalle et al. 1997; Wai et al. 2004; Bayatti et al. 2008a), acetylcholinesterase (Kostovic and Rakic 1980), NADPH-diaphorase i.e., nitric oxide synthase (Yan et al. 1996; Yan and Ribak 1997; Judaš et al. 1999, 2010b; Downen et al. 1999; DeAzevedo et al. 2002), MAP2 (Sims et al. 1988; Honig et al. 1996; Bayatti et al. 2008a, b), p75 low affinity nerve growth factor (NGF) receptor (Kordower and Mufson 1992), plasma proteins albumin, prealbumin, transferrin and alpha-fetoprotein (Mollgard and Jacobsen 1984; Mollgard et al. 1984, 1988; Dziegielewska et al. 1993a, b; Saunders et al. 1991, 2008; Wang et al. 2010), transcription factor *Tbr1* (Bayatti et al. 2008a, b; Suárez-Solá et al. 2009; Ip et al. 2010), reelin (Suárez-Solá et al. 2009), calbindin (Yan et al. 1997; Suárez-Solá et al. 2009), calretinin (Suárez-Solá et al. 2009), parvalbumin (Honig et al. 1996), GAP-43 (Benowitz et al. 1989; Honig et al. 1996; Bayatti et al. 2008a, b), nicotinic acetylcholine receptors (Schröder et al. 2001), various glutamate receptors (Talos et al. 2006), vesicular GABA transporter vGAT and synaptophysin (Bayatti et al. 2008a, b), a potassium/chloride cotransporter KCC2 (Bayatti et al. 2008a, b; Wang et al. 2010), a marker for nonphosphorylated neurofilament high molecular weight SMI 32 (Ang et al. 1991; Haynes et al. 2005).

GABAergic neurons were also demonstrated in the subplate zone of the monkey (Huntley et al. 1988; Meinecke and Rakic 1992), as well as $GABA_A$ receptors (Meinecke and Rakic 1992; Huntley et al. 1990). The GABA labeling in neurons beneath the cortical plate appears very early – as early as embryonic days E45–E50 in the monkey (Meinecke and Rakic 1992) or the 14th week of gestation in the human (Yan et al. 1992). Finally, choline-acetyltransferase-immunoreactive subplate neurons were observed in fetal monkey cortex (Hendry et al. 1987a), and monkey subplate and interstitial neurons also contain a variety of neuropeptides: neuropeptide Y (Huntley et al. 1988; Hayashi et al. 1989; Kuljis and Rakic 1989), cholecystokinin (Hayashi et al. 1989), somatostatin (Huntley et al. 1988; Yamashita et al. 1989), substance P (Yamashita et al. 1990) and VIP (Benson et al. 1991).

The presence of a significant population of nitrinergic neurons in the fetal white matter (Judaš et al. 1999) and within the adult subcortical white matter has been reported in almost all studies of the mammalian neocortex and their molecular phenotypes have been investigated in a number of co-localization studies (for extensive review, see Judaš et al. 1999, 2010b). In the human cortex, the majority of nitrinergic interstitial neurons co-express somatostatin and neuropeptide Y. About 70% of nitrinergic interstitial neurons in the subcortical white matter of monkey and human neocortex also contain muscarinic m2-receptors, and approximately 90% of these cells were rich in acetylcholinesterase (Smiley et al. 1998). Nitrinergic axons often form perivascular fiber networks and contact blood vessels (DeFelipe 1993). Thus, it has been frequently suggested that nitrinergic subcortical interstitial neurons are involved in local regulation of cortical microvascular circulation (Estrada and DeFelipe 1998; Suárez-Solá et al. 2009).

7.3 The Transformation of the Cortical Plate into Neocortical Layers II – VI

7.3.1 The Maturation of Morphological and Molecular Phenotypes of Neocortical Neurons

The detailed description of development of several hundreds of distinct morphological and molecular phenotypes of cortical neurons would require a book in itself. The reader may wish to consult our detailed descriptions based on the use of Golgi impregnations (Mrzljak et al. 1988, 1990, 1992) and NADPH-diaphorase histochemistry which also provides a Golgi-like staining of nitrinergic cortical neurons (Judaš et al. 1999, 2010b). In this section, I will rather focus on two topics: (a) a life-span development of prefrontal cortical neurons (Petanjek et al. 2008), and (b) those few studies describing development of neuropeptides (Kostović et al. 1991b; Delalle et al. 1997; Uylings and Delalle 1997; Bayatti et al. 2008a, b; Wang et al. 2010) and calcium-binding proteins (Cao et al. 1996; Yan et al. 1997; Letinic and Kostovic 1998) in the human cerebral cortex.

In a recent quantitative study, we analyzed the postnatal development and lifespan alterations in basal dendrites of large layer IIIC and layer V pyramidal neurons in human prefrontal cortex (Petanjek et al. 2008). The major findings of this study can be summarized as follows. First, both classes of neurons displayed a rapid dendritic growth during the first postnatal months. Second, after a more than year-long "dormant" period of only fine dendritic rearrangement, layer IIIC pyramidal neurons displayed a second period of dendritic growth, starting at the end of the second year and continuing in the third year. Thus, layer IIIC pyramidal neurons (which are the major source of long corticocortical associative connections) appear to show a biphasic pattern of postnatal dendritic development. Finally, subtler forms of dendritic organization were noted until late adolescence and adulthood. In other words, both corticocortical layer IIIC neurons and subcortically projecting layer V neurons in the human prefrontal cortex continue their maturation during the rapid cognitive development in preschool children as well as in the period of protracted cognitive maturation during puberty and adolescence (Petanjek et al. 2008).

Neurons expressing the neuropeptide Y (NPY) display very protracted maturation in the human prefrontal cortex (Delalle et al. 1997; Uylings and Delalle 1997). In the fetal cortex, the majority of NPY neurons were found in the subplate zone (where they appeared already at 14 PCW), and during the first postnatal year subcortical interstitial neurons (surviving remnants of the subplate) also represented the majority of cortical NPY neurons (Delalle et al. 1997). The density of NPY neurons transiently increased within the cortex between 4 and 7 years, and the adult pattern of relatively low density of cortical NPY neurons was reached from about 8 years (Delalle et al. 1997). It is interesting to note that, while at 14 PCW NPY neurons appeared predominantly in the deep subplate, at 28 PCW, the upper subplate contained significantly more NPY neurons than the deep subplate (Delalle et al. 1997); this shift may occur even earlier, during midgestation (Bayatti et al. 2008a; Wang et al. 2010). Very few NPY neurons are present in the CP and SVZ at 15 PCW, but their density increased in all fetal zones from 17 PCW onward (Delalle et al. 1997).

The earliest somatostatin-immunoreactive cells of the human fetal frontal cortex appear in the subplate at 22 PCW (Kostović et al. 1991b). Around 32 PCW the number of somatostatin neurons increases at the interface between the subplate and the cortical plate, but the newborn cortex shows a decline in the overall number of deep somatostatin neurons in parallel with the increase of their numbers in superficial cortical layers (Kostović et al. 1991b).

Calcium-binding proteins calbindin and parvalbumin appear in the human visual cortex prenatally, already at midgestation (parvalbumin; Cao et al. 1996) or in the case of calbindin mainly from 26 PCW onward (Yan et al. 1997), and develop in an inside-out fashion. However, while calbindin expression was consistently high in the visual cortex of newborn, the peak of parvalbumin development occurred only after the second postnatal month (Letinic and Kostovic 1998). Moreover, there was a postnatal reorganization in cortical calbindin expression: the neonatal pattern of high calbindin in layers IV-VI was transformed during infancy and childhood into an adult pattern of high calbindin in layer II, but low calbindin in layer IV and infragranular layers (Letinic and Kostovic 1998). Finally, it should be noted that the development of acetylcholinesterase activity in cortical pyramidal neurons continues until young adulthood (Kostović et al. 1988).

7.3.2 The Development of Brodmann's Ontogenetic Six-Layered Grundtypus and Cytoarchitectonic Differentiation of the Cortical Map

Korbinian Brodmann (Brodmann 1906) was first to note that cytoarchitectonic regional and areal differentiation of the human neocortex begins at 6–8 months of intrauterine life (depending on the region) and occurs by various modifications of the initial (tectogenetic) six-layered Grundtypus (Fig. 5). All cortical areas which develop from this initial six-layered basic type belong to the isocortex (that is, neocortex), while the remaining areas which start to develop from different laminar arrangements belong to the allocortex (that is, paleocortex, archicortex, and several transitional – mesocortical – types between them and the isocortex, such as peripaleocortex, periarchicortex, proisocortex). While this concept over the past century has been criticized on various grounds, it still serves as the basis for recognizing six major neocortical layers (with a number of sublayers). However, Brodmann's initial conception of the allocortex has been substantially modified in studies of Maximilian Rose (Rose 1926, 1927) and I.N. Filimonov (Filimonov 1957), and many others.

Substantial differences in tempo and mode of the prenatal cytoarchitectonic differentiation of isocortical vs. allocortical areas were already noted in classical studies on development of the human brain (His 1904; Brodmann 1906; Hochstetter 1919; Hines 1922; Von Economo and Koskinas 1925; Rose 1926,1927; Filimonov 1957; Macchi 1951; Humphrey 1966, 1967; Yakovlev 1968; Kahle 1969).

While regional and areal differentiation of the neocortex is relatively late perinatal and postnatal event (Kostović 1990a, b; Kostović and Judaš 1995, 2009), cytoarchitectonic specialization and area-specific differentiation of the prospective entorhinal cortex appear surprisingly early in the human fetuses (Kostović et al. 1993). Entorhinal area-specific large neurons appear already at 10 PCW, concomitantly with the appearance of a one-cell-thick layer at the interface between the CP and the marginal zone and with multilaminated spread of the deep part of the CP. This is the earliest sign of area-specific cytoarchitectonic differentiation of all pallial regions characterized by the presence of the typical cortical plate (Kostović et al. 1993). The first subareal differentiation within the entorhinal region begins at 13 PCW with uneven development of fiber-rich lamina dissecans and the appearance of characteristic cell islands of the prospective cortical layer II (Kostović et al. 1993). Similar early development of the hippocampal formation was also noted in several recent studies (Kostović et al. 1989a; Arnold and Trojanowski 1996a, b; Hevner and Kinney 1996; Zaidel 1999; Abrahám et al. 2004a, b). However, it should be noted that although hippocampal formation begins to develop very early in comparison to the neocortex, its entire development is nevertheless a protracted process and neuronal connectivity in the human hippocampus reaches an adultlike complexity between 2nd and 8th postnatal years (Seress and Mrzljak 1992; Seress et al. 2001; Abrahám and Meyer 2003; for an excellent review, see Seress and Abrahám 2008).

