CNS Neuroscience & Therapeutics

REVIEW

CNS Neuroscience & Therapeutics

The Relevance of Human Fetal Subplate Zone for Developmental Neuropathology of Neuronal Migration Disorders and Cortical Dysplasia

Ivica Kostović, Goran Sedmak, Mario Vukšić & Miloš Judaš

Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia

Keywords
Cortical dysplasia; Disorders of neuronal migration; Human fetal connectome; Radial migration; Tangential migration.

Correspondence
Prof. Ivica Kostović, Croatian Institute for Brain Research, University of Zagreb School of Medicine, 10 000 Zagreb, Croatia.
Tel.: +385-1-4596-902;
Fax: +385-1-4596-942;
E-mail: ikostov@hiim.hr
Received 27 June 2014; revision 31 July 2014; accepted 26 August 2014

doi: 10.1111/cns.12333

The first two authors contributed equally to this work.

SUMMARY

The human fetal cerebral cortex develops through a series of partially overlapping histogenetic events which occur in transient cellular compartments, such as the subplate zone. The subplate serves as waiting compartment for cortical afferent fibers, the major site of early synaptogenesis and neuronal differentiation and the hub of the transient fetal cortical circuitry. Thus, the subplate has an important but hitherto neglected role in the human fetal cortical connectome. The subplate is also an important compartment for radial and tangential migration of future cortical neurons. We review the diversity of subplate neuronal phenotypes and their involvement in cortical circuitry and discuss the complexity of late neuronal migration through the subplate as well as its potential relevance for pathogenesis of migration disorders and cortical dysplasia. While migratory neurons may become misplaced within the subplate, they can easily survive by being involved in early subplate circuitry; this can enhance their subsequent survival even if they have immature or abnormal physiological activity and misrouted connections and thus survive into adulthood. Thus, better understanding of subplate developmental history and various subsets of its neurons may help to elucidate certain types of neuronal disorders, including those accompanied by epilepsy.

Introduction

Recent advances in studying structural, physiological, and molecular features of the developing cortical circuitry clearly suggest that there are major organizational differences between fetal, perinatal, and postnatal human cerebral cortex and that the cortex develops through a series of complex reorganizational events [1–9]. These reorganizational events may underlie complex changes in motor, sensory, behavioral, and cognitive functions of human premature infants, newborns, children, and adolescents [2–4,10–14]. The disturbances of these processes, especially when they occur during the fetal period, are likely to be involved in etiopathogenesis of many developmental brain disorders, such as cerebral palsy [15], autism [16,17], schizophrenia [18,19], and epilepsy [20,21].

The prenatal development of the human cerebral cortex is characterized by both sequential and overlapping histogenetic events [22,23] accompanied by significant changes in gene expression patterns [6,9]. In addition, the late fetal period (from 22 postconceptional weeks, PCW, onwards), which corresponds to the period of prematurely born infants, is characterized by major changes in development of cortical circuitry and connectivity, synaptogenesis and physiological features [1–3], including the emergence of resting state activity. Various developmental disorders, including cortical dysplasia, probably emerge during this clinically important period [1–3,20,21,24–26].

The aim of this study is to review major histogenetic events and processes in the human fetal brain to provide a neurobiological framework for interpreting and analyzing developmental brain disorders frequently accompanied by epilepsy, such as disorders of neuronal migration and cortical dysplasias. We focus on the transient fetal subplate zone for the following reasons: (1) the subplate is the site of early synaptogenesis and synaptic interactions with thalamocortical and other cortical afferent systems [27–32] as well as the site of early endogenous oscillatory activity, as demonstrated experimentally in rodents [33–35] and in the human subplate [36]; (2) the transient subplate circuitry co-exists with early developing permanent cortical circuitry during the late fetal period [2], when long corticocortical and commissural pathways continue to grow, and (3) the subplate remnant exists even in the early postnatal period, when short corticocortical connections develop [7]. Finally, the subplate also serves as a prominent

compartment involved in neuronal migration and thus may be involved in pathogenesis of various migration disorders [37–39].

Sequential Development and Transient Cellular Compartments of the Human Fetal Cerebral Wall

The complex cellular, modular, laminar, areal, and regional organization of the adult human cortical map and connectome develops through a long series of sequential (but partially overlapping) histogenetic events which begin during the 4 PCW [23] and terminate during the late adolescence and early adulthood [11,12]. As there are already extensive reviews of fetal cerebral wall lamination and development [1–3,22,23,29,40], including the major role of subplate in cortical development [23,34,41–43] and the history of the subplate discovery [43], here we mention only the most relevant facts.

The cortical histogenesis begins with proliferation of progenitor neuroepithelial cells in the ventricular zone (VZ) of paired telencephalic vesicles [23]. Already at 5 PCW, the telencephalic wall consists of thin dorsal (pallium) and thick basal portion (subpallium). During the 6 and 7 PCW, first postmitotic neurons migrate from VZ towards the pial surface and form the so-called mantle layer [45], also described as the primordial plexiform layer [46] or the preplate [23,47]. The first preplate cells are Cajal-Retzius cells and early generated subplate neurons, which have no synapses but communicate through non-synaptic junctions.

During the 7 PCW, the new proliferative zone (subventricular zone, SVZ) is formed, and during the 8 PCW the cell-dense cortical plate appears, consisting of postmigratory neurons which migrate from the VZ along radial glial guides and finally settle in the cortical plate arranged in vertical ontogenetic columns [48]. Thus, the neocortical anlage consists of three transient fetal zones: the superficial and cell-poor marginal zone (MZ), the cell-dense cortical plate (CP), and the plexiform pre-subplate [29]. This neocortical anlage is also characterized by early bilaminar synaptogenesis, with synapses present in MZ and presubplate, but absent from the CP [23,27,29]. Between the neocortical anlage and periventricular proliferative zones (VZ-SVZ), the intermediate zone (IZ) appears and contains early growing afferent fibers originating from brain stem (monoaminergic axons [49–52]), basal forebrain (cholinergic axons [53]) and thalamus (glutamatergic axons [29,54,55]).

Between 12 and 15 PCW, the deep portion of the neocortical CP gradually transforms into new, prominent and synapse- and fiber-rich subplate zone [29,56,57]. The subplate becomes the thickest and most voluminous transient compartment of the human fetal cerebral wall between 15 and 35 PCW and represents the major site of synaptogenesis and neuronal maturation and differentiation. The subplate also contains a large amount of hydrophyllic extracellular matrix and thus can be easily visualized in both *in vitro* [58,59] and *in vivo* MRI studies [60–62]. From 15 to 24 PCW, the subplate serves as the waiting compartment for ingrowing cortical afferents [28,29,40]. From 24 to 28 PCW, there is gradual relocation of thalamocortical and basal forebrain afferents from the subplate into the cortical plate [1,3,29,40,53–55] with concomitant onset of synaptogenesis within the cortical plate [27,29]. This event represents a milestone in fetal cortical physiology because peripheral stimulation is for the first time able to synaptically activate cortical plate neurons [63,64]. Before that period, afferent axons predominantly activated subplate neurons and cortical activity was endogenous [1,2,29,34,41]. Between 28 and 34 PCW, the subplate remains at the peak of its development, because there is continuous growth and relocation of massive corticocortical pathways; this period is also characterized by extensive growth of fetal white matter, further formation of cortical convolutions, and exponentially increasing synaptogenesis in the cortical plate which also begins to develop its six-layered "Grundtypus" of cortical lamination [65]. In addition, dendritic differentiation of cortical plate neurons also intensifies during this period [66–68]. After 34 PCW, the subplate gradually diminishes in size, beginning at the depth of cortical sulci, but remains present even in the newborn and early postnatal brain as the subplate remnant [7]. It should be noted that most of the human fetal subplate neurons not only survive the perinatal period, but continue to develop postnatally and remain very numerous in the adult gyral white matter [44,69,70].

