REVIEW

Development of axonal pathways in the human fetal fronto-limbic brain: histochemical characterization and diffusion tensor imaging

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Abstract

The development of cortical axonal pathways in the human brain begins during the transition between the embryonic and fetal period, happens in a series of sequential events, and leads to the establishment of major long trajectories by the neonatal period. We have correlated histochemical markers (acetylcholinesterase (AChE) histochemistry, antibody against synaptic protein SNAP-25 (SNAP-25-immunoreactivity) and neurofilament 200) with the diffusion tensor imaging (DTI) database in order to make a reconstruction of the origin, growth pattern and termination of the pathways in the period between 8 and 34 postconceptual weeks (PCW). Histological sections revealed that the initial outgrowth and formation of joined trajectories of subcortico-frontal pathways (external capsule, cerebral stalk–internal capsule) and limbic bundles (fornix, stria terminalis, amygdaloid radiation) occur by 10 PCW. As early as 11 PCW, major afferent fibers invade the corticostriatal junction. At 13–14 PCW, axonal pathways from the thalamus and basal forebrain approach the deep moiety of the cortical plate, causing the first lamination. The period between 15 and 18 PCW is dominated by elaboration of the periventricular crossroads, sagittal strata and spread of fibers in the subplate and marginal zone. Tracing of fibers in the subplate with DTI is unsuccessful due to the isotropy of this zone. Penetration of the cortical plate occurs after 24–26 PCW. In conclusion, frontal axonal pathways form the periventricular crossroads, sagittal strata and 'waiting' compartments during the path-finding and penetration of the cortical plate. Histochemistry is advantageous in the demonstration of a growth pattern, whereas DTI is unique for demonstrating axonal trajectories. The complexity of fibers is the biological substrate of selective vulnerability of the fetal white matter.

Key words axonal pathways; development; fronto-limbic connectivity; human fetal brain; subplate.

Introduction

The establishment of long-range axonal pathways is a crucial neurogenetic event in the development of the expanded cerebral cortex of the large primate brain. The long-range axonal pathways form a basis for expanded connectivity related to the increased number and size of cortical areas which, in turn, have also increased the number and size of cortico–subcortical connections. The process of axonal growth of the long pathways is the most complex in the human cerebrum, where an increased number of areas and projection neurons (Rakic, 1988, 2009) is accompanied by an enormous expansion of axonal pathways (Von Monakow, 1905; Polyak, 1927, 1932; Makris et al. 1997; Schmahmann & Pandya, 2006; Petrides & Pandya, 2007). The expanded system of axonal pathways in the human cerebrum develops over a prolonged period of time. It begins at the end of the embryonic period (His, 1904; Hochstetter, 1909; Bartelmez & Dekaban, 1962, Kostović, 1990a,b) and lasts until the neonatal period (Kostović, 1990b; Kostović & Judaš, 2002, 2006; Berman et al. 2005; Huang et al. 2006, 2009; Huppi & Dubois, 2006; Kostović & Jovanov-Milošević, 2006; Counsell et al. 2007; Kasprian et al. 2008; Kostović et al. 2008; Ment et al. 2009). During this period of growth, the axonal pathways (i) pass the critical morphogenetic points at the diencephalic–telencephalic border and corticostriatal junction (pallial–subpallial boundary) and (ii) change the direction of the growth trajectory passing through the periventricular crossroads (Judaš et al. 2005).

They 'wait' in the subplate compartment before penetration into the cortical plate (Rakic, 1976, 1977; Kostović & Goldman-Rakic, 1983; Kostović & Rakic, 1984, 1990; Kostović & Jovanov-Milošević, 2006; Kostović & Judaš, 2007). Some of the fiber systems show transient phenomena, such as overgrowth and retraction of axon branches, which extend into the postnatal period (Innocenti & Price, 2005; Tau & Peterson, 2010). The peak of growth of the long axonal pathways, connecting the cortex with the subcortical centers, corresponds to the period when preterm infants are born [22–34 postconceptual weeks (PCW)] and survive due to the support provided by modern neonatal care (Counsell et al. 2007; Volpe, 2008, 2009; Ment et al. 2009; Miller & Ferriero, 2009). In this period the axonal pathways (the 'white' matter) are very vulnerable to hypoxic–ischemic injury, which is the basis of selective vulnerability (Miller & Ferriero, 2009; Sherlock et al. 2009; Volpe, 2009).