With respect to neocortex, due to the limits of space we provide only a brief overview, mainly to point out that neocortical maturation lasts at least two decades after birth. The prospective premotor cortical belt begins to differentiate toward the end of the human fetal life, but its areal specification continues well after birth (Kostović et al. 1987). Between 15 and 26 PCW, the entire frontal cortex displays typical fetal lamination pattern, and regional architectonic differences are more related to maturational gradients than to the areal specification itself. Between 26 and 32 PCW, Brodmann's six-layered Grundtypus and the first regional differentiation appear in the lateral frontal cortex (Fig. 5), but perinatal period is characterized by a notable cytoarchitectonic reorganization and areal parcellation is completed only after birth (Kostović et al. 1987; Kostović 1990a, b; Kostović and Judaš 2009). Typical cytoarchitectonic features of the human auditory cortex also develop during the early postnatal period (Krmpotić-Nemanić et al. 1984, 1988). We recently demonstrated that magnopyramidality (as a key cytoarchitectonic feature of Broca's speech region of the left hemisphere) of area 45 develops between 8 and 12 postnatal months in area 45, and between 8 and 14 months in area 44 (Judaš and Cepanec 2007; Cepanec 2009). These findings indicate that significant cytoarchitectonic changes of fronto-opercular cortex occur at the end of the first postnatal year, in parallel with major developmental changes in language processing/comprehension and production, speech, and other aspects of communication (Cepanec 2009).

Regional and areal specification of the cerebral cortex is also closely related to development of cortical gyri and sulci and corticocortical connections (see Sects. 7.4 and 8.3).

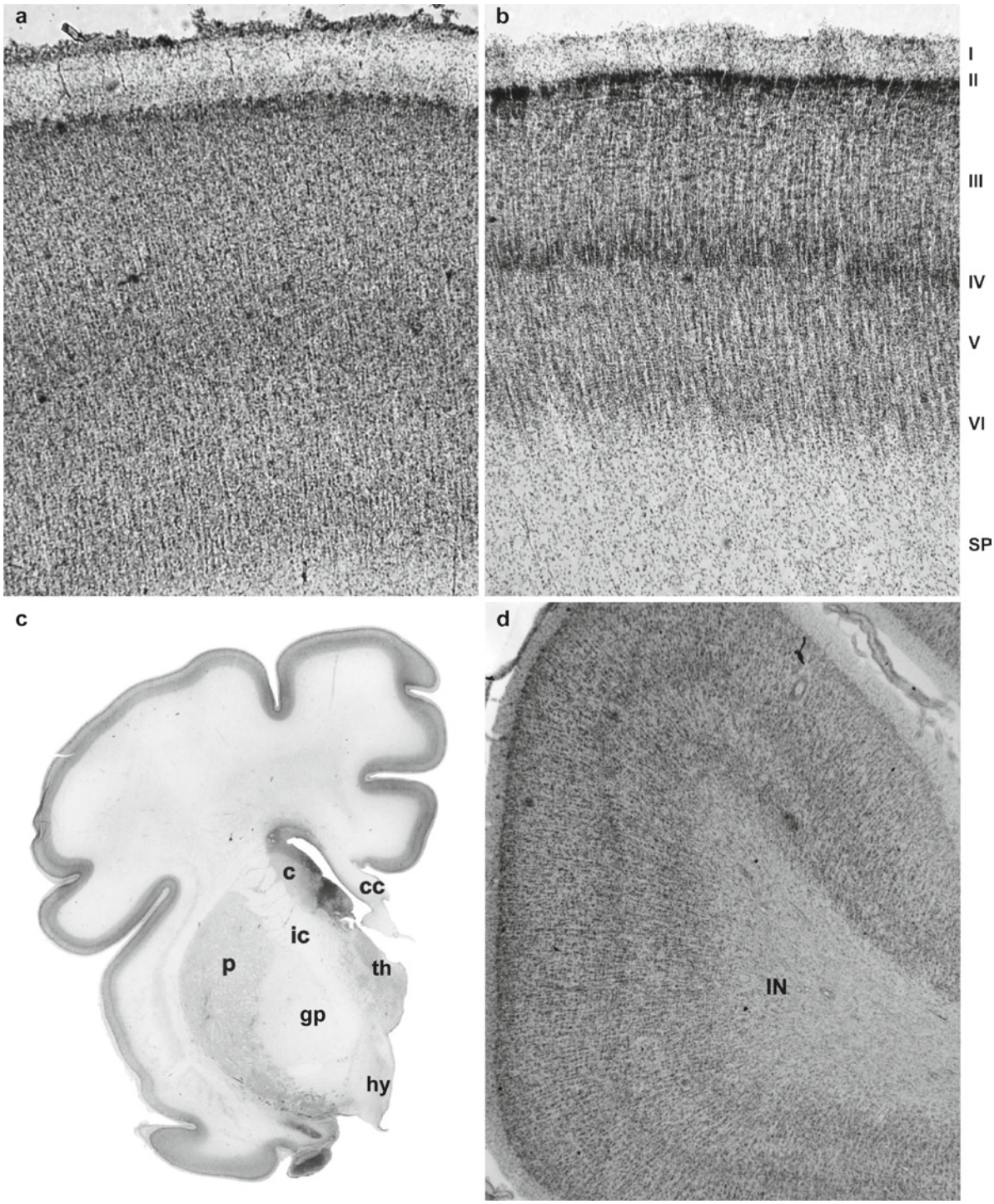


Fig. 5 During the last third of gestation, Brodmann's ontogenetic six-layered Grundtypus gradually develops within the neocortical plate. While at 28 PCW (**a**) its development is just beginning and the lamination is barely recognizable (one can clearly recognize only the uppermost dark band in the CP as the future layer II, a zone of small granular cells in the middle as the future layer IV and the paler band below it as the developing layer V), the Grundtypus is already fully developed at 36 PCW (**b**), after the onset of gyrification (**c** – low power view of Nissl stained section at 36 PCW; note the lamination within the cortical plate). In a 9-month-old infant (**d**) the neocortex is still immature in spite of its adult–like laminar appearance, because dendritic growth of cortical neurons continues during the second and third year after birth (see text) (*I–VI*, developing neocortical layers; *c*, caudate nucleus; *cc*, corpus callosum; *gp*, globus pallidus; *Hy*, hypothalamus; *ic*, internal capsule; *p*, putamen; *Th*, thalamus). IN (in **d**) denotes numerous interstitial neurons in the subcortical white matter, especially within the gyral crowns

7.3.3 The Development of the Cortical Map as Revealed by Recent Molecular and Genetic Studies

Regional and areal differentiation of the cerebral cortex can be revealed even before the appearance of Brodmann's Grundtypus, indicating that it does not depend exclusively on extrinsic afferent input but is largely determined in the cortical protomap (Rakic 1988, 1995; Smart et al. 2002; Lukasziewicz et al. 2005; Dehay and Kennedy 2007; Rakic et al. 2009). Differences between primary and associative visual cortical areas in the human and monkey fetuses can be revealed even by AChE-histochemistry (Kostovic and Rakic 1984, 1990). The development of correct topological connections in early enucleated monkeys indicates that basic connections and chemoarchitectonic characteristics can form in the absence of afferent input (Rakic 1988; Rakic et al. 1991; Dehay et al. 1991, 1993; Kennedy and Dehay 1993; Dehay and Kennedy 2007).

Previous work in rodents has identified a number of transcription factors expressed in gradients across the neocortex that appear to control cortical parcellation (Grove and Tole 1999; Bishop et al. 2000; Monuki and Walsh 2001; Ragsdale and Grove 2001; Fukuchi-Shimogori and Grove 2001; Muzio et al. 2002; O'Leary and Nakagawa 2002; Hamasaki et al. 2004; Molnár et al. 2006; O'Leary et al. 2007; Kim et al. 2007; Kudo et al. 2007). Changes in expression of morphoregulatory molecules can even shift anterior/posterior areal boundaries in the developing rodent neocortex (Fukuchi-Shimogori and Grove 2001).

However, there are few such studies in primates or humans. In fetal rhesus monkey, the gradients or region-specific distribution of various morphoregulatory molecules in the embryonic cerebral wall also contribute to the formation of specified axonal pathways and parcellation of cortical areas (Donoghue and Rakic 1999; Sestan et al. 2001; Watakabe et al. 2007). Several recent studies performed on embryonic and fetal human material have indicated that even with respect to gradients of gene expression there are significant differences between rodents and humans (Lako et al. 1998; Abu-Khalil et al. 2004; Lindsay and Copp 2005; Lindsay et al. 2005; Sarma et al. 2005; Bayatti et al. 2008a, b; for review see Kerwin et al. 2010; Ip et al. 2010; Wang et al. 2010). Especially interesting are findings from recent studies on the role of *WNT* and *BMP* genes in the establishment of dorso–ventral (Lako et al. 1998; Patapoutian and Reichardt 2000; Abu-Khalil et al. 2004) and left-right polarity axis (Gebbia et al. 1997; Geschwind and Miller 2001; Yost 2001) in human embryos because the functional specialization of the human cerebral cortex for language depends on the asymmetric development of cerebral hemispheres.

7.4 The Development of the Human Cortical Gyrification

According to the radial unit hypothesis (Rakic 1988, 1995), the surface area of the cortex is determined by the number of radial units in the protomap formed during the phase of symmetrical divisions, while the cortical thickness is determined by number of asymmetrical divisions within radial units. Greater surface area equates to a larger amount of cortical gray matter and thus greater computational power (White and Hilgetag 2008), and the phylogenetic increase in the surface area of the human brain has far exceeded growth in the cortical thickness (Welker 1990). For example, in comparison to macaque monkeys, the surface area of the human brain is approximately ten times greater (see Fig. 1), whereas the human cortex is only twice as thick (Rakic 1995). The convoluted human cortex is about three times as large as the inner surface of the skull (Welker 1990; Van Essen 1997; Hilgetag and Barbas 2005, 2006; Toro and Burnod 2005). It also appears that gyrification is strongly related to absolute increases in brain size, because prosimian and primate brains of up to 10 cm^3 volume are generally lissencephalic, while for larger volumes there is a close correlation between the degree of gyrification and absolute brain size (Zilles et al. 1989; White and Hilgetag 2008).

The development of gyri and sulci is also closely related to the ingrowth of thalamocortical afferents (White et al. 2002) and especially to the amount and diversity of long and short commissural and ipsilateral corticocortical fibers (Kostovic and Rakic 1990; Price et al. 2006). This notion is also supported by experimental findings in rhesus monkeys, in which local and remote changes of gyrification have been observed after experimental white matter lesions in the developing animal (Goldman-Rakic 1980; Goldman-Rakic and Rakic 1984).

While most visible changes in brain morphology occur primarily during the third trimester (between 24 and 38 PCW, see Fig. 1) and continue during the first few years after birth (Retzius 1896; Chi et al. 1977; Sidman and Rakic 1982; Feess-Higgins and Larroche 1987; Kostović 1990b; Leuba and Kraftsik 1994; Naidich et al. 1994; Armstrong et al. 1995; Bayer and Altman 2004; Dubois et al. 2008a, b), more subtle brain changes (e.g., density changes of cells within the neuropil, dendritic and synaptic alterations, an increase in myelination) can be seen throughout childhood and adolescence, even into early to middle adulthood (White and Hilgetag 2008). For example, there are life-span changes of dendrites and dendritic spines (Jacobs et al. 1997). The so-called gyrification index (Zilles et al. 1988, 1989) increases dramatically during the third trimester of fetal life, then remains relatively constant throughout development (Armstrong et al. 1995; but see Magnotta et al. 1999 for different interpretation).

