Development of Structural and Functional Connectivity

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Glossary

Fiber myelination brain maturational mechanism corresponding to the ensheathment around neuronal axons of oligodendrocytes' processes that form the myelin sheaths. It leads to an increase in the conduction speed of the nerve impulse and progresses from the second part of pregnancy to the end of adolescence with a specific calendar across white matter bundles and cerebral regions.

Subplate transient cerebral compartment containing the most differentiated postmigratory neurons, observed between the intermediate zone (fetal white matter) and the cortical plate between 13 PCW and around term age (still observed in the first postnatal months in some frontal association regions).

Abbreviations

AF	Arcuate fasciculus
ALIC	Anterior limb of the internal capsule
CC	Corpus callosum (g/b/s, genu/body/splenium)
CG	Cingulum (inf/sup, inferior/superior parts)
CST	Corticospinal tract (inf/mid/sup, inferior/middle/superior portions)
DSI	Diffusion spectrum imaging
DTI	Diffusion tensor imaging
DWI	Diffusion-weighted imaging
EC	External capsule
EEG	Electroencephalography
ERP	Event-related potentials
FA	Fractional anisotropy
fcMRI	Functional connectivity MRI
FX	Fornix
GA	Gestational age
GM	Gray matter
iFOF	Inferior fronto-occipital fasciculus
ILF	Inferior longitudinal fasciculus
MD	Mean diffusivity
MRI	Magnetic resonance imaging
OR	Optic radiations
PCW	Postconceptional weeks
SLF	Superior longitudinal fasciculus
STT	Spinothalamic tract
T_1	Longitudinal relaxation time
T_1w	T_1-weighted
T_2	Transverse relaxation time
T_2w	T_2-weighted
UF	Uncinate fasciculus
w GA	Weeks of gestational age

Introduction

During the early fetal period, there are few axonal pathways and synaptic connections already established in the human brain. Thus, starting with this period, we have a unique opportunity to follow the step-by-step, complex, but sequential development of cerebral connectivity, until all major connections become established in the late fetal (preterm) period. Even though the pathways' connectivity and the cortical circuitry are not fully established yet in preterm newborns, brain regions are organized early on into networks specialized to process sensorimotor and cognitive functions (Mahmoudzadeh et al., 2013). These functional networks further develop, mature, and refine until the end of adolescence. In this article, we aim to describe the early development of connectivity, from the fetal to the postnatal periods, as mapped in postmortem histological studies and *in vivo* MRI studies of fetuses, newborns, and infants. We successively detail (1) how the structural connectivity first develops, (2) how the white matter pathways then become myelinated and functionally mature, and (3) how functional connectivity emerges in the course of development.

Development of the Structural Connectivity: Fetal and Preterm Periods

It is important to note that (1) transient fetal patterns of cerebral connectivity differ significantly from postnatal connectivity; (2) prenatal development of connectivity is regulated and coordinated through interactions with other histogenetic events, such as proliferation, migration, cell aggregation, molecular specification of neuronal phenotypes, cell death, and myelination; and (3) two major connectivity networks (extrinsic modulatory and intrinsic local cortical networks) (for reviews, see Kostovic & Judas, 2006, 2007, 2010) remain largely unexplored because their structural and functional development cannot be visualized by current imaging methods. While there are many well-described phases of connectivity development (Kostovic & Judas, 2002, 2006, 2007, 2010; Kostovic & Rakic, 1990; Marin-Padilla, 1978; Meyer, Schaaps, Moreau, & Goffinet, 2000), here, we use a simplified division of connectivity formation into (a) early fetal (9–15 postconceptional weeks (PCW)), (b) midfetal (15–23 PCW), (c) early preterm (24–28 PCW), and (d) late preterm (29–34 PCW) period.

Early Fetal Period (9–15 PCW)

During this period, the overall density of connectivity and synaptic contacts is low, and dominant processes are growth and pathfinding of major afferent and efferent pathways within the intermediate zone (fetal white matter) and widespread innervation of target regions by modulatory monoamine and acetylcholine afferent fibers (Figures 1 and 5(a)). While most neurons giving rise to future cortico-cortical connections are not yet generated, there is already a well-defined internal capsule (between the thalamus and striatum) that contains massive thalamocortical fibers directed toward the lateral cerebral wall and growing efferent (motor) cortico-subcortical projection pathways. Although thalamocortical fibers radiate toward the cerebral wall, they do not penetrate the cortical plate and do not establish synapses in it (Figure 1). The modulatory monoamine brain stem afferent fibers are already present above and below the cortical plate (Berger & Alvarez, 1994; Berger, Alvarez, & Goldman-Rakic, 1993; Nobin & Bjorklund, 1973; Olson, Boreus, & Seiger, 1973; Verney, 1999; Verney, Lebrand, & Gaspar, 2002; Zecevic & Verney, 1995). In contrast to neocortical fiber systems, which do not display compact bundles but spread widely in radial direction, there are several limbic bundles (Figures 1 and 5(a)), which can already be easily delineated and identified on histological and MRI/DTI images (Vasung et al., 2010). These bundles are the fornix, stria terminalis, and cingulum, which originate

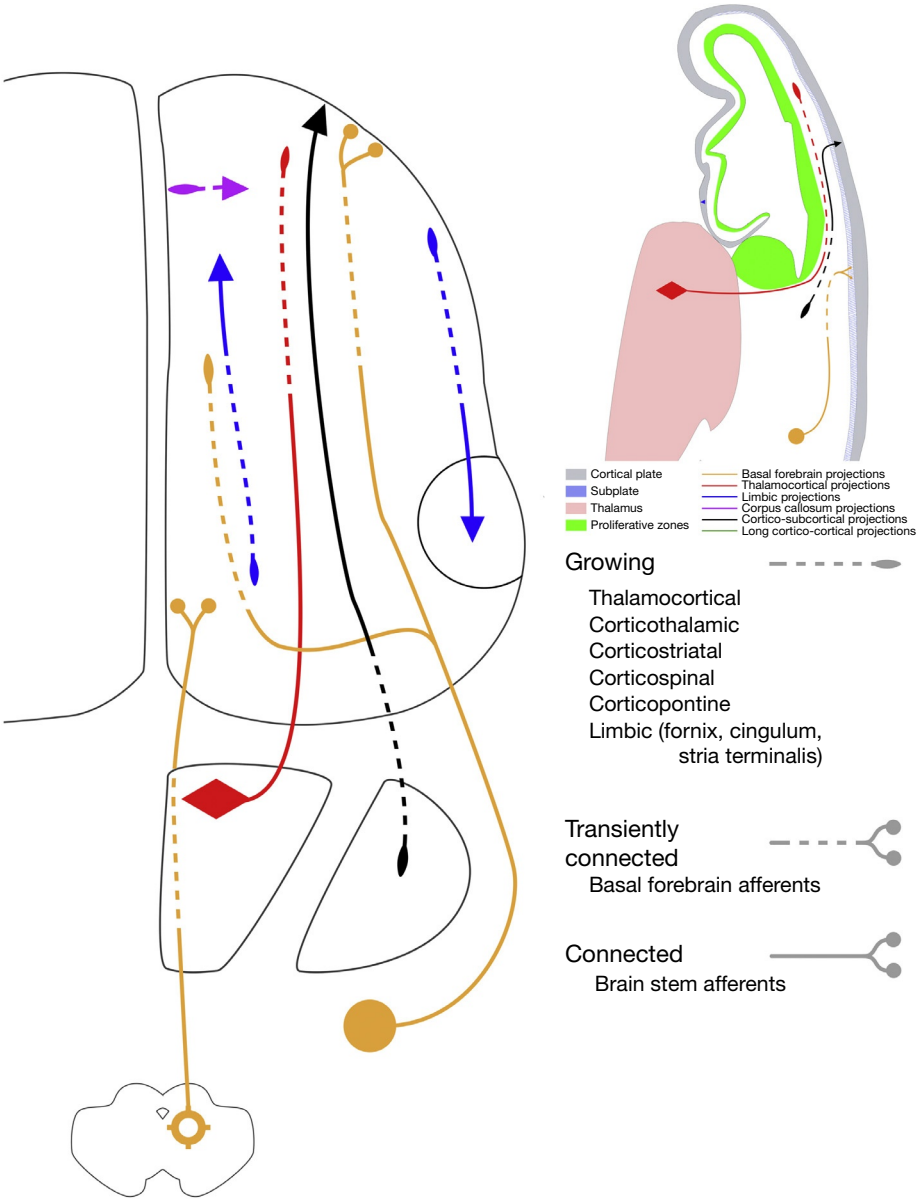

Figure 1 Growing pathways during the early fetal period. During the early fetal period (here illustrated at 11 PCW), growing pathways are predominantly longitudinally oriented, involved in growth and pathfinding within the intermediate zone and establishing transient connections within the subplate.