The application of modern diffusion tensor imaging (DTI) allows the *in-vivo* analysis of abnormal changes of the axonal pathways during vulnerable periods (Huang et al. 2006, 2009; Kasprian et al. 2008; Kim et al. 2008; Rutherford et al. 2008; Aeby et al. 2009; Hoon et al. 2009; Ment et al. 2009; Ramenghi et al. 2009). It has been shown that the DTI technique is very useful for the 3D study of the macroscopic fiber bundle architecture and their maturational changes. However, from a microscopic point of view, there are several important limitations of DTI. DTI cannot identify the points of origin, chemical properties and 'waiting' periods of axonal pathways. When axonal anatomy is complex in terms of the pixel dimension, such anatomical information (e.g. non-uniform tract orientations within a pixel) could be lost. These issues would lead to unknown validity of DTI results if the results deviate from existing anatomical knowledge. Although sophisticated data acquisition and analysis methods have been postulated to ameliorate these issues, we cannot expect that they will be completely resolved. Careful histological studies based on the histochemical preparations of the sequential histological sections of the brain specimens within different developmental phases (Kostović & Molliver 1974; Kostović & Goldman-Rakic, 1983; Krmpotić-Nemanić et al. 1983; Kostović & Rakic, 1984, 1990; Kostović, 1986, 1990b; Kostović et al. 1988, 1989a; Mrzljak et al. 1988, 1992; Kostović & Judaš, 2002, 2006, 2007; Kostović et al. 2002; Judaš et al. 2005; Kostović & Jovanov-Milošević, 2006; Radoš et al. 2006; Petanjek et al. 2008, Jovanov-Milošević et al. 2009, Kostović & Vasung, 2009) will also be important in future DTI analysis.

The objective of this review is to compare evidence from the DTI analysis of fetal postmortem brains with the data on histochemically identified pathways. We have correlated the histochemical evidence (acetylcholinesterase (AChE) histochemistry, SNAP-25-immunoreactivity and neurofilament 200 staining) with the DTI reconstruction of pathways [code no. N01-HD-4-3368 and N01-HD-4-3383, University of Maryland Brain and Tissue Bank, for details on DTI data

acquisition; for imaging protocol, postprocessing and visualization of DTI, DTI-based fiber tractography and region of interest drawing strategy see Huang et al.(2009)] in order to reconstruct the origin, growth pattern and termination of the axonal pathways. In addition, we have scanned 3-T DTI of the postmortem specimen at 24 PCW [Fig. 9C, similar to the protocol of Huang et al. (2009) but with lower resolution] as well as T2-weighted magnetic resonance imaging (MRI) (Fig. 9D) to elaborate different structural MRI characteristics of the fetal brain. We have examined the period between 8 and 34 PCW.

Our basic approach in the study of the long axonal pathways of the human fetal cerebrum is illustrated in Fig. 1. This approach uses a combination of structural, histochemical and imaging data of the growing fiber system obtained at the different developmental ages, expressed in the reference to common spatial (cellular, laminar and areal) landmarks. For a detailed timetable of thalamocortical as well as cerebral connection development see Kostović & Jovanov-Milošević (2006) and Kostović & Judaš (2010).

Using these histological and DTI techniques we have compared the development of axonal pathways of the prefrontal cortex and limbic bundles (Vasung et al. 2009). Our goal was not only to show the differences between the neocortical and allocortical patterns but also to show the possible developmental relationships between these diverse but functionally connected cortical systems (Nauta, 1971; Goldman-Rakic, 1987; Schmahmann & Pandya, 2006; Barbas, 2007; Petrides & Pandya, 2007). We believe that the review of existing data on the development of cerebral connections is a necessary step in studying the consequences of the white matter damage and will facilitate the analysis of structural organization and the possible recovery after perinatal brain damage.