The brain surface morphology continues to change as well during the adolescence and adult life (Jernigan and Tallal 1990; Jernigan et al. 1991a, b; Pfefferbaum et al. 1994; Caviness et al. 1996; Giedd et al. 1996a, b, 1999a; Sowell et al. 1999a, b, 2001a, b, 2002a, b, 2003, 2004a, b; Giedd 2004; Gogtay et al. 2004; Shaw et al. 2006; for review, see Lenroot and Giedd 2006; O'Hare and Sowell 2008). During that period, the gyri become steeper and the sulci develop a broader appearance (White and Hilgetag 2008). Thus, the processes of gyrification lead to systematic morphologic differences in different cortical regions and areas, affecting overall thickness, lamination and cellular morphology (Kostovic and Rakic 1990; Welker 1990; Van Essen 1997; Hilgetag and Barbas 2005, 2006; Toro and Burnod 2005). The potential clinical relevance of these observations lies in the fact that systematic differences have been observed in white matter as well as gyrification between normal subjects and patients with a variety of developmental, neurological or mental disorders (for review, see White and Hilgetag 2008; Rakic 2009).

There is a significant cortical sulcal variability in children (Sowell et al. 2002a, b) and adults (Narr et al. 2001). There is also a sexual dimorphism (Giedd et al. 1997; De Bellis et al. 2001), with the female cerebral cortex more strongly convoluted than the male cortex (Luders et al. 2004). The surface morphology of the human brain displays much greater variability than brain volume or subcortical brain regions (Bartley et al. 1997; White et al. 2002). In monozygotic twins, the deeper and developmentally earlier sulci are more highly correlated than the tertiary sulci (Lohmann et al. 1999). However, it should be noted that in monozygotic twins the majority of the morphologic variance between the brain surface morphology was a result of random environmental effects, while brain size appeared to be strongly determined by genetic factors (Bartley et al. 1997; Thompson et al. 2001; White et al. 2002). In addition, monozygotic twins discordant for handedness exhibited differing degrees of asymmetry of the planum temporale (Steinmetz et al. 1995).

Finally, it should be noted that neurobiological mechanisms underlying the development of cortical gyri and sulci are as yet unknown. Accordingly, there are several concurrent theories, such as the theory that the gyri form as a result of active growth of specific brain regions (Le Gros Clark 1945) or various mechanical theories of gyrification which assume the physical self-organization of the brain (Richman et al. 1975; Van Essen 1997; Hilgetag and Barbas 2005, 2006; Toro and Burnod 2005; for an excellent review, see Welker 1990).

7.5 Other Transient and/or Human-Specific Structures and Populations of Neurons

7.5.1 The Corpus Gangliothalamicum

The corpus gangliothalamicum is a transient structure located beneath the surface of the pulvinar adjacent to the telo-diencephalic sulcus in human fetuses between 15 and 34 PCW (Rakic and Sidman 1969; Letinić and Kostović 1997; Letinic and Rakic 2001). In Nissl-stained sections, the gangliothalamic body is a thin cellular layer situated beneath the thalamic surface near the telo-diencephalic junction, and in Golgi- and MAP2-stained sections it is a stream of mostly bipolar cells extending from the ganglionic eminence to the medial thalamus (Letinić and Kostović 1997). It was subsequently shown that this structure is composed of tangentially migrating GABAergic interneurons from the ganglionic eminence to the pulvinar and lateral posterior nucleus of the thalamus, because these migrating neurons are GAD- and Dlx-positive and guided by

homotypic-neurophilic cues (Letinic and Rakic 2001). The corpus gangliothalamicum and its migrating cells could not be identified in any nonhuman species so far examined including rodents, carnivores and even nonhuman primates (Clowry et al. 2010).

7.5.2 The Perireticular Nucleus

The internal capsule of the human fetus contains a large number of distinct interstitial neurons which express MAP2, somatostatin, calbindin-D28k, AChE, and p75 low-affinity NGF receptor (Letinić and Kostović 1996a). This cell population corresponds to the perireticular nucleus (Mitrofanis and Guillery 1993; Earle and Mitrofanis 1996) previously described in the rat (Mitrofanis and Baker 1993; Adams and Baker 1995), cat, and ferret (Clemence and Mitrofanis 1992; Mitrofanis 1994). The number of neurons in the human perireticular nucleus gradually increased up to 32 PCW (Tulay et al. 2004), but subsequently the nucleus rapidly decreases in size during early infancy (Tulay et al. 2004; Letinić and Kostović 1996a) and few cells are apparent in the 1-year-old infant (Letinić and Kostović 1996a).

7.5.3 Intracallosal and Subcallosal Neurons

Transient cells are also present in the human fetal subcallosal zone, which occupies a paramedian territory situated between the developing corpus callosum dorsally and bundles of the fornix ventrally (Kostović et al. 2002b). The midline portion of this subcallosal region is the part of the septohippocampal continuum and corresponds to the nucleus septohippocampalis, while the left and right paramedian portions contain radial glial cells and continue directly into the SVZ of the dorsal neocortical telencephalic wall. In other words, paramedian subcallosal zones represent a dorsal allocortical counterpart of the SVZ (Kostović et al. 2002b). Transient fetal presence of neurons and glial cells in the subcallosal zone suggests that they may be involved in the guidance of callosal axons, while the cells of the septohippocampal continuum may have a pivotal role in the bidirectional growth of fornix system fibers (Kostović et al. 2002b; Jovanov-Milošević et al. 2009). Furthermore, we recently described a separate population of fetal intracallosal neurons, which remain to be present even in the postnatal human corpus callosum as a special subset of interstitial neurons (Jovanov-Milošević et al. 2010).

7.5.4 Transient Patterns in the Human Fetal Striatum and Amygdala

Transient patterns of organization are also notable in the human fetal striatum, as revealed by calbindin-D28k expression (Letinić and Kostović 1996b) or by compartmentalization of NADPH-diaphorase staining (Sajin et al. 1992) and AChE-staining and Nissl staining (Vukšić et al. 2008). In the human fetus, the developing lateral amygdaloid nucleus (which is the largest and most differentiated of all nuclei in the amygdaloid complex of man) displays a transient presence of discrete cytoarchitectonic units which are especially prominent between 12.5 and 16 PCW (Nikolić and Kostović 1986).

7.5.5 Nucleus Subputaminalis (Ayala)

Giuseppe Ayala was first to describe the nucleus subputaminalis, that is, a small magnocellular group of neurons located within the rostrolateral extension of the basal forebrain in the human and chimpanzee brain (Ayala 1915, 1924). We recently demonstrated that the nucleus subputaminalis is a special subgroup of cholinergic magnocellular neurons (Šimić et al. 1999). On the basis of their location and projection trajectory, these cholinergic neurons are probably connected with the frontal cortical speech area and may be human specific since they were not described in nonhuman primates (Šimić et al. 1999).

8 The Development of Cortical Synapses, Input–Output Connectivity and Intracortical Neuronal Circuitry

The synaptogenesis, morphological and chemical maturation of cortical neurons, and the development of cortical circuitry are all tightly related to ingrowth of cortical afferents and outgrowth of cortical efferent projections (Mrzljak et al. 1988, 1990, 1992; Kostović 1990a, b; Kostović and Judaš 2002a, 2006, 2007, 2010; Kostović and Jovanov-Milošević 2006). While all of

these processes begin prenatally, most of them continue and even intensify during the first two postnatal years, and some of them (for example, synaptogenesis, fine reorganization of dendritic spines, and terminal dendritic and axonal arborizations) in fact continue throughout the life-span, reaching the adult steady-state dynamical equilibrium during the third decade (for review, see Petanjek et al. 2008; Kostović et al. 2008; Kostović and Judaš 2009; Rakic et al. 2009).

8.1 *Synaptogenesis Begins during the Initial Formation of the Cortical Plate, Intensifies during the Third Trimester and Even More after Birth, Reaches its Peak in Early Childhood, and Then Slowly Diminishes until the Third Decade of Life*

8.1.1 Initial Synaptogenesis (8–20 PCW) is Bilaminar and Occurs outside the Cortical Plate, within the Marginal and the Subplate Zone

The study of synaptogenesis was instrumental in the initial discovery of the human subplate zone (Kostović and Molliver 1974; for review, see Judaš et al. 2010a). The first synapses appear in the neocortical anlage very early – in the marginal zone at 7 PCW, that is, in a 20 mm CRL human embryo (Larroche 1981; Larroche and Houcine 1982), or at 8 PCW, concurrently with the formation of the cortical plate (Molliver et al. 1973; Zecevic 1998). It is important to note that the initial distribution of early synapses is bilaminar – they are situated above and below the cortical plate but not within it (Molliver et al. 1973). This early bilaminar synaptogenesis in the neocortex has been confirmed in subsequent studies of 10 PCW-old human fetuses (Povlishock 1976; Larroche et al. 1981). In fact, in the human dorsolateral (motor-sensory) pallium, between 8.5 and 18 PCW synapses are present above and below the cortical plate, but never within it (Molliver et al. 1973). At 15 PCW, the E.M. of the subplate revealed a band of swollen processes and an increased extracellular space; all the synapses were presumably axo-dendritic and asymmetric (Molliver et al. 1973). From its initial formation (between 10 and 15 PCW) until 23/24 PCW, the SP represents the major site of neocortical synaptogenesis. The synaptogenesis also starts in the human cingulate subplate as early as 11 PCW (Kostović and Krmpotić 1976). Early bilaminar synaptogenesis was also demonstrated above and below the hippocampal cortical plate in 15 and 16.5 PCW human fetuses (Kostović et al. 1989a). However, in contrast to the neocortex (where the majority of early synapses were present in the subplate zone), the hippocampal archicortex displayed the prevalence of early synaptogenesis in the superficial marginal zone (Kostović et al. 1989a).

8.1.2 The Synaptogenesis within the Cortical Plate (Ca. 23 PCW Onward) Begins with Relocation of Waiting Afferents from the Subplate into the Cortical Plate

The earliest synapses found within the cortical plate were at 23 PCW – but the onset of synapse formation within the CP cannot be precisely dated because no fetuses from 19 to 22 PCW were analyzed (Molliver et al. 1973). The synaptogenesis within the CP occurs progressively in a deep-to-superficial fashion from 23/24 PCW onward, when thalamocortical and other afferent axons start to relocate from the "waiting" compartment of the subplate into the cortical plate (Kostović and Judaš 2002a, 2010). Thus, intense synaptogenesis within the cortical plate occurs in parallel to the ingrowth of cortical afferents as well as an intense dendritic differentiation of CP neurons; both processes intensify during the last trimester (Mrzljak et al. 1988, 1990, 1992; Kostović and Judaš 2002a, 2010). However, it is important to note that both synaptogenesis and neuronal differentiation are predominantly postnatal processes, which start during the last trimester but continue for several years after birth. Similarly, the myelination begins during the last trimester, but reaches its peak during the first and second postnatal year and continues until adulthood (see Sect. 8.6).