from the subcortical limbic nuclei (the amygdala) and within the medial limbic cortex (the hippocampus and gyrus cinguli). The key event between 13 and 15 PCW is the formation of fiber- and synapse-rich fetal subplate zone (Kostovic & Rakic, 1990), which occurs by expansion and delamination of the deep cortical plate in which afferent fibers are significantly evolved. The subplate also contains the most differentiated postmigratory neurons.

Midfetal Period (15–23 PCW)

This period is characterized by transient lamination of fetal cerebral wall and transient connectivity patterns (Kostovic & Judas, 2002, 2006, 2007, 2010; Kostovic, Judas, Rados, & Hrabac, 2002). Thalamocortical and basal forebrain afferent fibers form a plexiform network within the subplate 'waiting' compartment and establish numerous transient synapses with subplate neurons (Figure 2). Subplate neurons contain both GABA and glutamate and numerous neuropeptides. They not only serve as cortical 'input' targets for ingrowing afferent fibers and 'output' sources of early efferent projections but also form important and already active endogenous cortical circuitry (Kostovic & Judas, 2006, 2007, 2010). Moreover, the subplate already serves as an associative cortico-cortical system for the medial cortex. Namely, in the gyrus cinguli, the subplate receives voluminous fiber projection from the precingulate area and the anterior cingulate cortex, which connect these areas with the intermediate and posterior cingulate areas (Figure 2). Thus, at least, the cingulate component of medial network hubs (Hagmann et al., 2010) should be already developed during

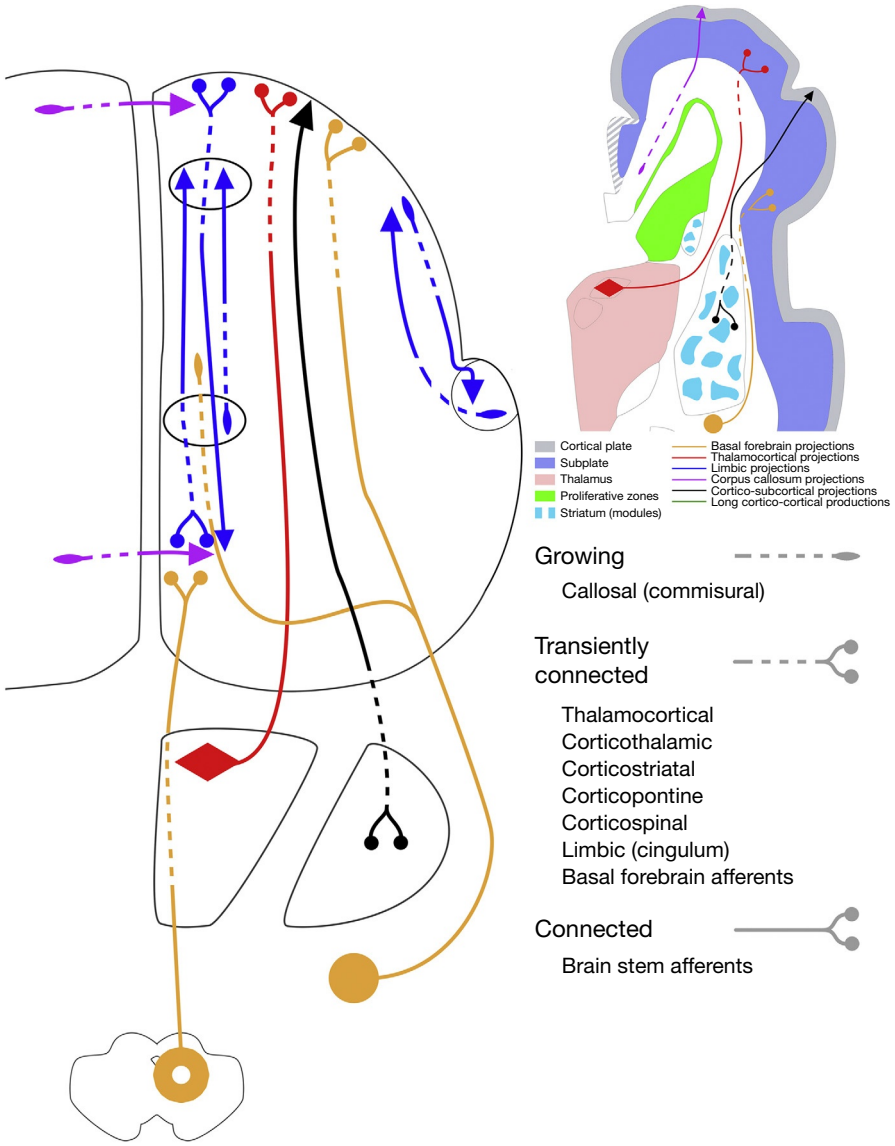

Figure 2 Growing pathways during the early preterm period. At the beginning of the early preterm period (24 PCW), the relocation of thalamocortical and basal forebrain afferent fibers from the subplate into the cortical plate begins and leads to initial synaptogenesis within the cortical plate and the establishment of the first permanent connectivity. Note the early growth of long and short medial (limbic) cortico-cortical connectivity and modular termination of efferent corticostriatal projections.

the midfetal period. The early development of the cingulum bundle is associated with early synaptogenesis in the cingulate cortex (Bourgeois, Goldman-Rakic, & Rakic, 1994; Kostovic & Krmpotic, 1976; Rakic, Bourgeois, & Goldman-Rakic, 1994). Major cortical efferent pathways already penetrate their targets in the striatum, the pons, and the spinal cord. The corticostriatal projections display a modular pattern (**Figures 2** and **3**) because they selectively target the striatal island and matrix compartments (Goldman-Rakic, 1981). The massive corticopontine pathway (**Figure 5(a)**) can be easily identified on DTI images (Vasung et al., 2010). On the other hand, the corpus callosum is still growing, but it can be already visualized by modern imaging methods both *in vivo* and *in vitro* (Bui et al., 2006; Dubois et al., 2013; Judas et al., 2005; Kasprian et al., 2008; **Figure 4**). There is also a progressive differentiation of fiber systems in well-defined tangential axon strata within the intermediate zone, especially in frontopolar and occipitopolar regions (Judas et al., 2005; Kostovic & Judas, 2010; Kostovic et al., 2002). Another important feature is the development of periventricular crossroads (Judas et al., 2005), that is, intersections of growing radial (thalamocortical and corticofugal), transverse (callosal), and sagittal (associative) pathways (**Figure 5(b)**).