Structural and Functional Organization of the Human Subplate

The human fetal subplate has a complex structure and consists of various cellular, fibrillar and extracellular elements [23,29]. Its composition is continuously changing throughout the midfetal, late fetal, perinatal, and early postnatal period [1–3]. However, in all these periods, the subplate consists of migratory and postmigratory neurons, glial cells, significant amount of extracellular matrix, and various contingents of afferent and efferent axons involved in intense synaptogenesis. This intense synaptogenesis is clearly demonstrated by E.M. studies, but it is possible that not all of these early synapses are functionally active, as suggested in a recent study on acute slices of the postmortem human fetal brain tissue [36]. Thus, to delineate the subplate in various developmental periods, one has to use a combination of various E.M., histological, histochemical, and immunocytochemical techniques [7,29,42,58].

Morphological and Molecular Phenotypes of Subplate Neurons

The subplate contains early differentiated postmigratory and polymorphic (multipolar) neurons [44,66–70]. On the basis of Golgi method (Fig. 1), these neurons can be described as fusiform, inverted pyramidal, polymorphous and large multipolar [66–68]. Even if we limit the review just to the studies of human and rhesus monkey brain, it is clear that these neurons also express a large variety of molecular markers, such as different neurotransmitters (Table 1), various receptors (Table 2), calcium-binding proteins (Table 3) and synaptic and cytoskeletal markers as well as growth factors and axon guidance molecules (Table 4). Along with numerous neuropeptides [34,41,42], two major neurotransmitters, glutamate and GABA, are also present in subplate pyramidal neurons and interneurons [33,101–104]. However, their respective roles and exact distribution in specific types of subplate neurons (especially in the human brain) are far from being satisfactorily elucidated.

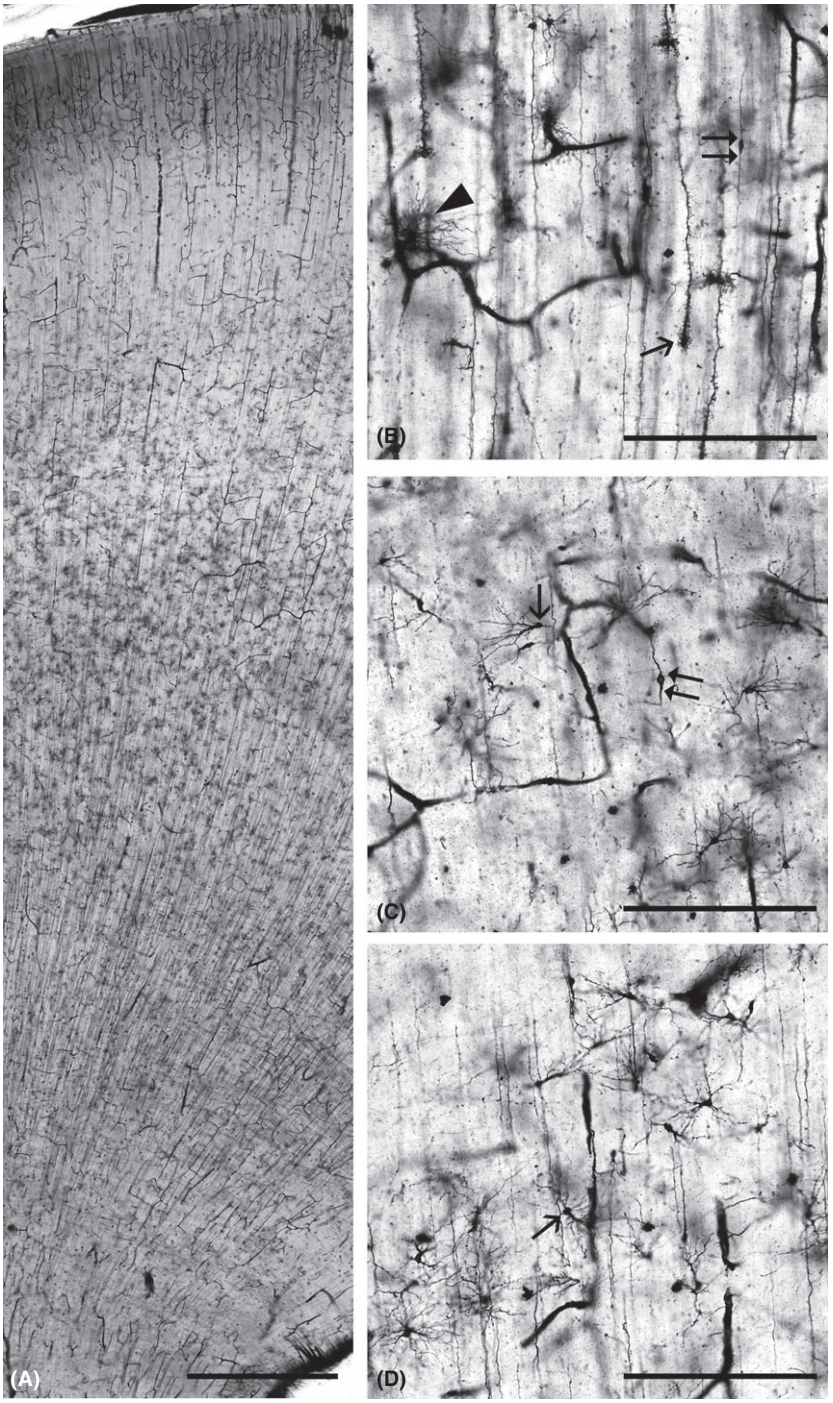

Figure 1 Microphotographs of Golgi stained human fetal somatosensory cortex (Stensaas' modification of Del Rio Hortega method) in 23 PCW-old preterm infant. Note the radial orientation of cellular elements in the telencephalic wall (**A**) due to the presence of radial glia and vertical arrangement of blood vessels; the subplate is recognized as a wide pale zone below the cortical plate (**A**). The subplate contains postmigratory cortical neurons (**B**, double arrows), radial glial cells starting to transform into astrocytes (**B**, arrow) as well as already formed fibrillar astrocytes in contact with blood vessels (**B**, arrowhead). The subplate contains several types of neurons: polymorphic (**C**, arrow), fusiform (**C**, double arrow), and inverted pyramidal (**D**, arrow). Bar = 1 cm (**A**) and 200 μm (**B**, **C**, **D**).