8.1.3 The Postnatal Continuation of Synaptogenesis: Rapid Initial Overproduction and Protracted Elimination of Supernumerary Synapses

Cortical synaptogenesis in primates, and particularly in the human, is a prolonged postnatal process that involves overproduction of axons, synapses and dendritic spines and their later elimination in response to

environmental influences (Rakic et al. 1994; Bourgeois et al. 2000; Rakic et al. 2009; Kostovic and Judas 2009, 2010). In the macaque monkey, the synaptogenesis peaks after birth and lasts at least 3–4 years (Bourgeois et al. 2000), and in the human it lasts at least 15–19 years (Huttenlocher 1979; Huttenlocher et al. 1982; Huttenlocher and Dabholkar 1997; Rakic et al. 2009) and probably extends into the third decade (Petanjek et al. 2008; Kostović et al. 2008; Kostović and Judaš 2009, 2010). In the rhesus monkey, during the first 2–3 postnatal months, synaptic density increases rapidly and reaches a peak that is about two times higher than in the adult and remains well above the adult level throughout infancy and adolescence (for review, see Rakic et al. 1994; Bourgeois et al. 2000). Pasko Rakic and collaborators calculated that in the visual cortex (single hemisphere) of the rhesus monkey during puberty about 1.8×10^{11} synapses are lost – meaning that during this period about 2,500 synapses were lost each second (Bouergeois et al. 2000; Rakic et al. 2009). Nevertheless, because of concurrent overproduction of synapses, the net number still remains above the adult value. The density of major neurotransmitter receptors in the monkey cortex also reaches its peak between 2 and 4 months of age and then declines to the adult level during the period of sexual maturation (Lidow et al. 1991).

Postnatal synaptogenesis is not restricted to neocortical layers I–VI, but also continues on interstitial white matter neurons (Kostovic and Rakic 1980, 1990) which are surviving subplate neurons (for review, see Judaš et al. 2010a, b). Synaptic junctions are observed on both the perikarya and dendrites of interstitial neurons, but the number of synapses on the perikaryon is relatively low (Kostovic and Rakic 1980). The number of axosomatic synapses decreases with age in parallel with an increase in the number of synapses on the dendrites (Kostovic and Rakic 1980). Axosomatic synapses were both symmetrical and asymmetrical, and both types lack dense core vesicles but contain round and clear vesicles. Axodendritic synapses were asymmetrical, with clear round vesicles and their number increased during postnatal maturation (Kostovic and Rakic 1980). Therefore, Kostovic and Rakic (1980) proposed that axons forming asymmetrical synapses may originate from thalamus or other cortical areas (or even from monoaminergic brain stem neurons), while axons forming symmetrical synapses may arise from nearby interstitial cells, that is, from local circuit neurons. The polymorphic interstitial neurons situated immediately subjacent to the cortex might also receive a local circuit input from overlying cortical cells.

8.2 Cortical Afferents Initially Navigate through the Intermediate Zone, Then Establish Temporary Synapses in the Waiting Compartment of the Subplate Zone, and Finally Relocate into the Cortical Plate

Before cortical afferent axons can reach the appropriate target cells within the cortical plate, they first have to navigate through the intermediate zone and then wait (that is, establish temporary synapses) in the subplate zone. All that occurs while neurons of the cortical plate are still being generated in VZ/SVZ and migrate through the intermediate and subplate zone. Thus, one can expect that the subplate zone is not only the waiting compartment for ingrowing afferents but also enables important signaling interactions between these afferents and migrating cortical neurons before they reach the cortical plate. The midgestation represents a crucial period for these interactions, because cortical afferents accumulate and wait in the subplate between 15 and 23 PCW, and relocate to the cortical plate approximately between 24 and 28 PCW – to be precise, that occurs at least with thalamocortical and cholinergic afferents, while corticocortical connectivity displays much more protracted development (see below).

As already stated, the fetal white matter occupies the inner (periventricular) half of the telencephalic wall, and consists predominantly of the intermediate zone (Fig. 6). However, it should be noted that in the human fetal brain a significant contingent of input and/or output connections also grows through the SVZ (Kostovic et al. 2002a; Smart et al. 2002; Judaš et al. 2005; Rakic 2009). The fetal white matter is composed of a number of different contingents of growing axons: (1) noradrenergic, dopaminergic, and serotoninergic afferents from the brain stem; (2) histaminergic afferents from the hypothalamus; (3) cholinergic afferents from the basal forebrain; (4) thalamocortical afferents; (5) afferents from amygdala and claustrum; (6) corticofugal efferent projections to thalamus, striatum, claustrum, amygdala, and various brain stem and

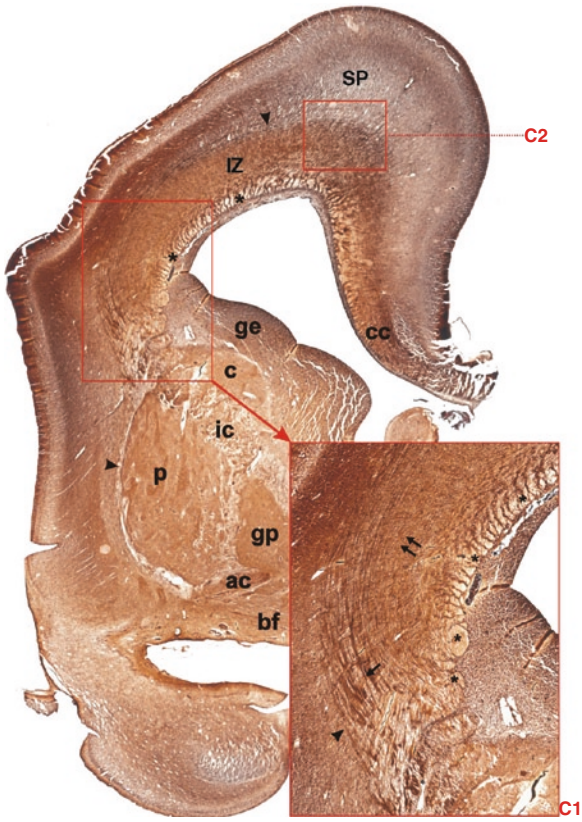


Fig. 6 The coronal section through the telencephalon at 18 PCW, Gallyas silver impregnation by means of physical development. Note that fiber bundles and their crossings are located in the fetal white matter, that is, in the periventricular region (C1, C2, and *asterisks*), and the intermediate zone (IZ), whereas the subplate zone (SP) is characterized by a loose ("isotropic") argirophylic network of fibers. The fetal white matter consists of tangentially stratified fiber bundles such as external capsule (*arrowheads*), corpus callosum radiation (cc), thalamocortical projection fibers (*arrow*), and the deep system (*double arrows*, see insert C1). In addition, a prominent periventricular system of unstained and transversely or obliquely cut fiber bundles (*row of asterisks*) is situated in the subventricular zone (*a*, amygdala; *ac*, anterior commissure; *bf*, basal forebrain; *c*, caudate nucleus; *C1*, *C2*, crossroad areas; *cc*, corpus callosum; *ge*, ganglionic eminence; *gp*, globus pallidus; *ic*, internal capsule; *iz*, intermediate zone; *p*, putamen; *sp*, subplate zone; *th*, thalamus) (From Judaš et al. (2005). With permission)

spinal cord targets; and (7) last, but not least, the huge amount of corticocortical (ipsilateral and commissural/callosal) fibers. At the same time, the fetal white matter contains radially and tangentially migrating neurons, oligodendrocyte precursors and developing astrocytes.

While some of those axonal systems are relatively well studied in both human and monkey fetuses (e.g., thalamocortical, monoaminergic, cholinergic, corticospinal, commissural and some long ipsilateral corticocortical projections), very few data are available on development of corticostriatal, corticothalamic, and short corticocortical projections, while there are simply no available data on development of potentially important bidirectional connections between cortex and amygdala or claustrum, as well as histaminergic hypothalamic projections.

These growing axons in the human fetal white matter can be visualized by a variety of classical and modern approaches: any modification of classical Weigert method (Yakovlev and Lecourse 1967), Bielschowsky's silver impregnation to identify the intensely argyrophilic neurofilaments (Haynes et al. 2005), Gallyas silver impregnation by means of physical development (Judaš et al. 2005), histochemical staining with Luxol-fast-blue for myelin (Brody et al. 1987; Kinney et al. 1988, 1994), acetylcholinesterase (AChE) histochemistry (Kostovic and Goldman-Rakic 1983; Kostovic and Rakic 1984, 1990; Kostovic 1986), or immunocytochemical visualization of growth associated protein GAP-43 which is a marker of axonal growth and elongation (Milosevic et al. 1995; Kanazir et al. 1996; Honig et al. 1996; Haynes et al. 2005), anti-SMI 312, a pan-marker of neurofilaments (Sasaki et al. 1988; Haynes et al. 2005), anti-SMI 32, a marker for nonphosphorylated neurofilament high molecular weight – NFH (Ang et al. 1991; Haynes et al. 2005), anti-SMI 31 which stains phosphorylated NFH and is used as a marker of axonal maturity (Verney and Derer 1995; Zecevic et al. 1999; Haynes et al. 2005), myelin basic protein (MBP) immunocytochemistry (Back et al. 2001, 2002; Jakovcevski and Zecevic 2005a; Haynes et al. 2005), synaptophysin or SNAP25 (Judaš et al. 2005; Vasung et al. 2010a, b) or even DiI tracing method on postmortem material (Burkhalter 1993; Burkhalter et al. 1993; DeAzevedo et al. 1997; Hevner 2005).

Most of these methods are useful for a general analysis of axonal growth, but only few of them enable visualization of specific projection system; for example, AChE-histochemistry for thalamocortical afferents (Kostovic and Rakic 1984, 1990) or cholinergic basal forebrain afferents (Kostović 1986), and immunocytochemical visualization of catecholaminergic (Verney 1999) or serotoninergic afferents (Verney et al. 2002). For example, GAP-43 fibers (which probably corresponded to monoaminergic afferents) were

observed in human embryos as early as 4 PCW (Milosevic et al. 1995). Honig et al. (1996) demonstrated that between 14 and 22 PCW the GAP-43 immunoreactivity was prominent in the subplate and marginal zone neuropil and in the fibers running near the VZ, while GAP-43 fibers appeared in the cortical plate from 22 PCW onward. Similarly, Haynes et al. (2005) noted the highest level of GAP-43 expression from 21 to 64 PCW. On the other hand, anti-SMI 312 stained axons as early as 23 PCW, anti-SMI 31 showed relatively low levels of staining from 24 to 34 PCW, and anti-SMI 32 primarily stained neuronal cell bodies (Haynes et al. 2005).