Early Preterm Period (24–28 PCW)

The period after 22 PCW is interesting both biologically and clinically, because the development of the brain and its functions may now be monitored *in vivo* even in the extrauterine

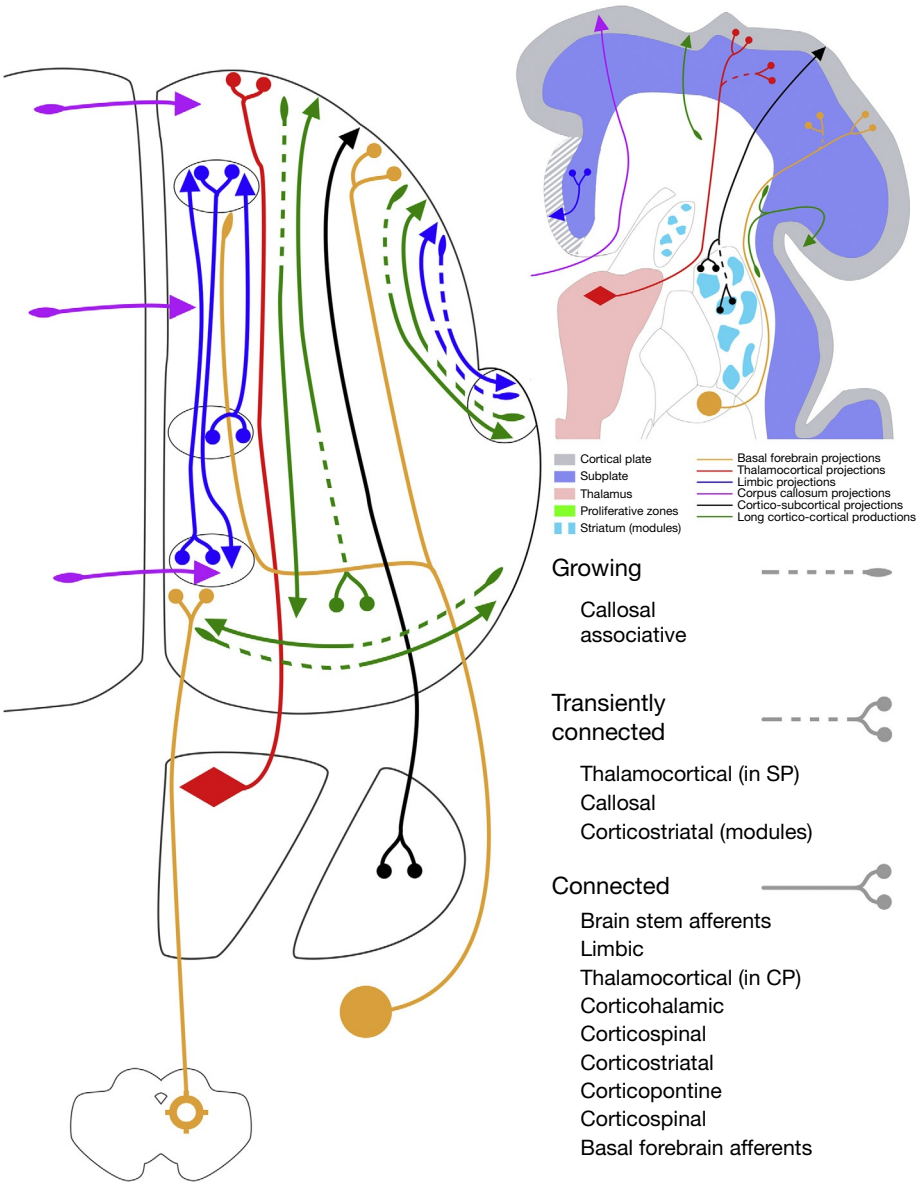

Figure 3 Growing pathways during the late preterm period. At the end of the early preterm period (28 PCW) and during the later preterm period (29–34 PCW), there is a rapid development of both afferent cortical connectivity and efferent cortical connectivity in both longitudinal and transverse directions. Note that, although few neocortical associative pathways develop early (see text), most cortico-cortical long pathways are still growing and short cortico-cortical connections remain poorly developed.

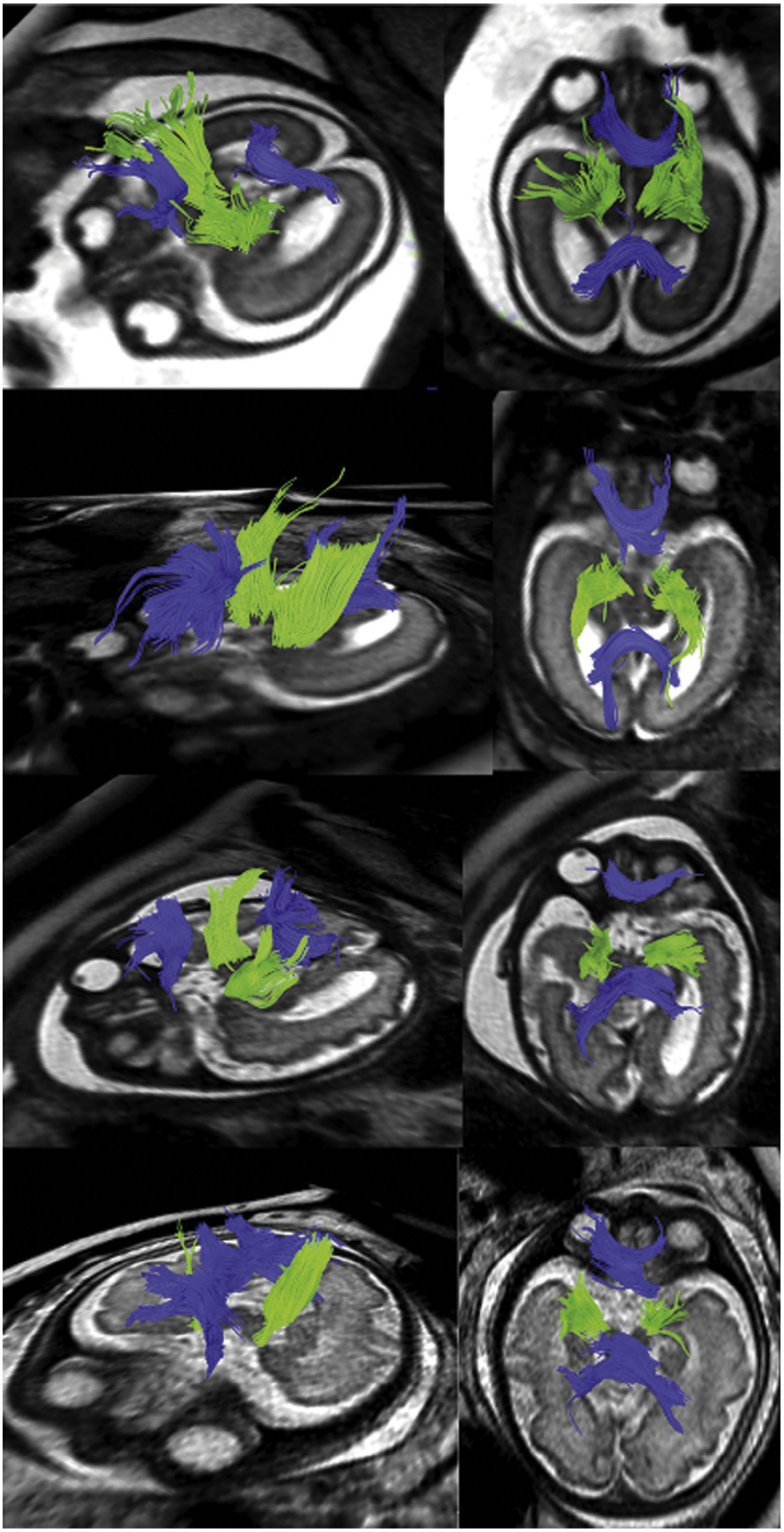

Figure 4 Pathways tractography in fetuses *in utero*. Sensorimotor and callosal trajectories at 24w GA (upper row), 26w GA, 31w GA, and 35w GA (lower row). Reproduced with permission from Kasprian, G., Brugger, P. C., Weber, M., Krssak, M., Krampl, E., Herold, C., et al. (2008). In utero tractography of fetal white matter development. *Neuroimage*, *43*(2), 213–24.

environment, in the case of prematurely born babies, by combining structural approaches such as MRI, volumetric studies of fiber- and synapse-rich transient compartments of the fetal cerebral wall, and functional approaches such as electroencephalography (EEG), near-infrared spectroscopy (NIRS), and resting-state fMRI.