Subplate Represents a Waiting Compartment for Cortical Afferent Fibers and Subplate Neurons Serve as Postsynaptic Targets for Various Inputs

The first afferent fibers to reach subplate neurons, already at the presubplate stage, originate from modulatory monoaminergic pathways ascending from the brain stem [29,49–52]. In the rodent brain, early monoaminergic axons also make synapses below the cortical plate in the zone which corresponds to the human subplate [105]. During the expansion of the deep cortical plate and the formation of the proper subplate (13–15 PCW), two new and massive afferent systems enter the subplate: basal forebrain cholinergic fibers [53], and thalamocortical fibers [29,54,55]. A subset of human subplate neurons display strong AChE-reactivity [69] and express M2 muscarinic receptors [106]. The cholinergic activation of subplate neurons has been also demonstrated in the

Table 1 Expression of neurotransmitters in subplate neurons

Marker	Species	Age	Source
GABA	Human	14–32 GW	Yan et al. [71]
		7–13 PCW	Zecevic and Milosevic [72]
			Huntley et al. [73]
	Monkey	E70–E141	Meinecke and Rakic [74]
NO & NADPH	Human	15–32 GW	Yan et al. [75]
		15–28 PCW	Yan and Ribak [76]
		18–Newborn	Downen et al. [77]
		15–37 PCW	Judaš et al. [42]
		25–35 PCW	deAzevedo et al. [78]
NPY	Human	14 PCW–34 years	Delalle et al. [79]
		14 PCW–34 years	Uylings and Delalle [80]
		11 PCW–Newborn	Wai et al. [81]
		13–16 PCW	Bayatti et al. [82]
		16 PCW	Wang et al. [83]
			Huntley et al. [73]
	Monkey	E60–160	Mehra and Hendrickson [84]
Somatostatin	Human	22–34 PCW	Kostović et al. [85]
	Monkey		Huntley et al. [73]
Substance P	Monkey	E90–E160	Mehra and Hendrickson [84]

Table 2 Expression of various receptors in subplate neurons

Marker	Species	Age	Source
GABA A receptor	Monkey	E121–E155	Huntley et al. [86]
		E70–E141	Meinecke and Rakic [74]
α1 and α2 adrenergic receptor	Monkey	E65–E143	Lidow and Rakic [87]
β adrenergic receptor	Monkey	E90–128	Lidow and Rakic [87]
α4 nAChR	Human	17–24 GW and 34–42 GW	Schroder et al. [88]
p75NGFR	Human	16–40 PCW	Kordower and Mufson [89]
		14–34 GW	Chen et al. [90]
	Monkey	E56–E121	Meinecke and Rakic [91]
EphA3, 6, 7	Monkey	E65–E95	Donoghue and Rakic [92]
Trk	Human	14–34 GW	Chen et al. [90]

Table 3 Expression of Ca^{2+} binding proteins in subplate neurons

Marker	Species	Age	Source
Calbindin	Human	20 PCW>	Ulfig [93]
Calretinin	Human	20 PCW>	Ulfig [93]
		13–16 PCW	Bayatti et al. [82]
		16 PCW	Wang et al. [83]
Parvalbumin	Human	26 PCW–Newborn	Honig et al. [94]
S100A4	Human	12–32 GW	Chan et al. [95]
S100A5	Human	12–32 GW	Chan et al. [95]
S100A13	Human	12–32 GW	Chan et al. [95]

Table 4 Expression of other markers in subplate neurons

Marker	Species	Age	Source
GAD (67/65)	Human	26 GW – 2 years	Xu et al. [96]
GAP43	Human	14–Newborn PCW	Honig et al. [94]
		13–17 PCW	Bayatti et al. [82]
vGAT	Human	10 PCW	Bayatti et al. [82]
KCC2	Human	16 PCW	Bayatti et al. [82]
		16 PCW	Wang et al. [83]
MAP2	Human	16–22 GW	Sims et al. [97]
		14 PCW–Newborn	Honig et al. [94]
		16 PCW	Bayatti et al. [82]
	Monkey	E75–160	Mehra and Hendrickson [84]
Synaptojanin	Human	15–37 GW	Arai et al. [98]
Synaptophysin	Human	10 PCW	Bayatti et al. [82]
NURR1	Human	15–22 PCW	Wang et al. [83]
TBR1	Human	9–12 PCW	Bayatti et al. [82]
α2zinc-binding globulin	Human	14 PCW	Wang et al. [83]
CTGF	Human	22 PCW	Wang et al. [83]
Fetuin	Human	14 PCW	Wang et al. [83]
		24–40 PCW	Elsas et al. [99]
Nogo-A	Human	16–36 PCW	Haybaeck et al. [100]

rodent brain [107]. Activation of subplate neurons by glutamatergic thalamocortical axons has been demonstrated in fetal brains of cats and rodents [101,103] (for review see [34,41]). While there is no convincing evidence on the activation of subplate neurons by glutamatergic corticocortical fibers, it stands to reason to assume its existence because corticocortical fibers represent the most massive component of axons waiting in the subplate [1,3,29,40].

The first experimental evidence for the existence of "waiting" thalamocortical axons in the subplate was provided in the visual cortex of fetal rhesus monkeys [28], and it was since extensively documented that all afferent axons wait in the subplate (and eventually establish temporary synapses with subplate neurons) for a prolonged period of time, at least in humans and nonhuman primates [1,3,29,34,40,41]. The ingrowth of different cortical afferent systems (thalamocortical, basal forebrain, corticocortical) in the subplate is sequential (but partly overlapping) and enfolds throughout the entire fetal period. The same holds for the relocation of these afferents from the subplate into the cortical plate after 24 PCW. For example, thalamocortical axons in the human fetal brain invade the presubplate already at 13 PCW [29,57], form extensive axonal plexuses in the subplate throughout the midfetal period (15–20 PCW), accumulate in the superficial subplate around 22 PCW, and penetrate the cortical plate after 24 PCW [29,54,55]. The example of thalamocortical afferents suggests that the subplate serves as a substrate for a special geometry and directionality of fiber growth [23,29]: fibers are first directed from basal to dorsal pallial segments, and later grow radially through the subplate into the cortical plate. During their basal-to-dorsal growth,

fibers are forming large axonal bundles or strata in the intermediate zone, that is, the fetal white matter, then turn obliquely to enter the subplate, and after a prolonged waiting period they finally radially relocate from the subplate into the cortical plate.

During their waiting period within the subplate, afferent axons are loosely arranged [29] and embedded in a voluminous and hydrophyllic extracellular matrix [58,60], which contains a variety of axon guidance molecules. Some of these axons make early synapses with subplate neurons and thus make the subplate the major site of early synaptogenesis in the fetal human cortex.

The damage of the subplate during the waiting period and relocation of thalamocortical afferents can damage not only the development of thalamocortical circuitry but also the columnar development of the cortical plate [30,31] (for review see [34,41]). Accordingly, the damage of thalamocortical system in the human preterm infant may lead to abnormal cerebral development [108,109]. Our long-term studies suggest that the most critical period is during the accumulation of thalamocortical fibers in the superficial subplate (around 22 PCW) and during their relocation into the cortical plate at 24–28 PCW [1–3,29,40,110]. However, it should be noted that subplate continues to function as waiting compartment for growing long corticocortical afferents until birth [3] and it may continue to serve as mini-waiting compartment for growth of short cortico-cortical connections even after birth [7].

Subplate Neurons Serve as Presynaptic Elements in the Fetal Cortical Circuitry

The axons of subplate neurons establish synapses with (1) other subplate neurons, (2) thalamus, and (3) cortical plate neurons. It seems that glutamatergic presynaptic axons originate from subplate inverted pyramidal neurons which represent up to 50% of subplate neuronal population [68,111]. However, glutamatergic NMDA receptors in the subplate are different from those in the adult cortex and are active at −70 mV [33]. Some subplate cells also project to the thalamus [31,112] but it is not clear whether their neurotransmitter is really glutamate.

Various subplate interneurons contain GABA and neuropeptides and seem to contact other subplate neurons. However, GABA receptors on subplate neurons are also functionally different from those in the adult brain [113] and activation of subplate GABA neurons in rodents leads to the activation of depolarizing GABA receptors on other subplate neurons [33,114].

The subplate neurons also send ascending axons to the overlying cortical plate [34,41]. Such projections were not directly demonstrated in the human fetal cortex, but if they are present their synaptic action in the cortical plate should occur after 23 or 24 PCW, because there are no synapses in the cortical plate before that time [27].