Early initial outgrowth and formation of 'joint trajectories' of cerebral pathways (before 10 PCW)

Classical studies on the developing brain have demonstrated that fiber bundles of the major projection pathways appear very early, at the end of the embryonic period, around 8 PCW (His, 1904; Hochstetter, 1909; Bartelmez & Dekaban, 1962; Molliver et al. 1973; Kostović, 1990a; O'Rahilly & Müller, 2006). The standard techniques applied in this study did not stain the fibers directly and the fibers were identified on the basis of topography and pale appearance in the Nissl type of staining (Fig. 2B–D). Applications of histochemical staining techniques showed that the basal forebrain is the early source of afferents in the telencephalon (Fig. 2A). The basal forebrain neurons belong to the magnocellular cholinergic system (Matthews et al. 1974; Mesulam et al. 1983, 1984; Kostović, 1986). These early basal forebrain afferents travel to the pallium via the external capsule, which is well delineated in this early phase (Fig. 2B,
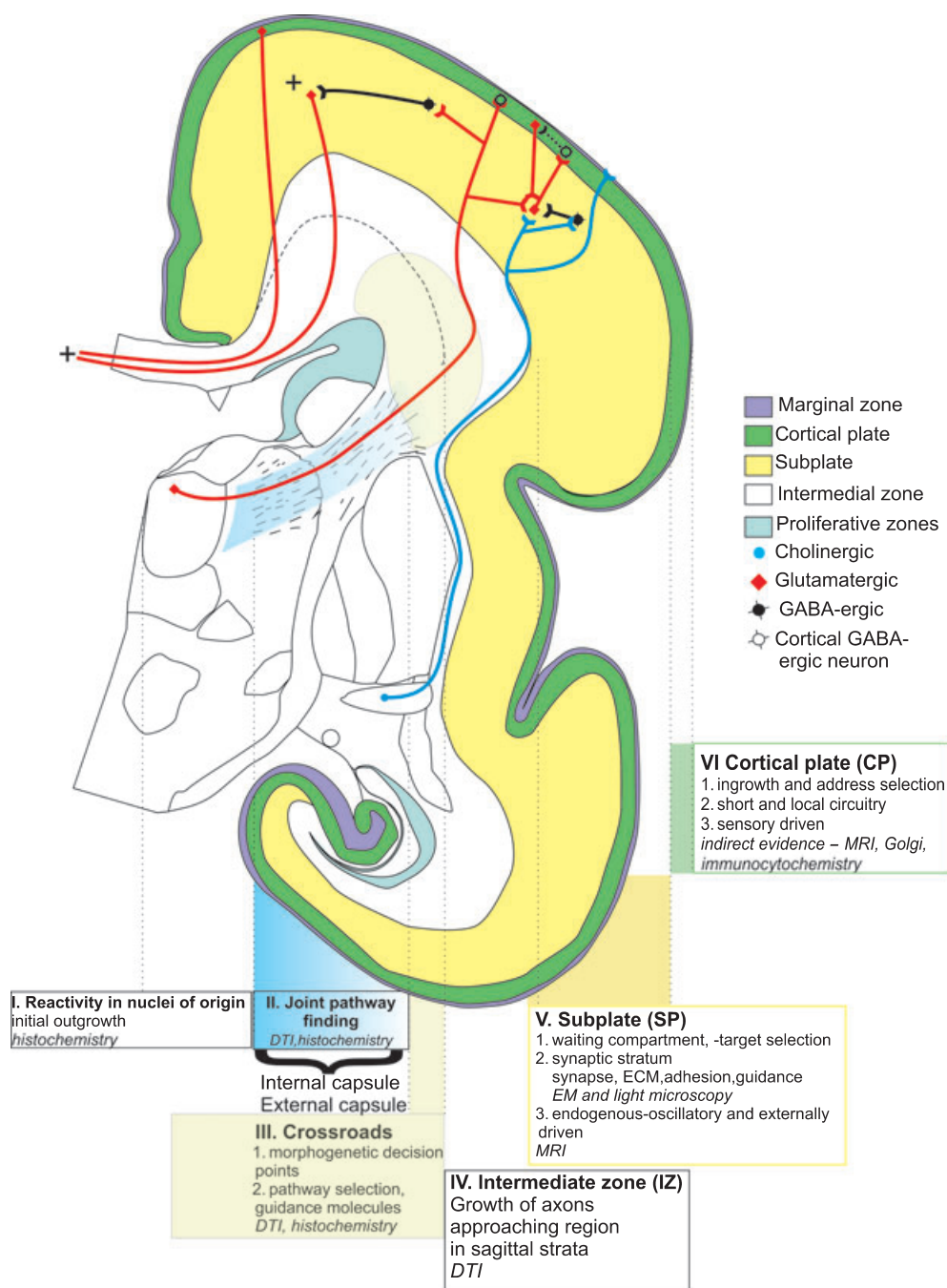
Legend:

- Marginal zone
- Cortical plate
- Subplate
- Intermedial zone
- Proliferative zones
- Cholinergic
- Glutamatergic
- GABA-ergic
- Cortical GABA-ergic neuron

VI Cortical plate (CP)
1. ingrowth and address selection
2. short and local circuitry
3. sensory driven
indirect evidence – MRI, Golgi, immunocytochemistry

I. Reactivity in nuclei of origin
initial outgrowth
histochemistry

II. Joint pathway finding
DTI, histochemistry

Internal capsule
External capsule

III. Crossroads
1. morphogenetic decision points
2. pathway selection, guidance molecules
DTI, histochemistry

V. Subplate (SP)
1. waiting compartment, -target selection
2. synaptic stratum
   synapse, ECM, adhesion, guidance
   EM and light microscopy
3. endogenous-oscillatory and externally driven
   MRI

IV. Intermediate zone (IZ)
Growth of axons approaching region in sagittal strata
DTI

Fig. 1 Schematic illustration of our approach to the development of the cortical connectivity in the human brain. DTI, diffusion tensor imaging; ECM, extracellular matrix; EM, electron microscopy; MRI, magnetic resonance imaging.

curved arrow). Cholinesterase staining also helps in visualizing pathways from the tegmentum, which are probably dopaminergic (Fig. 2A, double curved arrows). Other monoaminergic early afferents were demonstrated with monoamine-fluorescence techniques (Nobin & Bjorklund, 1973; Olson et al. 1973; Zecevic & Verney, 1995). Early afferents from the thalamus form a massive bundle, the so-called cerebral stalk (Fig. 2C, cs) (His, 1904; Hemisferenstiel by Hochstetter, 1909). This massive thalamocortical bundle almost fills the diencephalic–telencephalic (Fig. 2C, red arrows) junction, appearing as a real cerebral stalk (Fig. 2C, cs). Thus, the two major afferent cortical systems from the thalamus and basal telencephalon show early outgrowth and join two major fiber trajectories: (i) the developing cerebral stalk – internal capsule (Fig. 2C, cs) and (ii) the external capsule (Fig. 2B, curved arrow).

The limbic bundles develop along the midline and, at a very early stage, form the compact, well-delineated bundles
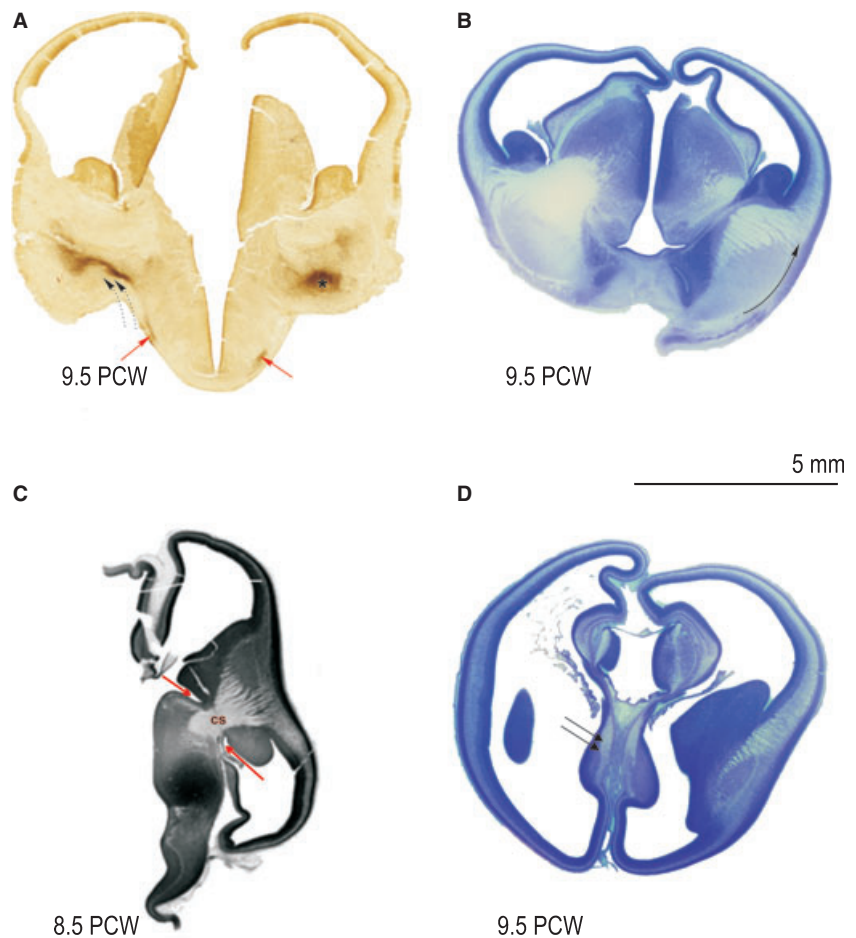
A