The major event in the structural development of connectivity is relocation of thalamocortical and basal forebrain afferent fibers from the subplate to the cortical plate (**Figure 2**) in the central, frontal, temporal, and occipital regions (Kostovic, 1986; Kostovic & Goldman-Rakic, 1983; Kostovic & Rakic, 1984, 1990; Krmpotic-Nemanic, Kostovic, Kelovic, & Nemanic, 1980; Krmpotic-Nemanic, Kostovic, Kelovic, Nemanic, & Mrzljak, 1983). This leads to initial synaptogenesis within the cortical plate (Kostovic & Rakic, 1990; Molliver, Kostovic, & van der Loos, 1973) and the establishment of the first permanent connectivity with future cortical layer IV neurons (**Figures 2** and **3**). These initial thalamocortical connections are crucial for establishment of sensory-expectant cortical functions. For example, peripherally elicited pain stimuli are now conveyed directly to the somatosensory cortical plate and cause activation of its neurons (Slater et al., 2006). Other types of sensory stimulation also elicit cortical evoked potentials (Graziani, Katz, Cracco, Cracco, & Weitzman, 1974; Hrbek, Karlberg, & Olsson, 1973; Novak, Kurtzberg, Kreuzer, & Vaughan, 1989; for review (Kostovic, Judas, Petanjek, & Simic, 1995). This formation of permanent thalamocortical connectivity occurs while the transient fetal circuitry still exists within the subplate, which is the most voluminous compartment in the early preterm brain (Corbett-Detig et al., 2011; Kostovic & Judas, 2006, 2007, 2010; Kostovic & Vasung, 2009; Maas et al., 2004). This prolonged coexistence of transient and permanent cortical circuitry is a salient feature of the developing human cortical connectome (Kostovic & Judas, 2006, 2007).

It should be noted that, in the early preterm brain, some other afferent and efferent pathways also establish permanent contact with their target areas. The most notable is an early development of limbic cortico-cortical connections in the cingulate, entorhinal, and hippocampal cortices (**Figures 2** and **5(b)**). The early growth of long and short limbic cortico-cortical connectivities (Hevner & Kinney, 1996; Kostovic et al., 1989; Kostovic, Petanjek, & Judas, 1993) is in contrast with the much later development of such connectivity in the neocortex. These medial components of the human fetal cortical connectome display high density of synaptically coupled connectivity (**Figure 3**) because short pathways are well developed between the entorhinal and hippocampal cortices already during the midfetal period (Hevner & Kinney, 1996) and the massive cingulum bundle synaptically connects active cingulate cortical areas (Bourgeois et al., 1994; Kostovic & Krmpotic, 1976). In contrast, in the lateral neocortex, long cortico-cortical pathways are still growing and short cortico-cortical connections remain poorly developed (Burkhalter, 1993; Hevner, 2000). However, three neocortical associative pathways develop early in the fetal brain: (1) the periventricular fronto-occipital fascicle (Kostovic et al., 2014), (2) the uncinate fascicle (Takahashi, Folkerth, Galaburda, & Grant, 2012), and (3) the deep portion of the external capsule that contains basal forebrain projections and some rostrocaudally directed associative projections (**Figures 2** and **5(b)**).

Efferent corticostriatal projections display a characteristic modular termination in the island and matrix compartments of the striatum (Goldman-Rakic, 1981), which is more prominent than in the midfetal period but will significantly change after the birth.

The earlier-described changes in the structural development of fetal connectivity may explain the fast maturation of general cortical activity and appearance of behavioral states, such as sleep and wake periods. These maturational shifts are clearly reflected in EEG recordings and readily documented in routine monitoring in intense care units. The most characteristic developmental EEG features are great amplitude (giant) waves and transitions from desynchronized pattern to synchronized pattern (Dreyfuss-Brisac, 1979; Kostovic et al., 1995; Milh et al., 2007; Vanhatalo et al., 2005). Unfortunately, there are very few fMRI data on this early preterm period.

Late Preterm Period (29–34 PCW)

Structural and functional studies revealed that this period is characterized by fast development of connectivity (**Figures 3** and **5(b)**). The main structural event is simultaneous growth of long associative and commissural pathways and the significant increase in the volume of the cerebral white matter (Scott et al., 2011) with clear delineation of most adultlike white matter segments including the initial formation of the gyral white matter (Judas et al., 2005; Judas, Sedmak, & Pletikos, 2010; Judas, Sedmak, Pletikos, & Jovanov-Milosevic, 2010). However, the transient subplate is still present and serves for ingrowth of short cortico-cortical fibers (Kostovic et al., 2014). At the functional level, there is fast and progressive spatiotemporal differentiation with decrease of discontinuous EEG activity. There is also an evident resting-state activity. Somatosensory, visual, and auditory thalamocortical pathways are synaptically active, and transient immature cortical responses are well documented in human premature infants.

In the late preterm, major projection pathways established connection with their target areas (**Figure 3**) where increased synaptophysin immunoreactivity indicates progressive synaptogenesis. Thalamocortical system responses to sensory stimulation are enhanced by the development of local circuitry GABA and peptidergic interneurons in the cortical layer IV. Corticostriatal projections and striatal modular compartments display continuous reorganization, but did not reach adultlike modular pattern.

As there are no reliable immunocytochemical markers for long cortical (glutamatergic) associative and commissural pathways, their growth is at present better visualized by modern diffusion-weighted imaging techniques (DTI or DSI). However, the direction of their growth remains unresolved even when using such techniques. The likely origin of these pathways is the layer III pyramidal neurons (Schwartz & Goldman-Rakic, 1991), which are born relatively late during the midfetal period. *In vivo* and *in vitro* DTI/DSI studies thus far have been able to identify the following associative pathways (**Figure 5**): the periventricular fronto-occipital and uncinate fascicles, already from earlier stages (Huang et al., 2006; Takahashi et al., 2012; Vasung et al., 2010); the inferior fronto-occipital fascicle (Huang et al., 2006); and, close to the term, the superior longitudinal fascicle. In the late preterm infant, the

emergent short cortico-cortical associative pathways also develop between the central and parietal regions (Takahashi et al., 2012) and display early myelination (Kostovic & Vasung, 2009), which was termed 'premyelination' (Dubois et al., 2013) and was noted already in classical neuroanatomical studies (Flechsig, 1920; Von Monakow, 1905) and in modern MRI studies (Counsell et al., 2002; Huppi, Maier, et al., 1998). The short cortico-cortical fibers display arcuate trajectory but are not identical to U-fibers, which connect two adjacent gyri and develop after birth (Kostovic et al., 2014). In the preterm brain, the presence of all projection pathways and growing cortico-cortical pathways contributes to further segmentation of the white matter (Judas et al., 2005; Von Monakow, 1905): (1) periventricular fiber system with the corpus callosum, (2) internal capsule with periventricular crossroad area at its exit, (3) the corona radiata and centrum semiovale, and (4) the gyral white matter (Judas et al., 2005; Kostovic et al., 2014; Vasung et al., 2010). The subplate remnant remains interposed between the gyral white matter and the developing cortical layer VI (Kostovic et al., 2014). The formation of the corona radiata marks the transformation of fetal fiber-architectonic stratification in two perinatal radiating arrangements of major projection pathways (Kostovic et al., 2002, 2014). The postmortem DTI/DSI studies revealed an opposite trend in the development of the cortical plate and distal (gyral) white matter segments; that is, the dominant radial organization of early and midfetal period gradually disappears toward the age at term (Takahashi et al., 2012). In conclusion, the development of long cortico-cortical pathways with emerging short cortico-cortical fibers and already well-developed limbic bundles makes the late fetal cerebral connectome quite dense and similar to the dense connectivity of the newborn brain (**Figures 3** and **5(b)**).