Subplate Neuronal Circuitry and its Functions

The physiological properties of subplate neurons and their local and extrinsic (input–output) circuitry were first described in the cat [41,101,102,111]. This was subsequently thoroughly elaborated in neurophysiological studies using rodents [33–35,104,107,115,116]. The early subplate circuitry displays oscillatory features [33,116] and has been described as having an endogenous activity which does not depend on extrinsic input [34].

In the human fetal brain, synapses may be found as deep as 4–6 mm below the cortical plate, on cell bodies and dendrites of subplate neurons [29]. This shows that human subplate neurons also serve as postsynaptic elements for early cortical circuitry. While most of these synapses are asymmetric (excitatory?), some symmetrical (inhibitory?) synapses are located on cell bodies of subplate neurons [29]. Similar findings were reported in fetal cats [103].

As already mentioned, before 24 PCW, the subplate is the major site of synaptogenesis in the human fetal brain, whereas there are no synapses in the cortical plate; but, cortical plate neurons seem to communicate through gap junctions [29,33,34,104,117,118]. However, synapses are also present on apical dendritic branches of cortical plate pyramidal neurons situated in the marginal zone, which serves as another early site of synaptogenesis in the fetal cortex [27,29]. The fact that the subplate serves as the major site of synaptic activity in midfetal and preterm brain has obvious functional and clinical implications: (1) first external stimuli (such as tactile or pain stimuli), travelling along thalamocortical axons, reach the subplate circuitry and extend to the cortical plate only after 24 PCW; (2) early influences of monoaminergic and cholinergic modulatory systems are also centered on transient subplate circuitry; (3) initial corticocortical connections remain centered on the subplate circuitry even after 28 PCW (when thalamocortical and basal forebrain afferents are already settled and active in the cortical plate); (4) the prolonged co-existence of transient (subplate-centered) and permanent (cortical plate-centered) cortical circuitry represents a salient feature of human cortical development [1,2] during at least 6 months (i.e., three last prenatal and three-first postnatal months); (5) the transient subplate circuitry probably represents an important component of the emerging resting state activity during the perinatal period [119–122].

In conclusion, the transient subplate-centered cortical circuitry consists of elaborated local (modular?) circuits (Fig. 2) which receive specific inputs and send specific outputs, and continues to exist during the initial formation of the equivalent cortical plate-based (i.e., adult-like) cortical circuitry. Thus, the subplate represents vital but hitherto neglected component of the human fetal cortical connectome.

Subplate Involvement in Neuronal Migration and Developmental Brain Disorders

Subplate as the Zone of Neuronal Migration

After its formation (13–15 PCW), the subplate becomes the thickest and the most voluminous transient compartment of the human fetal cerebral wall, reaching its developmental peak (6–10 mm in thickness!) between 28 and 32 PCW. It should be noted that during this entire period postmitotic cortical neurons migrate through the subplate on their way to the cortical plate. This also means that radial glial guides (along which these neurons migrate) are continuously present in the subplate. Thus, the

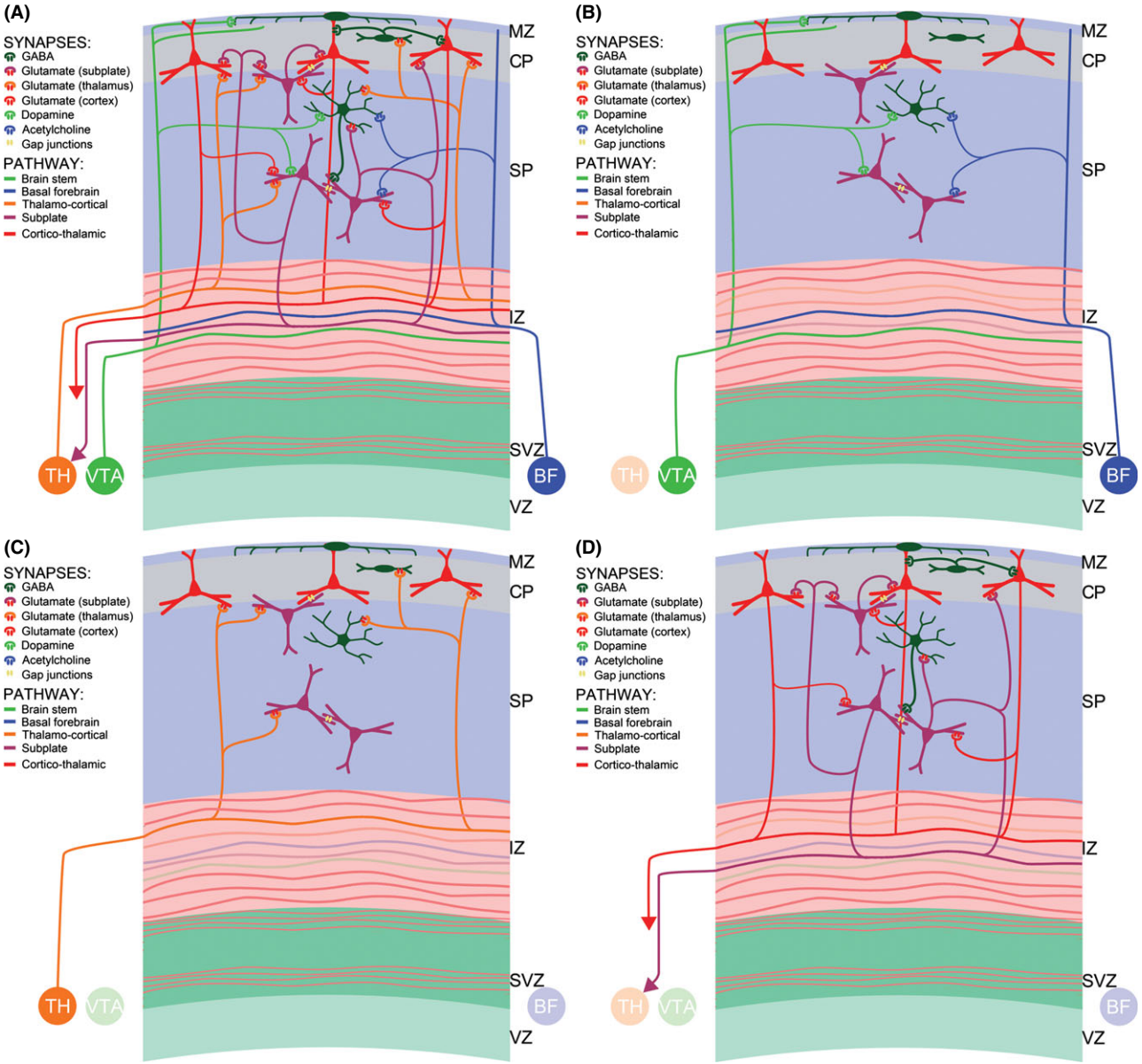

Figure 2 Simplified diagram (A) of transient subplate circuitry during the late midfetal period (24–26 PCW). Different presynaptic axons and postsynaptic receptors are represented by different colors (see legends along the diagrams). To enhance the understanding and visibility, three major circuitry systems are displayed separately: monoaminergic (**B**), thalamocortical (**C**) and intrinsic subplate plus corticothalamic (**D**). VZ and SVZ, ventricular and subventricular zone; IZ, intermediate zone; SP, subplate; CP, cortical plate; MZ, marginal zone.

subplate not only represents a large portion of the total migratory route, but may in fact represent a sort of "mine-field" for travelling last-generated migratory neurons (destined to corticocortical layers II and III); namely, these neurons continue to migrate after 24 PCW, when many radial glial cells are already transforming into astrocytes within the subplate and thus may not be able to serve as radial guides to migratory neurons.