8.2.1 MRI Tractography Enables the in Vivo Analysis of Growing Cortical Pathways

Over the past decade the development of MRI tractography, such as diffusion tensor imaging (Hüppi et al. 1998, 2001; Prayer et al. 2001; Prayer and Prayer 2003; Hüppi and Dubois 2006; Chung et al. 2009; Ment et al. 2009; Lodygensky et al. 2010) has increasingly enabled the visualization and analysis of growing axonal pathways in the human fetal brain (Berman et al. 2005; Bui et al. 2006; Huang et al. 2006, 2009; Counsell et al. 2007; Dubois et al. 2008c; Kasprian et al. 2008; Kim et al. 2008; Aeby et al. 2009). In an initial MRI-histological correlation study of 15 to 36 PCW human fetuses, we demonstrated the presence of periventricular fiber crossroads rich in extracellular matrix and axonal guidance molecules (Judaš et al. 2005). These periventricular crossroads of growing cortical pathways (Figs. 6 and 8) represent a hitherto unrecognized and vulnerable cellular and topographic target in which combined damage of association-commissural and projection fibers may explain the complexity of cognitive, sensory, and motor deficit in survivors of periventricular white matter lesions (Judaš et al. 2005). We recently succeeded in combining histological approaches with diffusion tensor imaging to investigate prenatal development of human fronto-limbic pathways (Vasung et al. 2010a) and to demonstrate the existence of early, prominent and hitherto undescribed periventricular fiber system which is related to ganglionic eminence and striatum and contains forerunners of adult associative and projection cortical pathways (Vasung et al. 2010b). This periventricular system of growing pathways appears in the early fetal period (10–13 PCW), and in the midfetal period (15–18 PCW) already consists of four major components: the corpus callosum, the fronto-occipital fascicle, the fronto-pontine pathway, and the subcallosal fascicle of Muratoff (Vasung et al. 2010b).

8.2.2 The Development of Catecholaminergic and Serotoninergic Cortical Afferents

The presence of monoaminergic cell bodies at 7 PCW (Olson et al. 1973) and early ingrowth of monoaminergic afferents to the human telencephalic wall at 12 PCW were demonstrated already in classical histochemical studies (Nobin and Björklund 1973; Olson et al. 1973). Later immunocytochemical studies have confirmed and expanded these findings. The tyrosin hydroxylase (TH) immunoreactive catecholaminergic groups of neurons are present in human embryos at 4.5–6 PCW (Puelles and Verney 1998; Freeman et al. 1991; Verney et al. 1991; Zecevic and Verney 1995; Ugrumov et al. 1996; Almqvist et al. 1996). At the end of the embryonic period, TH-positive (dopaminergic) axons run through the central tegmental tract from the medulla oblongata to the mesencephalon, and together with those from locus coeruleus and dopaminergic axons from substantia nigra and ventral tegmental area form the medial forebrain bundle (Zecevic and Verney 1995; Puelles and Verney 1998). No TH-positive fibers penetrate the primordial plexiform layer at 6 PCW, but when the cortical plate starts to form at 7/8 PCW, the first TH positive fibers penetrate the lateral frontal cortex (Verney 1999). These fibers run in the intermediate zone, below the cortical plate, and few fibers are also present in the marginal zone. Thus, the arrival of catecholaminergic axons coincides with the formation of the cortical plate (Zecevic and Verney 1995; Verney 1999). Noradrenergic (dopamine-beta-hydroxylase-immunoreactive, DBH-ir) axons penetrate the telencephalic wall in a pattern similar to dopaminergic axons and at the same time (Zecevic and Verney 1995; Verney 1999). The dopaminergic and noradrenergic axons penetrate the subplate before other afferents and their waiting period (before the penetration into the cortical plate) in the subplate lasts for about one month (Verney 1999). Therefore, it is also probable that the first synapses observed above and below the cortical plate at 7 or 8 PCW (Molliver et al. 1973; Larroche and Houcine 1982) in fact belong to catecholaminergic

axons. There is also a rostrocaudal gradient of penetration of catecholaminergic axons, so that at 13 PCW they invade occipital subplate while at the same time they already penetrate the cortical plate in the frontal region, mostly ascending from fibers in the subplate and only rarely descending from the marginal zone (Zecevic and Verney 1995; Verney 1999).

At 20–24 PCW, there is a widespread dopaminergic and noradrenergic innervation of the frontal cortex (Verney et al. 1993), with the densest dopaminergic innervation in the anlage of the motor and cingulate and insular cortices. Noradrenergic afferents are less numerous than dopaminergic in all cortical areas studied (Verney et al. 1993; Verney 1999). In all areas, the upper subplate and the deep cortical plate are densely innervated by catecholaminergic axons, whereas fewer axons are present in the molecular zone and intermediate zone (Verney 1999). However, the development of dopaminergic innervation continues in the cortex long after birth. For example, in rhesus monkeys prefrontal cortex a transient sprouting of dopaminergic fibers was observed during postnatal development with a peak at adolescence and a decrease in adulthood (Rosenberg and Lewis 1995).

The development of cortical serotoninergic innervation was studied in human embryos and fetuses by immunocytochemistry of the vesicular monoamine transporter (VMAT2 – a general monoaminergic marker) and the high-affinity serotonin transporter (SERT) which is a marker of the serotoninergic axons (Verney et al. 2002). The serotonergic fibers from brainstem raphe nuclei appeared as thick varicose fibers in the medial forebrain bundle, where they were less numerous than the VMAT2-immunoreactive axons (Verney et al. 2002). However, they displayed a similar developmental sequence as dopaminergic and noradrenergic fibers: they reached the cortical anlage at 8 PCW, reached the subplate at 10 PCW, and started to penetrate the cortical plate at 13 PCW (Verney et al. 2002). However, it should be noted that at 12–14 PCW, SERT-immunolabeled fibers were observed in the rostral and caudal limbs of the internal capsule that do not correspond to serotoninergic fibers, but do coincide with the calbindin D28k-labeled thalamocortical fiber tracts (Verney et al. 2002).

The early embryonic appearance of serotoninergic axons has also been reported in the entorhinal cortex of the rhesus monkey (Berger et al. 1993), and in monkey the serotonin terminal network matures very rapidly during early postnatal life, contrary to the protracted development of the dopaminergic innervation (Lambe et al. 2000).

8.2.3 The Development of Cholinergic Cortical Afferents

In the human fetus, the first sign of histochemical differentiation of the basal telencephalon is the appearance of a dark AChE-reactive spot situated between the developing striatum and basal telencephalic surface as early as 9 PCW (Kostović 1986). At 10.5 PCW, the nucleus basalis complex significantly increases, and strongly AChE-reactive neuropil occupies the sublenticular, diagonal and septal areas, while one well developed AChE-reactive fiber bundle extends through the external capsule toward the neocortical anlage (but does not reach it yet) and another fiber bundle runs through the precommissural septum toward the medial limbic cortex. At 15 PCW, the first AChE-reactive cells appear in the nucleus basalis complex, while its cholinergic fibers via the external capsule penetrate into the intermediate zone of frontal, temporal, parietal and occipital lobes (Kostović 1986). Between 15 and 18 PCW, cholinergic afferents spread through the IZ, and between 18 and 22 PCW they accumulate in the subplate. Between 22 and 30 PCW, cholinergic fibers gradually penetrate into the cortical plate and strong AChE-reactivity can be observed in the deep cortical plate and the marginal zone (Fig. 7).

8.2.4 The Development of Thalamocortical System

The subplate zone represents a waiting compartment for thalamocortical afferents in rhesus monkey visual cortex (Rakic 1977), human and monkey visual cortex (Kostovic and Rakic 1984), human and monkey prefrontal cortex (Kostović and Goldman-Rakic 1983), human and monkey somatosensory cortex (Kostović and Rakic 1990), and human auditory cortex (Krmpotić-Nemanić et al. 1983). The projection from pulvinar to the associative visual cortex enters the subplate at 17–20 PCW in humans (E60–E79 in rhesus monkeys), waits in the subplate at 21–25 PCW (E80–E99 in rhesus monkeys) and begins to penetrate the CP towards the end of this period (23/24 PCW), and finally relocates into the CP at 26–34 PCW (E100–E124 in rhesus

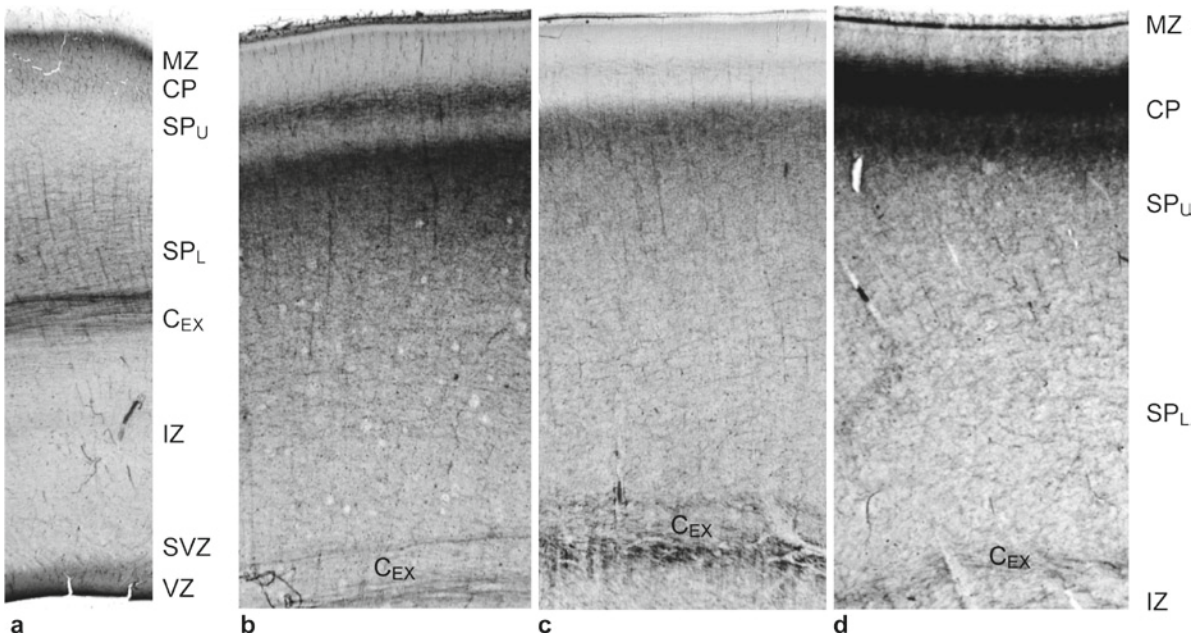


Fig. 7 Development of thalamocortical (thalamic MD nucleus to prefrontal cortex) projection between 19 and 28 PCW. At 19 PCW (**a**), thalamocortical afferents "wait" in the lower part of the subplate zone (SP_L). At 23 PCW (**b**), afferents relocated to the upper subplate (SP_U) and started to penetrate the deep part of the cortical plate (CP). At 26 PCW (**c**), the majority of afferents already relocated to the CP, and at 28 PCW (**d**) they are all within the CP. Cex – the external capsule, which demarcates the border between the subplate and the intermediate zone (IZ). For details, see text

monkeys) (Kostovic and Rakic 1984). The projection from the mediodorsal nucleus to the frontal cortex (Kostovic and Goldman-Rakic 1983) accumulates in the subplate between 16 and 18 PCW, shifts to the superficial part of the subplate at 19 PCW, and by 23–24 PCW enters the cortical plate (Fig. 7); from 28 PCW onward the AChE staining within the cortical plate spreads and exhibits a laminar pattern in which two intense bands of activity in prospective layers III and V are separated by a pale, thin band corresponding to future layer IV (Kostovic and Goldman-Rakic 1983; see also Fig. 7).

8.3 The Development of Commissural and Ipsilateral Corticocortical Connectivity

The ipsilateral and contralateral corticocortical connections arrive last and remain the longest in the subplate zone; they also represent the largest proportion of axons in the subplate in both monkeys and humans (Kostovic and Rakic 1990).