Besides, cortical synaptogenesis in primates is a prolonged postnatal process that involves overproduction of axons, synapses, and dendritic spines and their later elimination in

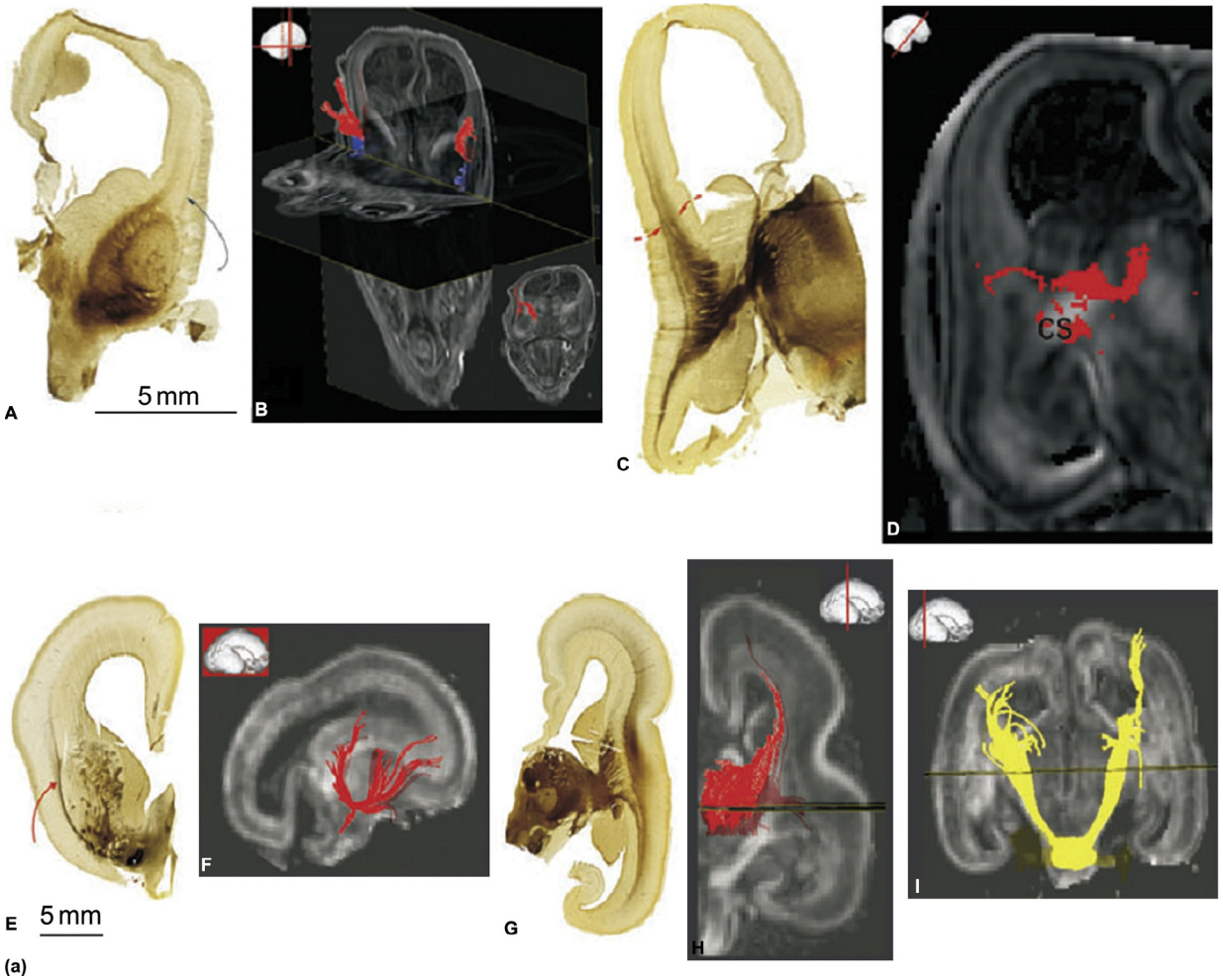

Figure 5 Histological and imaging observations of the developing pathways. (a) A–D: Development of afferent fibers at 11 PCW revealed by AChE histochemical staining (a, c) and diffusion tensor imaging (DTI) (B, D). Red arrows point to the diencephalon–telencephalon junction, and curved arrow to the external capsule; DTI reveals thalamocortical fibers passing through the cerebral stalk (cs) originating from the dorsomedial thalamic complex. E–I: At 15 PCW, basal forebrain fiber bundles are running through the external capsule (E, curved arrow) and external sagittal stratum at 15 PCW (F), while thalamocortical fibers are running through the internal sagittal stratum at 15 PCW (G) and at 17 PCW (H). The DTI also reveals corticopontine fiber bundles at 15 PCW (I). Reproduced with permission from Vasung, L., Huang, H., Jovanov-Milosevic, N., Pletikos, M., Mori, S., & Kostovic, I. (2010). Development of axonal pathways in the human fetal fronto-limbic brain: Histochemical characterization and diffusion tensor imaging. *Journal of Anatomy*, 217(4), 400–417.

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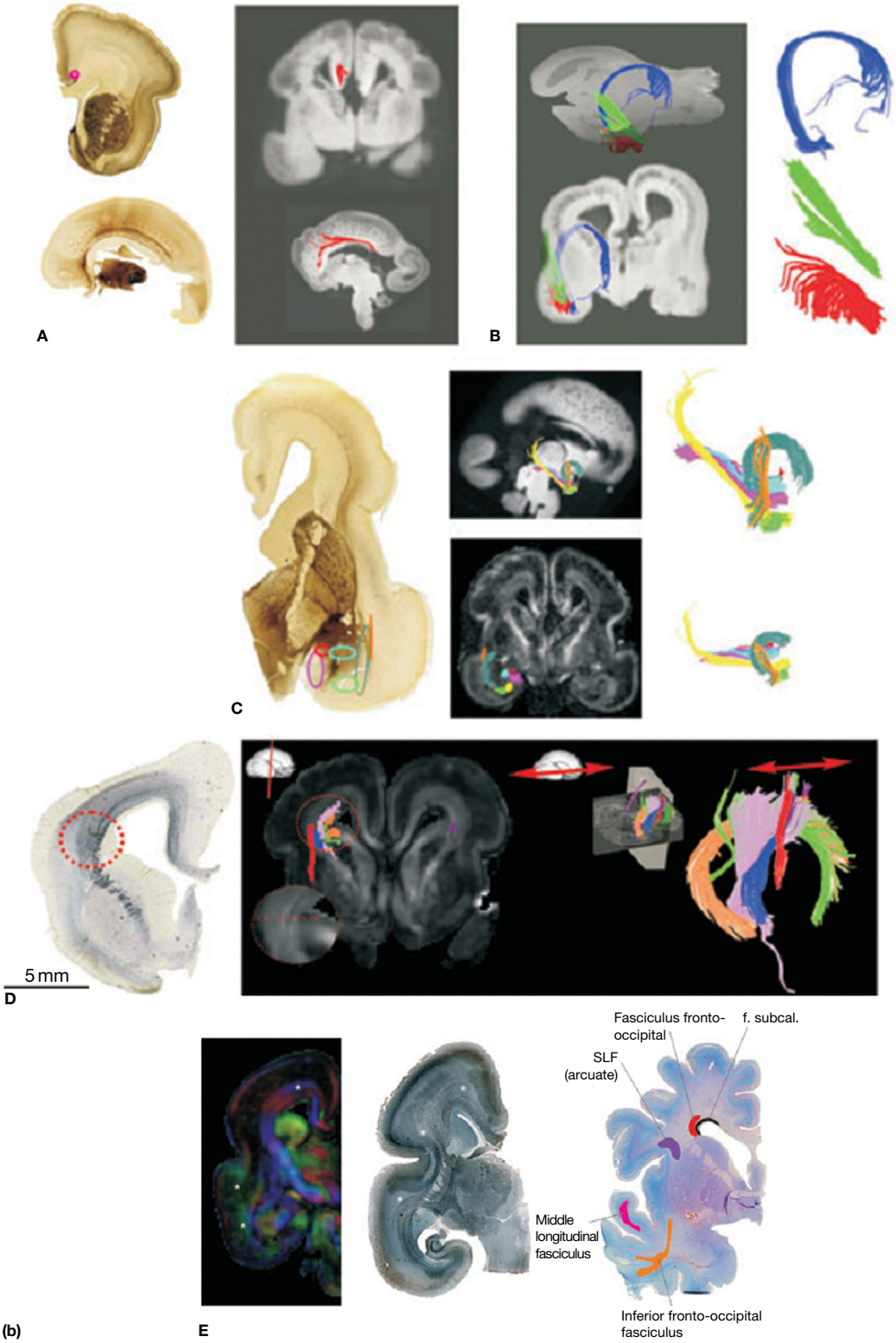