With respect to generation and migration of subplate neurons themselves in the human or primate brain, very little is known at present. While subplate pyramidal neurons probably use the same radial migratory route as pyramidal neurons of the cortical plate, it is not known why and how they detach from the radial glia already in the subplate instead of continuing their journey to the cortical plate. For example, the reelin produced by Cajal-Retzius cells in the marginal zone has been suggested to act as a stop signal for pyramidal neuron migration, but there is at present no evidence that subplate cells produce reelin [123,124]. Moreover, a recent study suggested that massive loss of Cajal-Retzius cells does not disrupt neocortical layer order [125]. On the other hand, migrating GABA interneurons seem to rely on mechanisms independent of reelin signaling [126] and use predominantly or exclusively tangential routes of migration. But, the exact migratory

route is still unexplored for many subsets of GABA interneurons even in the rodent brain. With respect to human and nonhuman primate brain, it is known that a significant subset of GABA interneurons is generated in the VZ-SVZ and uses tangential migratory route on their way to the cortical plate [127,128]. However, which (if any) of these interneurons are destined to the human subplate and how they settle there remains unknown. In distinction to the cortical plate, the subplate does not show clear laminar organization. Thus, it is difficult to analyze how and why different types of subplate neurons become settled at different subpial depths within the subplate.

Subplate may have a Key Role in Pathogenesis of Migration Disorders and Cortical Dysplasias

At present, there are several classifications of malformations of cortical development, which rely on combination of developmental, genetic and neuroimaging criteria [37–39]. For example, cortical malformations may be broadly divided in disorders of neuronal position, disorders of axonal projection and assembly, and syndromes of cortical disorganization, that is, cortical dysplasias [37]. As genetic studies have identified several genes associated with malformations of cortical development, and some of these genes are involved in pathogenesis of the largest malformation groups such as focal cortical dysplasia, heterotopia and polymicrogyria [39], molecular and genetic approaches opened new vistas for classifying and studying functional consequences and treatment options of various cortical abnormalities, for example, those associated with drug-resistant epilepsy [20,21,39].

Another approach is to classify cortical malformations based on the stage of development at which cortical development was first affected and to use genotype, rather than phenotype, as the basis for classifying disorders [38]. This revised classification [38] proposed that there are four major groups of cortical malformations: (1) Malformations due to abnormal proliferation/apoptosis; (2) Malformations due to abnormal migration; (3) Malformations due to abnormal late neuronal migration and cortical organization; and (4) Malformations of cortical development, not otherwise classified. The first three groups are useful for describing disorders of neurogenesis of all cortical neurons, the radial migration of projection (pyramidal) cortical neurons and tangential migration of cortical interneurons. These three groups can equally apply to the analysis of disorders in neurogenesis and migration of subplate neurons; unfortunately, that kind of analysis has not been applied to subplate neither in humans nor in experimental animals.

If subplate pyramidal neurons indeed use the radial glial cells as their migratory routes, any change in signaling properties and contact guidance with glial cells may lead to significant over- or underpopulation of subplate with putative excitatory (glutamatergic) and projection neurons. For example, this may cause the presence of supernumerary and immature subplate-like neurons in cortical dysplasia, as recently suggested [20,21]. However, it should be noted that this pathology cannot be explained by abnormal survival of fetal subplate neurons normally programmed to undergo developmental cell death, because in the human brain the large majority of subplate neurons survive into adulthood as interstitial neurons of the gyral white matter [44,70].

As already described, the subplate also contains a complex contingent of various axons distributed in a plexiform arrangement. If some subplate GABA- and neuropeptide-containing interneurons use the neurophillic mode of migration (i.e., migration along axonal fascicles), this may explain why they finish scattered within the subplate in a seemingly haphazard manner—and, perhaps, in inappropriate numbers. On the other hand, the subplate extracellular matrix contains all kinds of contact guidance molecules, which may help guide not only growing axons but also migratory neurons to their proper targets. But this also means that any disturbance of this extracellular matrix (e.g., by hypoxic-ischemic lesion in preterm infants) may cause serious disturbances in proper laminar and modular distribution of migratory neurons as well as various types of mis-connection or dis-connection of ingrowing cortical afferents. Therefore, subplate GABA interneurons (especially those of large multipolar type) may become not only supernumerary, but also misplaced at wrong positions and mis-connected with wrong postsynaptic targets as well as being themselves wrong targets for presynaptic afferent axons. This may be another cause for abnormal physiological features of these cells in various types of cortical dysplasia and epilepsy syndromes.

All this shows that, for growing axons and travelling neurons, the subplate may represent not just the "enchanted loom" (to use the well-known expression of Sherrington) for properly constructing adult cerebral cortex, but also the impenetrable and confusing jungle in which the weary travelers remain forever lost and thus contribute to all kinds of improperly designed and abnormal cortical arrangements. We are just becoming to be aware of numerous potential and important roles that subplate neurons may play in the pathogenesis of developmental brain disorders. The developmental neuropathology of the subplate is obviously in its infancy, but, thanks to the availability of modern molecular, genomic, and neuroimaging techniques, it may be steadily and prosperously advanced in the near future.

Acknowledgments

This work has been supported by Croatian Science Foundation (grant no. 09.01/414 to MJ) and University of Zagreb (grant no. 1101275 to MV).

Conflict of Interest

The authors declare no conflict of interest.

References

1. Kostović I, Judaš M. Prolonged coexistence of transient and permanent circuitry elements in the developing cerebral cortex of fetuses and preterm infants. *Dev Med Child Neurol* 2006;**48**:388–393.
2. Kostović I, Judaš M. Transient patterns of cortical lamination during prenatal life: Do they have implications for treatment? *Neurosci Biobehav Rev* 2007;**31**:1157–1168.
3. Kostović I, Judaš M. The development of the subplate and thalamocortical connections in the human foetal brain. *Acta Paediatr* 2010;**99**:1119–1127.
4. Huang H, Zhang J, Wakana S, et al. White and gray matter development in human fetal, newborn, and pediatric brains. *Neuroimage* 2006;**33**:27–38.