8.3.1 The Development of Forebrain Commissures

The forebrain commissures of primates consist of the corpus callosum, anterior commissure, hippocampal commissure, and the basal telencephalic commissure (LaMantia and Rakic 1990a). Unlike in most eutherian mammals (in which the anterior commissure is primarily an interhemispheric pathway for the olfactory system), in monkeys the few olfactory fibers are concentrated in the basal telencephalic commissure (LaMantia and Rakic 1990a). Again, unlike in most mammals, the dorsal hippocampal commissure has very limited connections to Ammon's horn, and instead includes substantial connections from entorhinal cortex, presubiculum, and parahippocampal gyrus (Amaral et al. 1984; Demeter et al. 1985, 1990). In the adult rhesus monkey, the anterior commissure has 3.15 million fibers, while the corpus callosum has 56 million fibers (LaMantia and Rakic 1990a, 1994). In the adult human, the anterior commissure has 2.4–4.16 million of fibers, of which about 66% are myelinated (Tomasch 1957). The number of fibers in the adult human corpus callosum varies from 200 to 350 million

with a mean value of about 250 million (Blinkov and Chernyshev 1936).

The forebrain commissures are unmyelinated at birth, progress gradually with myelination during childhood and adolescence, but still leave a substantial proportion of interhemispheric fibers unmyelinated in adults (Yakovlev and Lecourse 1967; Aboitiz et al. 1996; Doty 2007). For example, 70–94% of callosal axons (depending on region) are myelinated in rhesus monkeys (LaMantia and Rakic 1990a), while in humans 84% are myelinated in the genu and 95% elsewhere in the corpus callosum (Aboitiz et al. 1992). The protracted course of myelination and growth of the human corpus callosum until at least 20 years of age has been confirmed in recent MRI studies (Pujol et al. 1993; Rauch and Jenkins 1994; Giedd et al. 1996c, 1999b; Keshavan et al. 2002).

Another important feature of the primate cortex is the existence of acallosal areas. The primary visual cortex lacks interhemispheric connections in rhesus monkeys (Dehay et al. 1988; Chalupa et al. 1989), chimpanzees (Bailey et al. 1941) and humans (Clarke and Miklossy 1990). Similar acallosal regions are present in monkey motor and somatosensory cortical areas representing the hand and foot (Killackey et al. 1983; Killackey and Chalupa 1986; Rouiller et al. 1994). In addition, the density of callosal cells and terminals varies widely across the cortex, to give a patchy appearance in most mammals (Doty 2007), including humans (Clarke and Miklossy 1990).

In the human brain, the anterior commissure is crossing the midline already at 9 PCW (Bayer and Altman 2006). The corpus callosum also appears quite early at 11–12 PCW (Rakic and Yakovlev 1968), simultaneously with the emergence of the subplate (Kostović and Krmpotić 1976; Kostovic and Rakic 1990). However, a recent imaging, anatomical, and molecular analysis of callosal formation in human fetal brains ranging from 13 to 20 PCW (Ren et al. 2006) suggested that callosal axons do not cross a fused midline until 14 PCW, and no discernable corpus callosum, or even midline fusion, was observed at 13 PCW (Ren et al. 2006). The number of axons in the human corpus callosum increases from 13,000 at 10 PCW to 144 millions in the child aged 5 months (Luttenberg 1965).

In the human fetal brain between 25 and 32 PCW, the cingulate cortex contains callosally projecting neurons both in the cortical plate and in the subplate (DeAzevedo et al. 1997). These subplate callosal cells are smooth neurons of diverse dendritic morphology (radially oriented, horizontally oriented, multipolar, inverted pyramids), distributed widely throughout the subplate depth, while those in the cortical plate are spiny pyramidal cells with well developed basal dendrites and apical dendrites that consistently ramify within the marginal zone (DeAzevedo et al. 1997).

In the rhesus monkey, some fetal subplate neurons send callosal and association projections (Goldman-Rakic 1982; Schwartz and Goldman-Rakic 1982, 1991; Schwartz et al. 1991) and early growing callosal and association fibers wait in the subplate (Goldman-Rakic 1982). Experimental studies in the monkey have shown that commissural corticocortical fibers reside in the subplate zone between embryonic days E100 and E123 (Goldman-Rakic 1982). In addition, some subplate neurons transiently send their axons through the corpus callosum (Schwartz et al. 1991). In the monkey, callosal axons are at birth three times more numerous than in the adult (LaMantia and Rakic 1990b) and the final number is achieved by the process of competitive elimination during the early postnatal period (Chalupa and Killackey 1989; LaMantia and Rakic 1990b). A newborn rhesus monkey has almost 200 million callosal axons compared to less than 50 million in the adult (LaMantia and Rakic 1990b). The axons are lost at the rate of about 8 million per day or 50 per second during the first 3 weeks after birth. Thereafter, they are lost at an estimated rate of half a million per day or 5 per second until the adult value is reached (LaMantia and Rakic 1990b). Interestingly, this huge loss of callosal axons occurs in parallel with the major overproduction of cortical synapses in the rhesus monkey (Bourgeois et al. 2000). Similarly, the anterior commissure in rhesus monkeys contains 11 million fibers in newborns, but only about 3 million fibers in adults (LaMantia and Rakic 1994). Thus, there is a considerable postnatal reorganization of corticocortical connectivity. Since in the human cortex waiting associative and commissural pathways are major constituents of the subplate zone after 28 PCW (Kostovic and Rakic 1990), and since the development proceeds in humans more slowly than in the monkey, we expect that this protracted postnatal reorganization of corticocortical connectivity is even more pronounced in the human brain.

8.3.2 The Development of Ipsilateral Corticocortical Connectivity

There are few available data on the development of ipsilateral corticocortical connections in monkeys and no such data in humans. As already mentioned, in the rhesus monkey some fetal subplate neurons send callosal and association projections (Goldman-Rakic 1982; Schwartz and Goldman-Rakic 1982,1991; Schwartz et al. 1991) and early growing callosal and association fibers wait in the subplate (Goldman-Rakic 1982). Ipsilateral corticocortical fibers wait in the subplate zone for several weeks before entering the cortical plate (Schwartz and Goldman-Rakic 1982; Schwartz et al. 1991).

Adultlike projections from inferior temporal areas TE and TEO to orbitofrontal cortical areas have been described in one-week-old macaques (Webster et al. 1991). However, monkey inferotemporal cortex displays an extended period of postnatal development and may not be functionally mature until the end of the first year (Rodman 1994); moreover, cortical inputs and outputs of the inferotemporal cortex undergo considerable refinement of transient connections during the first postnatal months (Webster et al. 1991; Rodman 1994).

8.4 The Development of Cortical Efferent Projection Systems

While the development of corticospinal projection is relatively well studied in both monkeys and humans, there are very few data on development of other cortico-subcortical efferent projections in the human fetal brain. By using both MRI-histological correlation and DTI, we have recently provided a preliminary evidence on prenatal development of human corticostriate projections (Kostović et al. 2002a; Judaš et al. 2005; Vukšić et al. 2008) and frontopontine pathways (Vasung et al. 2010b).

In monkeys, functional corticospinal projections to alpha-motoneurons are not established until the first appearance of fine manipulative skills at 3 postnatal months (for review, see Armand et al. 1996, 1997). However, functional human corticospinal projections seem to develop prenatally, although their development was not associated with a significant developmental milestone of motor behavior (Eyre et al. 2000).

In humans, corticospinal axons reach the decussation area at 10 PCW, gradually cross the midline and complete the decussation by 17 PCW (Ten Donkelaar et al. 2004; Ramakers 2005). The lumbosacral area is reached by 29 PCW, but growth cones do not enter spinal cord gray matter for several weeks (Ten Donkelaar et al. 2004). The corticospinal tract is the last of the major descending fiber systems to enter the human spinal cord (Humphrey 1960; Tanaka et al. 1995; Grever et al. 1996; Weidenheim et al. 1992, 1993, 1996). According to a recent study (Eyre et al. 2000), corticospinal axons reach the cervical spinal cord by 24 PCW, by 27 PCW they are still growing, and by 33 PCW they increasingly penetrate the spinal gray matter. The progressive outgrowth of axons from the intermediate gray matter toward the dorsal and ventral horns is characteristic of corticospinal tract development in both monkeys (Galea and Darian-Smith 1995; Olivier et al. 1997) and humans (Eyre et al. 2000). The pathway length from cortex to spinal segment C5 in human newborns at term is 13–14 cm (Eyre et al. 1991). In man, group Ia afferents establish a monosynaptic projection to alpha-motoneurons early in fetal development (Okado 1981; Okado and Kojima 1984; Konstantinidou et al. 1995) and Eyre et al. (2000) have provided a compelling physiological evidence for the prenatal establishment of monosynaptic corticospinal projections to both alpha-motoneurons and group Ia inhibitory interneurons in human fetuses. Finally, significant levels of high affinity NMDA glutamate receptors are transiently expressed in man in the ventral horn from 24 PCW to 2 months postnatally, indicating that a critical period for plasticity in alpha-motoneuron development is also likely to occur in man in the perinatal period. Thus, monosynaptic corticomotoneuronal projections preceded the appearance of relatively independent finger movements by at least 12 months (Eyre et al. 2000). While initial corticospinal projections are bilateral, the ongoing normal development is characterized by a gradual weakening of ipsilateral projections, in parallel with strengthening of contralateral projections (Eyre et al. 2001). Finally, corticospinal system in humans displays a high degree of perinatal and early postnatal plasticity (Eyre et al. 2001, 2007; Staudt et al. 2002, 2004, 2006; for review, see Eyre 2007; Staudt 2007, 2010).

8.5 The Development of Bidirectional Pathways Connecting Cortex with the Amygdala and Claustrum

In distinction to caudate nucleus and putamen, which receive cortical input but have only subcortical outputs, the claustrum and amygdala are both bidirectionally connected with the cerebral cortex (Swanson and Petrovich 1998; Aggleton 2000). The amygdala and its cortical connections have an important role in development of social cognition (for review, see Bauman and Amaral 2008). While there are studies on prenatal cytoarchitectonic development of the human amygdala (Humphrey 1968; Nikolić and Kostović 1986; Müller and O'Rahilly 2006), there are no information on development of its connectivity. In rhesus monkeys, the neurogenesis of amygdala occurs between E33 and E65 (Kordower et al. 1992). This makes the amygdaloid complex, like the magnocellular basal forebrain (Kordower and Rakic 1990), among the earliest developing structures of the primate telencephalon; interestingly, the neurogenesis of the monkey hippocampus also begins at E33 (Rakic and Nowakowski 1981). By two weeks of postnatal age, macaque amygdalocortical connections already closely resemble those in the mature monkeys (Bauman and Amaral 2008). Adultlike projections from inferior temporal areas TE and TEO to both amygdala and orbitofrontal areas have also been described in one-week-old macaques (Webster et al. 1991); the distribution of opiate receptors within the amygdala and cingulate cortex is comparable to adult patterns as early as one week of age (Bachevalier et al. 1986) while the pattern of serotoninergic innervation of monkey amygdala resembles the adult within the first postnatal month (Bauman and Amaral 2008). Thus, several regions implicated in social processing appear to mature very early in postnatal development and may play a critical role in the emergence of species-typical social behavior (Bauman and Amaral 2008). On the other hand, monkey inferotemporal cortex displays an extended period of postnatal development and may not be functionally mature until the end of the first year (Rodman 1994); moreover, cortical inputs and outputs of the inferotemporal cortex undergo considerable refinement of transient connections during the first postnatal months (Webster et al. 1991; Rodman 1994). In the macaque inferotemporal cortex, response selectivity to faces appears already within the second month of life (Rodman 1994; Rodman et al. 1991, 1993), and infant monkeys that sustained damage to the inferior temporal visual area TE within the first postnatal month display less social contact compared to controls at 6 months of age, but do not show deficits in other aspects of social behavior such as eye contact and approach/withdrawal (Bachevalier et al. 2001). In addition, neonatal amygdala damage leads to pronounced changes in fear behaviors or deficits in social development (for review, see Bachevalier 1994, 1996). On the other hand, macaques that are reared in a social environment and receive selective amygdala lesions at two weeks of age do not demonstrate profound impairments in social development within the first year of life (Bauman et al. 2004a, b) but over time these amygdala-lesioned monkeys displayed changes, such as decreased social dominance, which may be due to an inability to regulate fear responses (Bauman et al. 2006). Finally, in this context it should be noted that neonatal temporal lobe lesions have been associated with delayed maturation of the prefrontal cortex (Bertolino et al. 1997). Obviously, developmental data on human cortico-amygdala connectivity are sorely needed and this topic represents an important challenge for future MRI tractography studies.