Figure 5 cont'd (b) A–D: Development of associative pathways and crossroad formation during midfetal period. The formation of the cingulum bundle (red color) at 17 PCW is shown by AChE staining (A) and DTI (B). At 15 PCW (B) and 17 PCW (C), the amygdala connections and crossroad C6 become more complex, as revealed by DTI (C). At 19 PCW, the crossroad C1 formation can be visualized by SNAP immunohistochemistry and DTI (D). Note that the crossroad C1 consists of axonal pathways running in radial (thalamocortical), sagittal (associative), and transverse (callosal) directions. (E) The development of associative fiber bundles revealed by DTI color-coded map (left), GNG staining (middle), and PAS staining (right). The prospective trajectories of the associative pathways are indicated by asterisks (left and middle) or outlined by colors (right). Reproduced with permission from Vasung, L., Huang, H., Jovanov-Milosevic, N., Pletikos, M., Mori, S., & Kostovic, I. (2010). Development of axonal pathways in the human fetal fronto-limbic brain: Histochemical characterization and diffusion tensor imaging. *Journal of Anatomy, 217*(4), 400–417.

response to environmental influences (Kostovic & Judas, 2010; Rakic et al., 1994). In humans, this process extends into the third decade (Petanjek et al., 2011). Postnatal synaptogenesis is not restricted to the neocortical layers I–VI but also continues on the interstitial white matter neurons, which are surviving subplate neurons (Judas, Sedmak, & Pletikos, 2010; Judas, Sedmak, Pletikos, & Jovanov-Milosevic, 2010). Thus, there is a considerable postnatal reorganization of cortico-cortical connectivity (for reviews, see Innocenti & Price, 2005; Judas, 2011). For example, during the early postnatal period, in both the rhesus monkey (LaMantia & Rakic, 1990) and human brains (for review, see Innocenti & Price, 2005), there is a huge loss of callosal axons in parallel with the major overproduction of cortical synapses. The postnatal pruning of callosal connections in the rhesus monkey lasts for at least 3–4 postnatal months (LaMantia & Rakic, 1990). On the basis of available data (Kostovic et al., 2014; Kostovic & Rakic, 1990; Petanjek et al., 2011), this process extends in the human brain throughout the first postnatal year and possibly even longer.

Aside from the investigation of precise white matter pathways, the wiring pattern of cerebral connections has recently been reinterpreted in the 'connectome' framework. Already at 30w of gestational age (GA), the networks' architecture demonstrates a small-world modular organization as in the adult brain (van den Heuvel et al., 2014), and cortical hubs are highly connected to form a 'rich club' enabling efficient network communication (Ball et al., 2014). Until 40w GA, the small-world topology further increases (van den Heuvel et al., 2014), and connections between core hubs and the rest of the brain proliferate (Ball et al., 2014). The networks further refine during development, with an increase in global efficiency and integration and a decrease in functional segregation during the first 2 postnatal years (Yap et al., 2011) and childhood (Hagmann et al., 2010). Besides the advantage of having no a priori on pathways' existence and trajectory, a major limitation of structural network analyses in the developing brain is that diffusion-based tractography is highly sensitive to the degree of fiber myelination: some connections would be artifactually missing in comparison with the adult brain insofar as their low maturation would prevent their full reconstruction between the cortical regions.

Maturation of the Structural Connectivity: Late Preterm and Postterm Periods

Indeed, concurrently and subsequently to the organization of white matter networks, connections become progressively mature and functionally efficient through fibers' myelination (Baumann & Pham-Dinh, 2001; Van der Knaap & Valk, 1995a,1995b; Volpe, 2008). This slow process begins after the process of axonal overproduction and pruning and enables to increase the conduction speed of the nerve impulse. In the human brain, its progression follows a different calendar in different bundles and varies across cerebral regions from the second part of pregnancy to the end of adolescence.

At the cellular scale, myelination relies on successive phenomena. The 'premyelinating' state generally refers to the initial period when preoligodendroglial cells increase and settle along the axons (Baumann & Pham-Dinh, 2001) and when the cholesterol and glycolipid concentration starts to increase (Barkovich, Kjos, Jackson, & Norman, 1988; Poduslo & Jang, 1984). The following 'true' myelination process corresponds to the ensheathment of oligodendroglial processes around axons and to the chemical maturation of the myelin sheath with a rising amount of macromolecules (Barkovich et al., 1988; Poduslo & Jang, 1984). At the microscopic scale, the myelination induces major modifications in water molecules' content and compartmentalization (Matsumae et al., 2001) and in protein and lipid contents (Barkovich et al., 1988; Kucharczyk, Macdonald, Stanisz, & Henkelman, 1994), leading to huge changes in MR images of the developing brain. Information about the myelination progression is now available *in vivo* with MR parameters that capture different mechanisms of maturation: T_1 and T_2 relaxation times, DTI, and myelin-related parameters (Dubois et al., 2013).

Regional Asynchrony of White Matter Myelination

Postmortem studies have detailed the myelination sequence (Brody, Kinney, Kloman, & Gilles, 1987; Flechsig, 1920; Gilles, Shankle, & Dooling, 1983; Kinney, Brody, Kloman, & Gilles, 1988; Yakovlev, 1962; Yakovlev & Lecours, 1967; for reviews, see Baumann & Pham-Dinh, 2001; Dubois et al., 2013). It follows a caudorostral gradient and progresses from the center of the brain to the periphery, occurring earlier and faster (1) in proximal pathways than in distal ones, (2) in sensory pathways (somatosensory, vision, and audition) than in motor ones, (3) in projection fibers than in associative ones, (4) in central regions than in polar ones, and (5) in the occipital pole than in the posterior parietal white matter and in the temporal and frontal poles.

Mapping the asynchrony of maturation in healthy newborns and infants with MRI has demonstrated acute changes during the first postnatal year, less rapid modifications during toddlerhood, and slower changes thereafter until young adulthood (Dubois et al., 2013). While there is early evidence of myelination in specific white matter regions before 28w GA (Counsell et al., 2002), an abrupt increase in myelinated white matter is detected on T_1-weighted and T_2-weighted images in preterm newborns between 35 and 41w GA (Huppi, Warfield, et al., 1998). Early differences between several projection and association bundles are identified between 28 and 43w GA by DTI (Partridge et al., 2004) and hold up between 4 and 18w of postnatal age as highlighted by modeling distinct maturational stages in infants (Dubois, Dehaene-Lambertz, Perrin, et al., 2008). The spatiotemporal pattern of myelination progression provided by the myelin water fraction between 3 and 60 months is coherent with histological studies (Deoni, Dean, O'Muircheartaigh, Dirks, & Jerskey, 2012), and the maturational delays across white matter bundles can be deduced by computing maturational distances between infants and adults from T_1, T_2, and DTI parameters (Kulikova, Hertz-Pannier, Dehaene-Lambertz, Poupon, & Dubois, 2014; **Figure 6(a)**). Within a single bundle, asynchronous fronts of maturation, relying on different pools of fibers, are even distinguished using tractography-based analyses, as demonstrated for the motor pathway and the somatosensory radiations within the corticospinal tract of preterm newborns (Berman et al., 2005) and for the thalamocortical fibers and corticothalamic fibers