5. Huang H, Xue R, Zhang J, et al. Anatomical characterization of human fetal brain development with diffusion tensor magnetic resonance imaging. *J Neurosci* 2009;**29**:4263–4273.
6. Kang HJ, Kawasawa YI, Cheng F, et al. Spatio-temporal transcriptome of the human brain. *Nature* 2011;**478**:483–489.
7. Kostović I, Jovanov-Milošević N, Radoš M. Perinatal and early postnatal reorganization of the subplate and related cellular compartments in the human cerebral wall as revealed by histological and MRI approaches. *Brain Struct Funct* 2014;**219**:231–253.
8. Fransson P, Metsäranta M, Blennow M, Aden U, Lagercrantz H, Vanhatalo S. Early development of spatial patterns of power-law frequency scaling in fMRI resting-state and EEG data in newborn brain. *Cereb Cortex* 2013;**23**:638–646.
9. Pletikos M, Sousa AM, Sedmak G, et al. Temporal specification and bilaterality of human neocortical topographic gene expression. *Neuron* 2014;**81**:321–332.
10. Zhang J, Evans A, Hermoye L, et al. Evidence of slow maturation of the superior longitudinal fasciculus in early childhood by diffusion tensor imaging. *Neuroimage* 2007;**38**:239–247.
11. Petanjek Z, Judaš M, Kostović I, Uylings HB. Lifespan alterations of basal dendritic trees of pyramidal neurons in the human prefrontal cortex: A layer-specific pattern. *Cereb Cortex* 2008;**18**:915–929.
12. Petanjek Z, Judaš M, Šimić G, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc Natl Acad Sci USA* 2011;**108**:13281–13286.
13. Colonnese M, Khazipov R. Spontaneous activity in developing sensory circuits: Implications for resting state fMRI. *Neuroimage* 2012;**62**:2212–2221.
14. Omidvarnia A, Fransson P, Metsäranta M, Vanhatalo S. Functional bimodality in the brain networks of preterm and term human newborns. *Cereb Cortex* 2014; **24**:2657–2668.
15. Volpe JJ. Brain injury in premature infants: A complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009;**8**:110–124.
16. McFadden K, Minshew NJ. Evidence for dysregulation of axonal growth and guidance in the etiology of ASD. *Front Hum Neurosci* 2013;**7**:671.
17. Ebert DH, Greenberg ME. Activity-dependent neuronal signaling and autism spectrum disorder. *Nature* 2013;**493**:327–337.
18. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci* 2002;**25**:409–432.
19. Lewis DA, Cruz D, Eggan S, Erickson S. Postnatal development of prefrontal inhibitory circuits and the pathophysiology of cognitive dysfunction in schizophrenia. *Ann N Y Acad Sci* 2004;**1021**:64–76.
20. Cepeda C, André VM, Levine MS, et al. Epileptogenesis in pediatric cortical dysplasia: The dysmature cerebral developmental hypothesis. *Epilepsy Behav* 2006;**9**:219–235.
21. Cepeda C, André VM, Wu N, et al. Immature neurons and GABA networks may contribute to epileptogenesis in pediatric cortical dysplasia. *Epilepsia* 2007;**48**(Suppl 5):79–85.
22. Kostović I. Structural and histochemical reorganization of the human prefrontal cortex during perinatal and postnatal life. *Prog Brain Res* 1990;**85**:223–239.
23. Bystron I, Blackemore C, Rakic P. Development of the human cerebral cortex: Boulder Committee revisited. *Nat Rev Neurosci* 2008;**9**:110–122.
24. Miller SP, Vigneron DB, Henry RG, et al. Serial quantitative diffusion tensor MRI of the premature brain: Development in newborns with and without injury. *J Magn Reson Imaging* 2002;**16**:621–632.
25. Miller SP, Ferriero DM, Leonard C, et al. Early brain injury in premature newborns detected with magnetic resonance imaging is associated with adverse early neurodevelopmental outcome. *J Pediatr* 2005;**147**:609–616.
26. Volpe JJ. Encephalopaty of prematurity includes neuronal abnormalities. *Pediatrics* 2005;**116**:221–225.
27. Molliver ME, Kostović I, van der Loos H. The development of synapses in cerebral cortex of human fetus. *Brain Res* 1973;**50**:403–407.
28. Rakic P. Prenatal development of the visual system in rhesus monkey. *Philos Trans R Soc Lond B Biol Sci* 1977;**278**:245–260.
29. Kostović I, Rakic P. Development history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. *J Comp Neurol* 1990;**297**:441–470.
30. Gosh A, Antonini A, McConnell SK, Shatz CJ. Requirement for subplate neurons in the formation of thalamocortical connections. *Nature* 1990;**347**:179–181.
31. Gosh A, Shatz CJ. A role for subplate neurons in the patterning of connections from thalamus to neocortex. *Development* 1993;**117**:1031–1047.
32. Catalano SM, Shatz CJ. Activity-dependent cortical target selection by thalamic axons. *Science* 1998;**281**:559–562.
33. Hanganu IL, Kilb W, Luhmann HJ. Functional synaptic projections onto subplate neurons in neonatal rat somatosensory cortex. *J Neurosci* 2002;**22**:7165–7176.
34. Kanold PO, Luhmann HJ. The subplate and early cortical circuits. *Annu Rev Neurosci* 2010;**33**:23–48.
35. Minlebaev M, Colonnese M, Tsintsadze T, Sirota A, Khazipov R. Early γ oscillations synchronize developing thalamus and cortex. *Science* 2011;**334**:226–229.
36. Moore AR, Zhou WL, Jakocevski I, Zecevic N, Antic SD. Spontaneous electrical activity in the human fetal cortex in vitro. *J Neurosci* 2011;**31**:2391–2398.
37. Ross ME, Walsh CA. Human brain malformations and their lessons for neuronal migration. *Annu Rev Neurosci* 2001;**24**:1041–1070.
38. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. *Neurology* 2005;**65**:1873–1887.
39. Guerrini R, Dobyns WB, Barkovich AJ. Abnormal development of the human cerebral cortex: Genetics, functional consequences and treatment options. *Trends Neurosci* 2008;**31**:154–162.
40. Kostović I, Judaš M. Correlation between the sequential ingrowth of afferents and transient patterns of cortical lamination in preterm infants. *Anat Rec* 2002;**267**:1–6.
41. Allendoerfer KL, Shatz CJ. The subplate, a transient neocortical structure: Its role in the development of connections between thalamus and cortex. *Annu Rev Neurosci* 1994;**17**:185–218.
42. Judaš M, Šestan N, Kostović I. Nitrinergic neurons in the developing and adult human telencephalon: Transient and permanent patterns of expression in comparison to other mammals. *Microsc Res Tech* 1999;**45**:401–419.
43. Aboitiz F. Evolution of isocortical organization. A tentative scenario including roles of reelin, p35/cdk5 and the subplate role. *Cereb Cortex* 1999;**9**:655–661.
44. Judaš M, Sedmak G, Pletikos M. Early history of subplate and interstitital neurons: From Theodor Meynert (1867) to the discovery of the subplate zone (1974). *J Anat* 2010;**217**:344–367.
45. His W. *Die Entwickelung des menschlichen Gehirns während der ersten Monate*. Leipzig, Hirzel: Untersuchungsergebnisse, 1904.
46. Marin-Padilla M. Dual origin of the mammalian neocortex and evolution of the cortical plate. *Anat Embryol* 1978;**152**:109–126.
47. Meyer G. Genetic control of neuronal migrations in human cortical development. *Adv Anat Embryol Cell Biol* 2007;**189**:1–111.
48. Rakic P. Specification of cerebral cortical areas. *Science* 1988;**241**:170–176.
49. Nobin A, Björklund A. Topography of the monoamine neuron systems in the human brain as revealed in fetuses. *Acta Physiol Scand* 1973;**388**(Suppl):1–40.
50. Olson L, Boreus LO, Seiger A. Histochemical demonstration and mapping of 5-hydroxytryptamine- and catecholamine-containing neuron systems in the human fetal brain. *Z Anat Entwicklungsgesch* 1973;**139**:259–282.
51. Zecevic N, Verney C. Development of the catecholamine neurons in human embryos and fetuses with special emphasis on the innervation of the cerebral cortex. *J Comp Neurol* 1995;**351**:509–535.
52. Verney C, Lebrand C, Gaspar P. Changing distribution of monoaminergic markers in the developing human cerebral cortex with special emphasis on the serotonin transporter. *Anat Rec* 2002;**267**:87–93.
53. Kostović I. Prenatal development of nucleus basal is complex and related fiber systems in man: A histochemical study. *Neuroscience* 1986;**17**:1047–1077.
54. Kostović I, Goldman-Rakic PS. Transient cholinesterase staining in the mediodorsal nucleus of the thalamus and its connections in the developing human and monkey brain. *J Comp Neurol* 1983;**219**:431–437.
55. Kostović I, Rakic P. Development of prestriate visual projections in the monkey and human fetal cerebrum revealed by transient cholinesterase staining. *J Neurosci* 1984;**4**:25–42.
56. Kostović I, Molliver ME. A new interpretation of the laminar development of cerebral cortex: Synaptogenesis in different layers of neopallium in the human fetus. *Anat Rec* 1974;**178**:395.
57. Duque A, Krsnik Ž, Kostović I, Rakic P. *Origin and secondary expansion of the transient subplate zone in the developing cerebrum of human and nonhuman primates*. Abstract. Washington DC: Society for Neuroscience, 2014.
58. Kostović I, Judaš M, Radoš M, Hrabač P. Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. *Cereb Cortex* 2002;**12**:536–544.
59. Widjaja E, Geibprasert S, Mahmoodabadi SZ, Blaser S, Brown NE, Shannon P. Alteration of human fetal subplate layer and intermediate zone during normal development on MR and diffusion tensor imaging. *AJNR Am J Neuroradiol* 2010;**31**:1091–1099.
60. Judaš M, Radoš M, Jovanov-Milošević N, Hrabač P, Štern-Padovan R, Kostović I. Structural, immunocytochemical, and MR imaging properties of periventricular crossroads of growing cortical pathways in preterm infants. *AJNR Am J Neuroradiol* 2005;**26**:2671–2684.
61. Prayer D, Kasprian G, Krampl E, et al. MRI of normal fetal brain development. *Eur J Radiol* 2006;**57**:199–216.
62. Corbett-Detig J, Habas PA, Scott JA, et al. 3D global and regional patterns of human fetal subplate growth determined in utero. *Brain Struct Funct* 2011;**215**:255–263.
63. Vanhatalo S, Palva JM, Andersson S, Rivera C, Voipio J, Kaila K. Slow endogenous activity transients and developmental expression of K^+-Cl^- cotransporter 2 in the immature human cortex. *Eur J Neurosci* 2005;**22**:2799–2804.
64. Slater R, Cantarella A, Gallella S, et al. Cortical pain responses in human infants. *J Neurosci* 2006;**26**:3662–3666.
65. Brodmann K. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Leipzig: Johann Ambrosius Barth, 1909.
66. Mrzljak L, Uylings HB, Kostović I, van Eden CG. Prenatal development of neurons in the human prefrontal cortex: I. A qualitative Golgi study. *J Comp Neurol* 1988;**271**:355–386.
67. Mrzljak L, Uylings HB, Van Eden CG, Judaš M. Neuronal development in human prefrontal cortex in prenatal and postnatal stages. *Prog Brain Res* 1990;**85**:182–222.