8.6 The Transformation of the Fetal into Adult White Matter and Protracted Postnatal Myelination

The transformation of the fetal white matter (the intermediate zone) occurs gradually during the third trimester, in parallel with gradual dissolution of the subplate and the SVZ, and continues postnatally. The period spanning the last prenatal and at least first six postnatal months is characterized by significant fiber-architectonic changes, that is, reorganization of the white matter, especially at the cortical/white matter interface (Hüppi et al. 1998, 2001; Prayer et al. 2001; McKinstry et al. 2002; Berman et al. 2005; Huang et al. 2006). This reorganization is related to the onset of myelination, the postnatal persistence of the subplate (at least in the associative cortical regions – Kostović et al. 2002a), the appearance of tertiary gyri and sulci (probably related to the protracted

development of short corticocortical connections, that is, Meynert's U-fibers), and probably a host of other, as yet poorly investigated factors, such as changes in microvascular network, changes in the molecular profile of the extracellular matrix, development of white matter astrocytes, and so forth. The myelination starts shortly before birth, but continues for at least two or three decades (see below).

8.6.1 Prenatal Development of Oligodendroglia in the Human Telencephalon

In a series of recent studies, Nada Zecevic and collaborators offered a detailed analysis of an early oligodendrocyte specification (Rakic and Zecevic 2003b; Filipovic et al. 2003; Jakovcevski and Zecevic 2005a, b), the onset of myelination (Jakovcevski et al. 2007), in vitro studies on the capacity of radial glia cells to generate oligodendrocytes (Mo and Zecevic 2009), interactions of oligodendrocyte progenitors with other cell types (Filipovic and Zecevic 2005, 2008) and interactions between oligodendrocytes and axons before the onset of myelination (Jakovcevski et al. 2007). For a recent review, see Jakovcevski et al. (2009). These studies demonstrated that oligodendrocyte development begins during the second trimester and progresses toward birth and further into adulthood (Rivkin et al. 1995; Back et al. 2001, 2002; Rakic and Zecevic 2003b; Jakovcevski and Zecevic 2005b). Early oligodendrocyte progenitor cells express the platelet derived growth factor receptor alpha (PDGFRα) and NG2 proteoglycans and display typical morphology with few ramified processes (Jakovcevski and Zecevic 2005b). They appear at 10 PCW, but increase in number only around 15 PCW when they are most numerous in the ganglionic eminence and in the cortical VZ/SVZ (Jakovcevski et al. 2009). By midgestation (19–22 PCW), oligodendrocyte precursor cells invade the dorsal telencephalic wall and the cortical plate, but remain most numerous in the SVZ until 24 PCW (Jakovcevski and Zecevic 2005b). Late oligodendrocyte precursor cells display O4 immunoreactivity, whereas pre-myelinating oligodendrocytes are reactive to O1 antibody (Jakovcevski et al. 2009). At 20–22 PCW, O4 and O1 cells are especially numerous in the subplate which indicates that the subplate may be important for maturation of oligodendrocytes (Rakic and Zecevic 2003b; Jakovcevski and Zecevic 2005b). The subplate during midgestation also attracts numerous GFAP-positive astrocytes (Zecevic 2004). Further maturation of oligodendrocytes is marked by the expression of myelin basic protein (MBP) and proteolipid protein (PLP). While MBP was observed already at 5 PCW, this expression was attributed to Golli/MBP splice variants (Zecevic et al. 1998; Tosic et al. 2002; Filipovic et al. 2002, 2003). In the telencephalon, first MBP-positive cells were found at 18 PCW, scattered through the intermediate zone (Back et al. 2001; Jakovcevski and Zecevic 2005b). It should be noted that the human fetal forebrain is characterized by a ventro-dorsal gradient in the oligodendrocyte precursor cell density (Rakic and Zecevic 2003b; Jakovcevski and Zecevic 2005a, b) and in the extent of myelination (Jakovcevski et al. 2007). Moreover, human cortical oligodendrocytes originate from multiple sites, such as ganglionic eminence and SVZ (Rakic and Zecevic 2003b; Jakovcevski and Zecevic 2005a, b). Transcription factors that are necessary and sufficient for generation of oligodendrocytes and for myelination are *Olig* genes, and *Olig2* is expressed in all MBP-positive cells in the human fetal forebrain at midgestation, and in around 50% of early oligodendrocyte progenitors in the SVZ (Jakovcevski and Zecevic 2005a). However, a subpopulation of MAP2-positive neuronal progenitors in the SVZ also expresses *Olig2* during midgestation (but not later), which suggests existence of a common progenitor cell for oligodendrocytes and at least some neuronal classes in the human telencephalon (Jakovcevski and Zecevic 2005a). Indeed, *Olig1* was colocalized in vimentin-positive radial glial cells, which are multiple neural progenitors (Mo et al. 2007; Mo and Zecevic 2009). Another important finding was that, in contrast to rodents where chemokine CXCL1 directly induces oligodendrocyte proliferation, in human fetal brain CXCL1 acts indirectly, through astrocyte secretion of interleukin IL-6, to increase oligodendrocyte proliferation (Filipovic and Zecevic 2008; Jakovcevski et al. 2009). It should also be noted that at midgestation numerous early oligodendrocyte precursor cells still persist in the SVZ. This is clinically relevant because it indicates prolonged proliferation of oligodendrocytes in the human fetal brain that can compensate for minor defects after hypoxic-ischemic periventricular damage (Jakovcevski and Zecevic 2005b).

8.6.2 The Onset and Progression of Myelination in the Human Telencephalon

Myelination in the human brain progresses over several decades, which is much longer than a complete lifespan of the commonly studied animals (Jakovcevski et al. 2009). For example, by 3–6 months, subcortical regions of the macaque brain are well myelinated, and most cortical regions contain some myelin, but cortical layers continue to acquire myelin until at least 3.5 years of age in macaque monkeys (Gibson 1991). The myelination of axons within inferotemporal cortex has not reached adultlike levels in 7-month-old macaque monkeys (Rodman 1994), while myelination within the macaque orbitofrontal cortex may take 1–2 years to reach adultlike levels (Gibson 1991).

Before myelination is initiated, oligodendrocyte precursors transform first to pre-myelinating oligodendrocytes and then into mature myelin-producing cells. In humans there is a clear dissociation between the time of oligodendrocyte differentiation and the beginning of myelination in the fetal forebrain (Back et al. 2001; Jakovcevski and Zecevic 2005b).

In the existing literature, the estimates of the onset of myelination in the human telencephalon vary widely, from 17 PCW (Yakovlev and Lecourse 1967; Tosic et al. 2002) to 30 PCW (Back et al. 2001) or even to the postnatal period (Kinney et al. 1994). At 20 PCW, myelinated axons were observed in the diencephalon, but they could not be observed in the telencephalon either by immunohistochemistry or electron microscopy (Jakovcevski and Zecevic 2005b). In the forebrain, first myelin sheaths detected by MBP-immunohistochemistry were present in the thalamus at 22 PCW (Jakovcevski and Zecevic 2005b). According to another study, the onset of myelination as seen by MBP expression, was postnatal at 54 PCW, with progression to adult-like staining by 72–92 PCW (Haynes et al. 2005).

8.6.3 The Importance of Myelination for a Proper Interpretation of MRI Findings in Brains of Children and Adolescents

The protracted and progressive postnatal myelination is quite important for proper interpretation of in vivo MRI studies of cortical volume and thickness during childhood, adolescence, and adulthood. Already Kaes (1907), by analyzing cortical thickness in myeloarchitectonic sections throughout the lifespan (3 months to 97 years of age), demonstrated the progressive spread of intracortical myelination into frontal and parietal cortices during the first four decades of life. This increase in myelin content in deep cortical layers leads to the apparent cortical thinning, especially when observed by MRI because nonmyelinated axons would appear more like gray matter at a gross level in MRI. This effect of late myelinization is much more significant than the often invoked effects of postnatal synaptic pruning and cell loss; in other words, the apparent thinning of cortex (loss of gray matter density) probably results from increased myelination (for review, see O'Hare and Sowell 2008). Similarly, a 95% increase in the extent of myelination relative to brain weight between the first and second decades of life has been observed within the superior dissecant lamina of the entorhinal cortex (Benes et al. 1994). Reductions in synaptic density are unlikely to account for the large volume decreases in the cortex observed throughout development; the balance between the decreasing number of neurons and the increasing size of glial cells attributable to myelination seems to be primarily responsible for determining the overall cortical thickness (Giedd et al. 1996a). However, it should be noted that a current consensus is that cortical neurons are generally preserved during adolescence and adulthood with at most a 10% reduction in neuronal numbers (Peters et al. 1998).