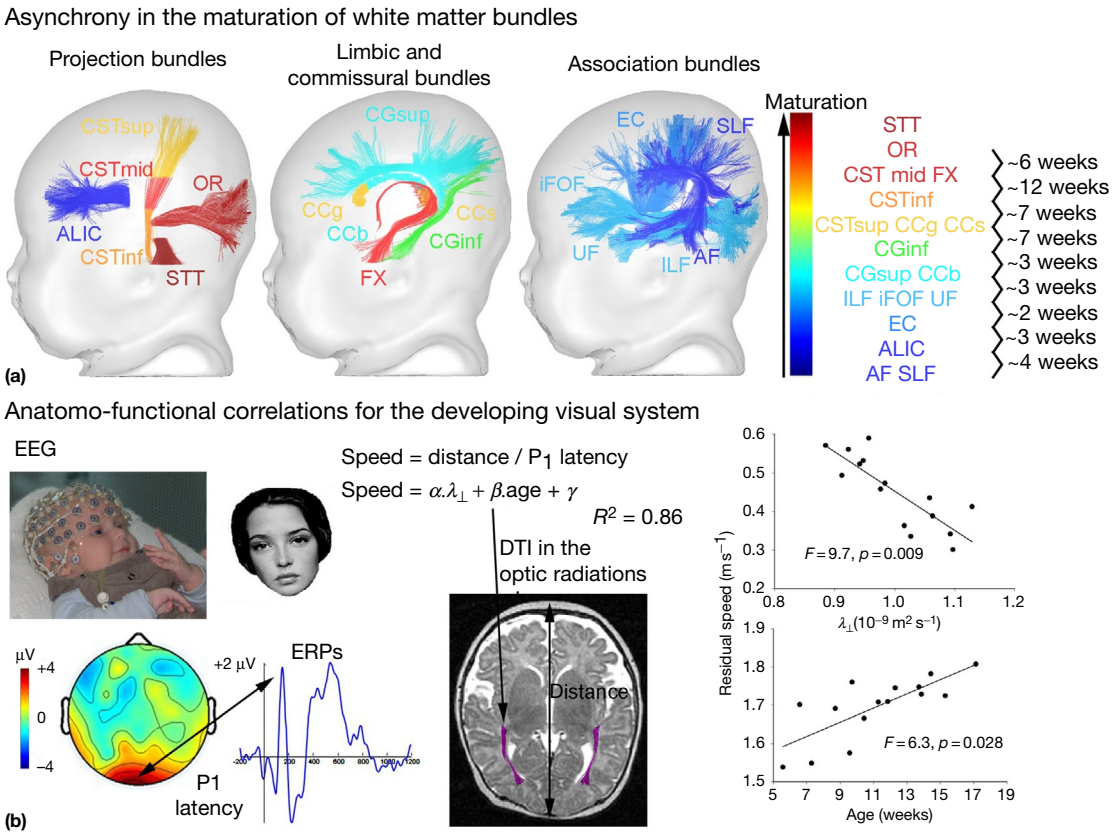

Figure 6 Maturation of the structural networks. (a) The regional asynchrony in white matter maturation is highlighted in healthy infants using multiparametric MRI. Projection, limbic, commissural, and association bundles are ordered and colored according to their maturation, and maturational delays (in weeks) are computed between pairs of bundles (Kulikova et al., 2014). Abbreviations: AF, arcuate fasciculus; ALIC, anterior limb of the internal capsule; CC, corpus callosum (g/b/s, genu/body/splenium); CG, cingulum (inf/sup, inferior/superior parts); CST, corticospinal tract (inf/mid/sup, inferior/middle/superior portions); EC, external capsule; FX, fornix; iFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; OR, optic radiations; SLF, superior longitudinal fasciculus; STT, spinothalamic tract; UF, uncinate fasciculus. (b) Correlations between the brain anatomical development and functional development are assessed for the visual system, whose maturation is intense during the first postnatal months. Cerebral responses are measured with EEG while the infant is looking at visual stimuli. The latency of the first positive peak (P1) of event-related potentials (ERP) strongly decreases after birth, in relation with the increase in the nerve impulse conduction speed. Indeed, this speed (defined as the ratio between traveled distance and P1 latency) increases more with the optic radiations myelination (assessed by MRI–DTI) than with age in 1–4-month-old infants. Reproduced from Dubois, J., Dehaene-Lambertz, G., Soares, C., Cointepas, Y., Le Bihan, D., & Hertz-Pannier, L. (2008). Microstructural correlates of infant functional development: Example of the visual pathways. *Journal of Neuroscience*, *28*(8), 1943–1948.

within the optic radiations of infants (Dubois, Dehaene-Lambertz, Soares, et al., 2008).

Functional Correlates of White Matter Myelination

Aside from the investigation of normal maturation through the modeling of time trajectories, *in vivo* longitudinal studies may provide early structural biomarkers of functional development. Fiber myelination leads to a spectacular increase in the conduction speed of the nerve impulse (Baumann & Pham-Dinh, 2001), which was confirmed in infants for the developing visual system by correlating the optic radiations maturation, measured by DTI, and functional responses assessed with EEG (Dubois, Dehaene-Lambertz, Soares, et al., 2008; **Figure 6(b)**). Myelination is thus assumed to improve the functional efficiency of brain networks (van der Knaap et al., 1991). As examples, expressive and receptive language abilities during toddlerhood are related to the myelin water fraction in the white matter underlying the frontal and temporal cortices (O'Muircheartaigh et al., 2014), and visuospatial working memory performance at 1 year of age correlates with microstructural characteristics of white matter tracts that connect involved brain regions (Short et al., 2013).

However, relationships between the structural maturation and functional maturation of the connectivity networks are probably much more complex. First, instead of triggering the development of functional networks, myelination may rather depend on it, since neuronal maturation and electrical activity control myelination induction (Barres & Raff, 1993; Demerens et al., 1996; Gyllensten & Malmfors, 1963; Kinney et al., 1988; Tauber, Waehneldt, & Neuhoff, 1980). Second, myelination appears uncorrelated with functional maturation in some cerebral systems (e.g., the auditory system), and extending myelination beyond a given age may enable to maintain similar latencies between cerebral regions across ages by compensating for brain growth (Dubois et al., 2013; Salami, Itami, Tsumoto, & Kimura, 2003). Conversely, oligodendrocytes and myelin may play an inhibitory role on neuritic growth, partly