68. Mrzljak L, Uylings HB, Kostović I, van Eden CG. Prenatal development of neurons in the human prefrontal cortex: I. A qualitative Golgi study. *J Comp Neurol* 1992;**316**:485–496.
69. Kostović I, Rakic P. Cytology and time of origin of interstitial neurons in the white matter in infant and adult human and monkey telencephalon. *J Neurocytol* 1980;**9**:219–242.
70. Judaš M, Sedmak G, Pletikos M, Jovanov-Milošević N. Populations of subplate and interstitital neurons in fetal and adult human telencephalon. *J Anat* 2010;**217**:381–399.
71. Yan XX, Zeng DS, Garey LJ. Prenatal development of GABA-immunoreactive neurons in the human striate cortex. *Dev Brain Res* 1992;**65**:191–204.
72. Zecevic N, Milosevic A. Initial development of γ-Aminobutyric acid immunoreactivity in the human cerebral cortex. *J Comp Neurol* 1997;**380**:495–506.
73. Huntley GW, Hendry SH, Killackey HP, Chalupa LM, Jones EG. Temporal sequence of neurotransmitter expression by developing neurons of fetal monkey visual cortex. *Brain Res* 1988;**471**:69–96.
74. Meinecke DL, Rakic P. Expression of GABA and $GABA_A$ receptors by neurons of the subplate zone in developing primate occipital cortex: Evidence for transient local circuits. *J Comp Neurol* 1992;**317**:91–101.
75. Yan XX, Garey LJ, Jen LS. Prenatal development of NADPH-diaphorase-reactive neurons in human frontal cortex. *Cereb Cortex* 1996;**6**:737–745.
76. Yan XX, Ribak CE. Prenatal development of nicotinamide adenine dinucleotide phosphate-diaphorase activity in the human hippocampal formation. *Hippocampus* 1997;**7**:215–231.
77. Downen M, Zhao ML, Lee P, Weidenheim KM, Dickson DW, Lee SC. Neuronal nitric oxide synthase expression in developing and adult human CNS. *J Neuropathol Exp Neurol* 1999;**58**:12–21.
78. deAzevedo LC, Hedin-Pereira C, Lent R. Diaphorase-positive neurons in the cingulate cortex of human fetuses during second half of gestation. *Anat Embryol* 2002;**205**:29–35.
79. Delalle I, Evers P, Kostović I, Uylings HBM. Laminar distribution of neuropeptide Y-immunoreactive neurons in human prefrontal cortex during development. *J Comp Neurol* 1997;**379**:515–522.
80. Uylings HBM, Delalle I. Morphology of neuropeptide Y-immunoreactive neurons and fibers in human prefrontal cortex during prenatal and postnatal development. *J Comp Neurol* 1997;**379**:523–540.
81. Wai SM, Kindler PM, Lam ETK, Zhang A, Yew DT. Distribution of neuropeptide Y-immunoreactive neurons in the human brainstem, cerebellum, and cortex during development. *Cell Mol Neurobiol* 2004;**24**:667–684.
82. Bayatti N, Moss JA, Sun L, et al. A molecular neuroanatomical study of the developing human neocortex from 8 to 17 postconceptional weeks revealing the early differentiation of the subplate and subventricular zone. *Cereb Cortex* 2008;**18**:1536–1548.
83. Wang WZ, Hoerder-Subedissen A, Oeschger FM, et al. Subplate in the developing cortex of mouse and human. *J Anat* 2010;**217**:368–380.
84. Mehra RD, Hendrickson AE. A comparison of the development of neuropeptide and MAP2 immunocytochemical labeling in the macaque visual cortex during pre and postnatal development. *J Neurobiol* 1993;**24**:104–124.
85. Kostović I, Štefulj-Fučić A, Mrzljak L, Jukić S, Delalle I. Prenatal and perinatal development of the somatostatin-immunoreactive neurons in the human prefrontal cortex. *Neurosci Lett* 1991;**124**:153–156.
86. Huntley GW, de Blas AL, Jones EG. GABAA receptor immunoreactivity in audult and developing monkey sensory-motor cortex. *Exp Brain Res* 1990;**82**:519–535.
87. Lidow MS, Rakic P. Unique profiles of the alpha 1-, alpha 2-, and beta-adrenergic receptors in the developing cortical plate and transient embryonic zones of the rhesus monkey. *J Neurosci* 1994;**14**:4064–4078.
88. Schröder H, Schütz U, Burghaus L, et al. Expressionof the alpha4 isoform of the nicotinic acetylcholine receptor in the fetal human cerebral cortex. *Dev Brain Res* 2001;**132**:33–45.
89. Kordower JH, Mufson EJ. Nerve growth factor receptor-immunoreactive neurons within the developing human cortex. *J Comp Neurol* 1992;**323**:25–41.
90. Chen EY, Mufson EJ, Kordower JH. TRK and p75 neurotrophin receptor systems in the developing human brain. *J Comp Neurol* 1996;**369**:591–618.
91. Meinecke DL, Rakic P. Low-affinity p75 nerve growth factor receptor expression in the embryonic monkey telencephalon: Timing and localization in diverse cellular elements. *Neuroscience* 1993;**54**:105–116.
92. Donoghue MJ, Rakic P. Molecular evidence for the early specification of presumptive functional domains in the embryonic primate cerebral cortex. *J Neurosci* 1999;**19**:5967–5979.
93. Ulfig N. Calcium-binding proteins in the human developing brain. *Adv Anat Embryol Cell Biol* 2002;**165**:1–92.
94. Honig LS, Hermann K, Shatz CJ. Developmental changes revealed by immunohistochemical markers in human cerebral cortex. *Cereb Cortex* 1996;**6**:794–806.
95. Chan WJ, Xia CL, Dong DC, Heizmann CW, Yew DT. Differential expression of S100 proteins in the developing human hippocampus and temporal cortex. *Microsc Res Tech* 2003;**60**:600–613.
96. Xu G, Broadbelt KG, Haynes RL, et al. Late development of the GABAergic system in the human cerebral cortex and white matter. *J Neuropathol Exp Neurol* 2011;**70**:841–858.