Initial quantitative structural MRI studies reported that children aged 8–10 years had significantly more cortical gray matter than young adults, although young adults had larger total brain volumes (Jernigan and Tallal 1990), and that the timing of gray matter loss displays regional differences (Jernigan et al. 1991a, b). The decrease in the cortical volume during development (along with concomitant increases in white matter) has been reported in subsequent studies (Pfefferbaum et al. 1994), especially in the dorsal associative frontal and parietal cortices (Giedd et al. 1999a; Sowell et al. 1999a, 2001a, b, 2002a, 2003). In another study, the postadolescent gray matter loss was localized to large regions of the dorsal, mesial, and orbitofrontal cortex, with relatively little gray matter loss in the parietal lobes (Sowell et al. 1999b). There is an initial increase in cortical density that peaks between 10 and 12 years, depending on gender, in both frontal and parietal lobes, and thereafter declines during the

adolescent and postadolescent periods (Giedd et al. 1999a; Gogtay et al. 2004). Thus, it has been concluded that there are regionally specific patterns of gray matter loss during late childhood and adolescence. In contrast, ventral temporal cortex changes less dramatically between childhood and adolescence (Giedd et al. 1999a; Sowell et al. 2002a). Finally, significant age-related increases in white matter density were observed in the motor and language-related cortical regions (Paus et al. 1999) and small increases in cortical gray matter density between childhood and young adulthood have been observed in bilateral posterior perisylvian regions (Sowell et al. 2002b, 2003, 2004a, b) and in the left inferior frontal sulcus, that is, Broca's area (Sowell et al. 2004a, b). More recent studies measured the cortical thickness (instead of cortical gray matter density) across development and revealed statistically significant cortical thinning of approximately 0.15–0.30 mm per year, most prominently in right dorsal frontal and bilateral parietal regions (Sowell et al. 2002a, b, 2003, 2004a, b). On the other hand, significant increases in cortical thickness (approximately 0.10–0.15 mm per year) were observed in frontal and temporal language regions (O'Hare and Sowell 2008). Recent MRI studies also suggested that there are significant relationships between frontal lobe structure and general intellectual functioning (Thompson et al. 2001; Toga and Thompson 2005; Shaw et al. 2006). In conclusion, a number of recent studies have consistently demonstrated a decrease in gray matter volume starting in late childhood or early adolescence and progressing into late adulthood – with notable exception of language-related cortical areas (Caviness et al. 1996; Giedd et al. 1996a, b; De Bellis et al. 2001; Sowell et al. 2002a, 2003, 2004a, b; Giedd 2004; Gogtay et al. 2004; Lenroot and Giedd 2006; O'Hare and Sowell 2008).

9 Concluding Remarks and Clinical Implications

As illustrated in Sect. 5 (and in most other sections of this chapter), there are profound and clinically relevant differences in cortical development between rodents and humans. There are numerous evolutionary modifications of developmental events that produce not only quantitative changes, such as the number of neurons and columns or timing and sequence of cellular events, but also qualitative ones (for example, the elaboration of new neuronal types, addition of specialized cytoarchitectonic areas and formation of new connections (Rakic et al. 2009)). Analyzing species-specific differences in the timing, sequence, and phenotypic differentiation could provide insight into the pathogenesis of cortical abnormalities and cortical evolution (Levitt 2003; Rakic et al. 2009; Preuss 2009). Thus, neither the genetic, the cellular, nor the circuitry basis of human cortical uniqueness can be deciphered by studying exclusively rodents (Rakic et al. 2009; Preuss 2009). Animal models are therefore not sufficient and appropriate human studies and human model systems are necessary.

For example, unlike in rodents, the SVZ in the human contributes the majority of interneurons to the neocortex (see Sect. 6.2.2). Thus, the modifications in the expression pattern of transcription factors in the forebrain may underlie species-specific programs for the generation of distinct lineages of cortical interneurons that may be differentially affected in genetic and acquired disorders related to neuronal migration (Jones 1997; Lewis 2000; Gleeson and Walsh 2000; Ross and Walsh 2001; Rakic 2003a, b; Hevner 2007; Guerrini et al. 2008). For example, a species-specific difference was discovered in the effect of the deletion of doublecortin (*Dbx*) mutation, which was found to have a profound effect on neuronal migration in the human telencephalon but does not affect formation and neurogenetic gradients of the mouse cerebral cortex (Corbo et al. 2002). There are already many examples of how unique structures and gene expression patterns that give rise to abilities, such as language, are also involved in disorders, such as autism, for which there is no accepted mouse model (Levitt 2005; Rakic 2009). As the development of human brain circuitry depends on the diversity and precise spatiotemporal regulation of its transcriptome (Johnson et al. 2009), and symptoms of many neurological and mental disorders are dramatically influenced by pre-existing regional molecular profiles and neuronal circuitry (Morrison and Hof 1997; Levitt 2005), such disorders are at least in part defined during development by differential gene expression determining regional differences in neuronal circuits (Johnson et al. 2009). The detailed and up-to-date knowledge on human cortical development is also highly relevant for understanding and analyzing the neurobiological basis and developmental origin of

major neurological and mental disorders, such as schizophrenia, (for review, see Kostović et al. 2010) or Down's syndrome (Vukšić et al. 2002), as well as developmental brain disorders such as lissencephaly (Judaš et al. 2009) and holoprosencephaly (Judaš et al. 2003b; Fertuzinhos et al. 2009).

Fortunately, new noninvasive methods from histology, neuroimaging, and genomics are making the human brain accessible for direct, detailed study as never before and we shoud use these methods not only to analyze human brain development, but to directly compare humans to other species (Preuss 2009). We should also increasingly use the correlation between the improving imaging and more diverse histological studies to aid clinicopathological diagnosis (Kostović and Vasung 2009; Vasung et al. 2010a, b; Wang et al. 2010). The number of new and powerful methods for analyzing human brain development is rapidly increasing. For example, one can use gene chips and human genome microarrays, rtPCR and cell culture (Ip et al. 2010), or purify specific subpopulations of developing human cortical cells, such as radial glia, in culture (Mo et al. 2007; Mo and Zecevic 2008). Another important goal is to establish the molecular taxonomy of diverse neuronal types, as a first step in identifying the subpopulations that may have very different roles during development and in various pathologies (Hevner 2007; Hoerder-Suabedissen et al. 2009). Such studies already opened the way for selective recognition of different subpopulations of neurons in experimental rodents (Hoerder-Suabedissen et al. 2009; Osheroff and Hatten 2009; Ayoub and Kostovic 2009) and we need similar studies to focus on the origins, categories, and functional roles of human cortical neurons. Combining knowledge of cell-type specific gene expression with modern imaging methods will enable a better understanding of neuropathologies involving cerebral cortex – for example, by selectively manipulating these cells in animal models and analyzing them in human histological slides (Wang et al. 2010). Another important step in this direction is represented by a development of the three-dimensional (3D) HUDSEN Atlas (http://www.hudsen.org) for studying gene expression in the embryonic human brain at Carnegie stages 12–23 (Lindsay and Copp 2005; Lindsay et al. 2005; Sarma et al. 2005; for review, see Kerwin et al. 2010).

The functional significance of transient fetal circuitry and the pivotal role of the subplate zone has already been extensively reviewed in both experimental model animals (Kanold and Luhmann 2010) and in humans (Kostović et al. 1995; Kostović and Judaš 2006, 2007, 2010). The subplate is involved in plasticity after perinatal hypoxic-ischemic lesion (Kostović et al. 1989b) and plays a major role in current interpretations of pathogenesis of this major pathology of prematurely born infants (McQuillen and Ferriero 2005; Leviton and Gressens 2007; Mathur and Inder 2009; Ment et al. 2009; Miller and Ferriero 2009; Volpe 2009). The reader may find extensive descriptions and analyses in the above mentioned reviews, but I wish to conclude this chapter by pointing out two specific features of late prenatal and perinatal human brain, one related to the complexity of the periventricular fetal white matter, and another to the pivotal role of the subplate zone.

The complexity of the structure of the fetal white matter as well as continuously changing variability of its cellular and axonal contents are bewildering (Fig. 8). In addition to numerous and variable contingents of growing axons (see Sects. 8.2–8.6), the fetal white matter (that is, the IZ and the subjacent outer SVZ) contain different populations of cells: radially migrating cortical projection neurons, radially and tangentially migrating cortical interneurons, various types of neuronal progenitor cells (see Sect. 6.2), early developing oligodendrocytes and astrocytes, a complex extracellular matrix (Kostović et al. 2002a), and at least six major crossroads of developing cortical pathways (Judaš et al. 2005). No wonder that hypoxic-ischemic lesions can cause a huge variety of neurodevelopmental outcomes, and we are just beginning to unveil the unprecedented complexity of these developmental processes and interactions (Leviton and Gressens 2007; Miller and Ferriero 2009; Ment et al. 2009; Volpe 2009; Staudt 2007, 2010).

As illustrated in preceding sections, histogenetic processes in the human fetal and perinatal brain are protracted and significantly overlap, but the subplate zone represents a playground for the majority of important events during that developmental window. Therefore, the human perinatal period is characterized by simultaneous existence of two separate (but interconnected) types of cortical circuitry organization: (a) transient fetal circuitry, centered at the subplate zone, and (b) immature but progressively developing permanent cortical circuitry, centered at the cortical plate (that is, developing cortical layers I–VI). Thus, the developing human cortex passes through three major

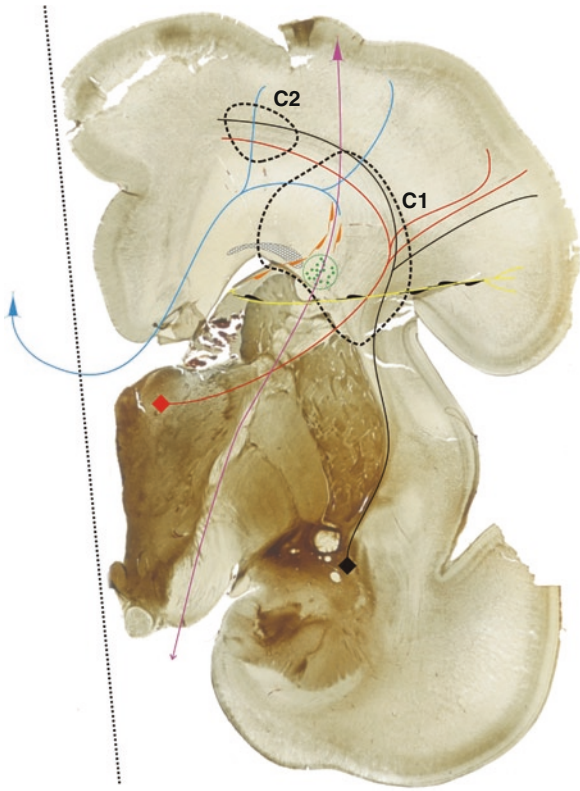


Fig. 8 Summary diagram, superposed on AChE-stained coronal section through a telencephalon of 28-week-old human fetus constructed on the basis of our data and evidence from current literature. Thick *black dashed lines* delineate the first (C1) and second (C2) frontal crossroad area. The honeycomb pattern area denotes the deep periventricular system of fiber bundles; and *circle with green dots* developing fronto-occipital system, both containing SNAP-25 immunoreactive fibers. *Colored lines* denote systems of projection, association and commissural fibers passing through the crossroads (with triangles or quadrangles depicting cell bodies of origin), as follows: black – basal forebrain afferents; red – thalamocortical afferents; blue – callosal fibers; violet – corticofugal efferents. Note that both radially migrating neurons (*black profiles* along the yellow radial glial fiber) and tangentially migrating neurons (*orange profiles*) pass through the major crossroad (C1) area, which is located at the main predilection site of hypoxic-ischemic lesion in preterm infants (From Judaš et al. (2005). With permission)

stages of functional development (Kostović and Judaš 2006, 2007, 2010; see also Vanhatalo and Kaila 2006; Vanhatalo et al. 2005; Milh et al. 2007): (1) initial fetal circuitry which is endogeneously (spontaneously) driven, (2) perinatal dual circuitry (co-existence of endogeneously driven SP-centered transient circuitry with developing CP-centered permanent circuitry) and (3) postnatally established permanent (externally driven) cortical circuitry.

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