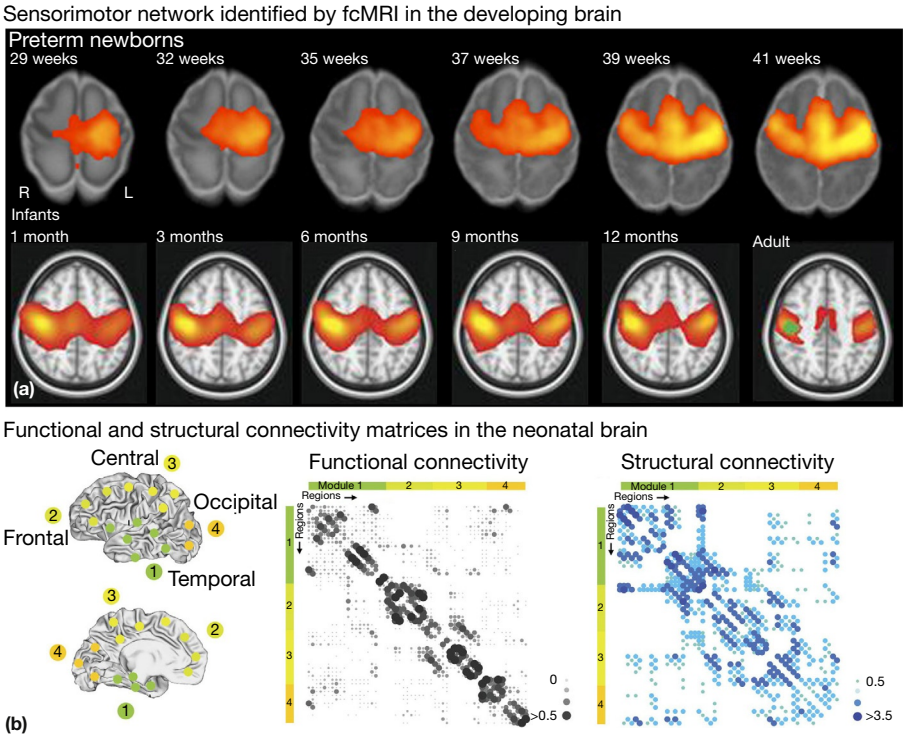

Figure 7 Development of functional networks. (a) Functional networks are present early on in the developing brain and further strengthen during the preterm and postterm periods. As an example, the sensorimotor network is mapped with fcMRI in preterm newborns between 29w and 41w GA (upper row) and in infants during the first postnatal year (lower row). Adapted with permission from Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., et al. (2010). Emergence of resting state networks in the preterm human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(46), 20015–20020; Gao, W., Alcauter, S., Elton, A., Hernandez-Castillo, C. R., Smith, J. K., Ramirez, J., et al. (2014). Functional network development during the first year: Relative sequence and socioeconomic correlations. *Cerebral Cortex*. (b) In the neonatal brain, a structural basis of functional connectivity is suggested by the clear overlap between functional and structural connectivity matrices (over all pairs of brain regions) of preterm newborns at 30 and 40w GA. Four functional communities (in the temporal, occipital, central, and frontal regions) are revealed based on functional connectivity, and levels of structural connectivity are computed according to the numbers of fibers reconstructed by tractography between regions. Reproduced with permission from van den Heuvel, M. P., Kersbergen, K. J., de Reus, M. A., Keunen, K., Kahn, R. S., Groenendaal, F., et al. (2014). The Neonatal connectome during preterm brain development. *Cerebral Cortex*.

explaining the weak plasticity of the adult brain (Ng, Cartel, Roder, Roach, & Lozano, 1996). Finally, intracortical myelinated fibers are not well developed even at 6 years of age (Kostovic et al., 2014). The functional maturation of structural connectivity, mediated by fiber myelination, and the role of experience-dependent mechanisms are still to be clarified in healthy infants in relation with the networks' critical periods. Then, exploring the development of functional networks may be used as a complementary approach.

Development of the Functional Connectivity

Resting-state networks have been mapped in the adult brain using multichannel EEG, NIRS, or functional connectivity MRI (fcMRI), with the hypothesis that distant brain regions within a network demonstrate synchronized fluctuations in spontaneous neural activity. Since the first study of sedated preterm newborns at term-equivalent age (Fransson et al., 2007), several groups have detailed the developing functional connectivity (Lubsen et al., 2011; Smyser, Snyder, & Neil, 2011), because this approach is easy to implement in babies during natural sleep.

Evolution of Functional Connectivity: Late Preterm and Postterm Periods

While it might be thought that resting-state networks emerge in parallel with the development of related cognitive functions mostly during the postterm period, they rather seem to settle during the third trimester of gestation. Between 19 and 39w GA, the fetal brain demonstrates in fcMRI an organization of modules that overlap functional systems observed postnatally (Thomason et al., 2014). In preterm newborns from 26w GA, functional networks involve varied cortical regions, the thalamus and cerebellum (Doria et al., 2010; Smyser et al., 2010), and during the preterm period, the connectome architecture strongly develops, the interhemispheric connectivity increases (van den Heuvel et al., 2014), and the age-related patterns of development differ across networks (Doria et al., 2010; Smyser et al., 2010; **Figure 7(a)**). By term age (40w GA), the full networks (visual, auditory, somatosensory, motor, frontoparietal, and executive control networks) are observed (Doria et al., 2010; Fransson et al., 2009; van den Heuvel et al., 2014); the architecture seems similar to that of the adult; nevertheless, cortical hubs and associated networks may remain mostly confined to primary sensorimotor regions, suggesting that architecture is first linked to support tasks related

to basal perception and action behavior (Fransson, Aden, Blennow, & Lagercrantz, 2011). During the first postnatal year, the maturation sequence progresses differently across networks, from the primary sensorimotor/auditory networks, to the visual networks, to the default-mode network (highly similar between 2-year-old toddlers and adults; Gao et al., 2009), finally to executive control networks (Gao et al., 2014). In newborns, note that only high-amplitude EEG events show strong spatial correlations (Omidvarnia, Fransson, Metsaranta, & Vanhatalo, 2013).

Origins of Functional Connectivity in the Developing Brain

While resting-state activities in the immature and mature brains present quite similar patterns, the former do not seem to be a precursor of the latter, since underlying mechanisms differ in terms of function and origin, particularly in primary sensory systems (Colonnese & Khazipov, 2012). During the preterm period, the default state of cortical networks is 'silence' in comparison with the continuous activity measured in the mature brain, and both endogenous and sensory-driven electrical activities are critical for wiring and refining the developing circuitry (Penn & Shatz, 1999). The spontaneous thalamocortical activity in immature primary sensory regions is generated largely by the sensory periphery, whereas intrinsic activity in the adult brain is generated within the cortical circuits (Colonnese & Khazipov, 2012).

FcMRI, EEG, and NIRS imaging modalities may further reflect different mechanisms underlying the development of functional connectivity. Functional connections related to high-amplitude EEG events in newborns may provide the endogenous guidance for the early activity-dependent development (Omidvarnia et al., 2013), whereas the origins of long-range spatial correlations detected with fcMRI in preterm newborns are not well understood yet, since the majority of long axonal pathways are still developing (Omidvarnia et al., 2013). Nonetheless, functional connections may be partly related to structural connections, since a positive coupling between both connectivity measures is observed in preterm newborns at 30 and 40w GA (van den Heuvel et al., 2014; **Figure 7(b)**) and strengthens with age during childhood (Hagmann et al., 2010). Because tractography demonstrates intrinsic technical limitations with fiber interruptions in the cortex, structural measures may reflect monosynaptic connections, whereas functional measures may also include polysynaptic connections (Smyser et al., 2011).

Conclusion

During normal development, the setting up of brain connectivity is a complex process based on several intermingled mechanisms at the structural and functional levels. Even though recent histological and MRI studies have enabled to highlight part of these mechanisms, the story is just beginning notably to understand how this development may be impacted by genetic, epigenetic, and environmental factors or early disturbances (e.g., *in utero* growth, preterm birth, hypoxic–ischemic lesion, neonatal stroke, and postnatal environment) (Ball et al., 2014; Fischi-Gomez et al., 2014; Gao et al., 2014; Grieve et al., 2008; Smyser et al., 2013). Despite challenges to studying fetuses and infants, combining complementary postmortem and *in vivo* approaches should provide a great opportunity to investigate the developing brain at different scales, from microstructure to functional organization.

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See also: **INTRODUCTION TO ACQUISITION METHODS**: Anatomical MRI for Human Brain Morphometry; Basic Principles of Electroencephalography; Diffusion MRI; Functional MRI Dynamics; Functional Near-Infrared Spectroscopy; Myelin Imaging; Obtaining Quantitative Information from fMRI; **INTRODUCTION TO ANATOMY AND PHYSIOLOGY**: Cytoarchitectonics, Receptorarchitectonics, and Network Topology of Language; Development of the Basal Ganglia and the Basal Forebrain; Embryonic and Fetal Development of the Human Cerebral Cortex; Fetal and Postnatal Development of the Cortex: MRI and Genetics; Functional Connectivity; The Resting-State Physiology of the Human Cerebral Cortex; **INTRODUCTION TO CLINICAL BRAIN MAPPING**: Developmental Brain Atlases; **INTRODUCTION TO METHODS AND MODELING**: Cortical Thickness Mapping; Diffusion Tensor Imaging; Fiber Tracking with DWI; Graph-Theoretical Analysis of Brain Networks; Modeling Brain Growth and Development; Probability Distribution Functions in Diffusion MRI; Q-Space Modeling in Diffusion-Weighted MRI; Resting-State Functional Connectivity; Tissue Microstructure Imaging with Diffusion MRI; Tissue Properties from Quantitative MRI; Tract Clustering, Labeling, and Quantitative Analysis; **INTRODUCTION TO SYSTEMS**: Hubs and Pathways.

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