97. Sims KB, Crandall JE, Kosik KS, Williams RS. Microtubule-associated protein 2 (MAP2) immunoreactivity in human fetal neocortex. *Brain Res* 1988;**449**:192–200.
98. Arai Y, Ijuin T, Itoh M, Takenawa T, Takashima S, Becker LE. Developmental changes of synaptojanin expression in the human cerebrum and cerebellum. *Dev Brain Res* 2001;**129**:1–9.
99. Elsas J, Sellhaus B, Herrmann M, et al. Fetuin-A in the developing brain. *Dev Neurobiol* 2012;**73**:354–369.
100. Haybaeck J, Llenos IC, Dulay RJ, et al. Expression of Nogo-A is decreased with increasing gestational age in the human fetal brain. *Dev Neurosci* 2012;**34**:402–416.
101. Antonini A, Shatz CJ. Relation between putative transmitter phenotypes and connectivity of subplate neurons during cerebral cortical development. *Eur J Neurosci* 1990;**2**:744–761.
102. Friauf E, Shatz CJ. Changing patterns of synaptic input to subplate and cortical plate during development of visual cortex. *J Neurophysiol* 1991;**66**:2059–2071.
103. Herrmann K, Antonini A, Shatz CJ. Ultrastructural evidence for synaptic interactions between thalamocortical axons and subplate neurons. *Eur J Neurosci* 1994;**6**:1729–1742.
104. Hanganu IL, Kilb W, Luhmann HJ. Spontaneous synaptic activity of subplate neurons in neonatal rat somatosensory cortex. *Cereb Cortex* 2001;**11**:400–410.
105. Molliver ME, Kristt DA. The fine structural demonstration of monoaminergic synapses in immature rat neocortex. *Neurosci Lett* 1975;**1**:305–310.
106. Smiley JF, Levey AI, Mesulam MM. Infracortical interstitial cells concurrently expressing m2-muscarinic receptors, acetylcholinesterase and nicotinamide adenine dinucleotide phosphate-diaphorase in the human and monkey cerebral cortex. *Neuroscience* 1998;**84**:755–769.
107. Hanganu IL, Luhmann HJ. Functional nicotinic acetylcholine receptors on subplate neurons in neonatal rat somatosensory cortex. *J Neuorphysiol* 2004;**92**:189–198.
108. Counsell SJ, Allsop JM, Harrison MC, et al. Diffusion-weighted imaging of the brain in preterm infants with focal and diffuse white matter abnormality. *Pediatrics* 2013;**112**:1–7.
109. Ball G, Boardman JP, Aljabar P, et al. The influence of preterm birth on the developing thalamocortical connectome. *Cortex* 2013;**49**:1711–1721.
110. Kostovic I, Judaš M. Early development of neuronal circuitry of the human prefrontal cortex. In: Gazzaniga MS, editors. *The cognitive neuroscience*, 4th edn. A Bradford Book. Cambridge/London: The MIT Press, 2009; 29–47
111. Friauf E, McConnell SK, Shatz CJ. Functional synaptic circuits in the subplate during fetal and early postnatal development of cat visual cortex. *J Neurosci* 1990;**10**:2601–2613.
112. Molnár Z, Adams R, Blakemore C. Mechanisms underlying the early establishment of thalamocortical connections in the rat. *J Neurosci* 1998;**18**:5723–5745.
113. Rivera C, Li H, Thomas-Crusells J, et al. BDNF-induced TrkB activation down-regulates the K^+-Cl^- cotransporter KCC2 and impairs neuronal Cl^- extrusion. *J Cell Biol* 2002;**159**:747–752.
114. Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsaki G. Early motor activity drives spindle bursts in the developing somatosensory cortex. *Nature* 2004;**432**:758–761.
115. Hanganu IL, Okabe A, Lessmann V, Luhmann HJ. Cellular mechanisms of subplate-driven and cholinergic input-dependent. Network activity in the neonatal rat somatosensory cortex. *Cereb Cortex* 2009;**19**:89–105.
116. Luhmann HJ, Kilb W, Hanganu-Opatz IL. Subplate cells: Amplifiers of neuronal activity in the developing cerebral cortex. *Front Neuroanat* 2009;**3**:19.
117. Zecevic N. Cellular composition of the telencephalic wall in human embryos. *Early Hum Dev* 1993;**32**:131–149.
118. Zecevic N, Milosevic A, Rakic S, Marin-Padilla M. Early development and composition of the human primordial plexiform layer: An immunohistochemical study. *J Comp Neurol* 1999;**412**:241–254.
119. Doria V, Beckmann CF, Arichi T, et al. Emergence of resting state networks in the preterm human brain. *Proc Natl Acad Sci USA* 2010;**107**:20015–20020.
120. Smyser CD, Inder TE, Shimony JS, et al. Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex* 2010;**20**:2852–2862.
121. Fransson P, Aden U, Blennow M, Lagercrantz H. The functional architecture of the infant brain as revealed by resting-state fMRI. *Cereb Cortex* 2011;**21**:145–154.
122. Hoff GE, Van den Heuvel MP, Benders MJ, Kersbergen KJ, De Vries LS. On development of functional brain connectivity in the young brain. *Front Hum Neurosci* 2013;**7**:650.
123. Pla R, Borrell V, Flames N, Marin O. Layer acquisition by cortical GABAergic interneurons is independent of Reelin signaling. *J Neurosci* 2006;**26**:6924–6934.
124. Morin SM, Gehlert DR. Distribution of NPY Y5-like immunoreactivity in the rat brain. *J Mol Neurosci* 2006;**29**:109–114.
125. Yoshida M, Assimacopoulos S, Jones KR, Grove EA. Massive loss of Cajal-Retzius cells does not disrupt neocortical layer order. *Development* 2006;**133**:537–545.
126. Tabata H, Nakajima K. Multipolar migration: The third mode of radial neuronal migration in the developing cerebral cortex. *J Neurosci* 2003;**23**:9996–10001.
127. Letinic K, Rakic P. Telencephalic origin of human thalamic GABAergic neurons. *Nat Neurosci* 2001;**4**:931–936.
128. Letinic K, Zoncu R, Rakic P. Origin of GABAergic neuron sin the human neocortex. *Nature* 2002;**417**:645–649.