9.5 PCW

B

9.5 PCW

5 mm

C

8.5 PCW

D

9.5 PCW

Fig. 2 Development of fibre bundles before 10 PCW. Appearance of basal forebrain revealed by AChE histochemistry (A); nucleus basalis complex (asterisk), supraoptic commisure fibres (A, red arrow) and pathways from tegmentum (double dotted arrows) at 9.5 PCW. At 9.5 PCW external capsule (B, along the curved arrow) can be shown by Nissl staining technique. Early formation (at 8.5 PCW) of cerebral stalk (C, cs) and diencephalic-telencephalic sulcus (border- C, shown by two red arrows) as well as the formation of fornix bundle at 9.5 PCW can be shown as Nissl pale staining (D, double arrow). cs, cerebral salk.

(Fig. 2D). The most prominent limbic bundle is the fornix (Fig. 2D, double arrow) (His, 1904; Hochstetter, 1909; Macchi, 1951; Bartelmez & Dekaban, 1962; Humphrey, 1967; Rakic & Yakovlev, 1968; Stephan, 1975). The early fornix is a short, slightly curved bundle that connects the hippocampus with the septal area. It is not known whether the early fornix contains more hippocampal-septal or septo-hippocampal fibers. Due to the fact that the pyramidal neurons, at that very early age, are in the process of proliferation of the ventricular zone (Nowakowski & Rakic, 1981), it is very likely that the early fornix contains mostly septo-hippocampal fibers. This is consistent with the early development of the septal area (Kostović et al. 1980).

Afferent pathways invade the corticostriatal junction (around 11 PCW)

A crucial step in axonal pathway development is crossing the border between the pallium and striatum–ganglionic eminence complex, the so-called corticostriatal junction (Molnar & Butler, 2002). An even better term for the corticostriatal junction would be the corticocaudate junction because, in the human brain, only the caudate nucleus is situated in the proximity of the ventricles. From the evolution-

ary point of view, this corresponds to the pallial-subpallial border (Molnar & Butler, 2002). From the practical, human neuroanatomical point of view, this border is frequently described as the lateral angle of the developing lateral ventricles or thalamocaudate grove. At this border, thalamocortical axons cross with efferent axons and turn towards various pallial regions. The axons for the frontal pallium turn towards the intermediate zone of the frontal portion of the telencephalic vesicles as described for the animal models (Molnar & Blakemore, 1995; Molnar et al. 1998; Sestan et al. 2001; Lopez-Bendito et al. 2002; Molnar & Butler, 2002; Bishop et al. 2003; Lopez-Bendito & Molnar, 2003; Bolz et al. 2004; Price et al. 2006).

This period of development is characterized by the massive invasion of projection fibers into the corticostriatal junction. The fibers arising from the basal telecephalon extend via the external capsule to the outermost portion of the intermediate zone of the developing neopallium (Fig. 3A, curved arrow). For the first time, the external capsule attains a bifurcated appearance where one branch is oriented to the frontal and the other to the parieto-occipital pallium (Fig. 3B). The process of growth of the afferents from the nucleus basalis complex was described in detail by Kostović (1986).
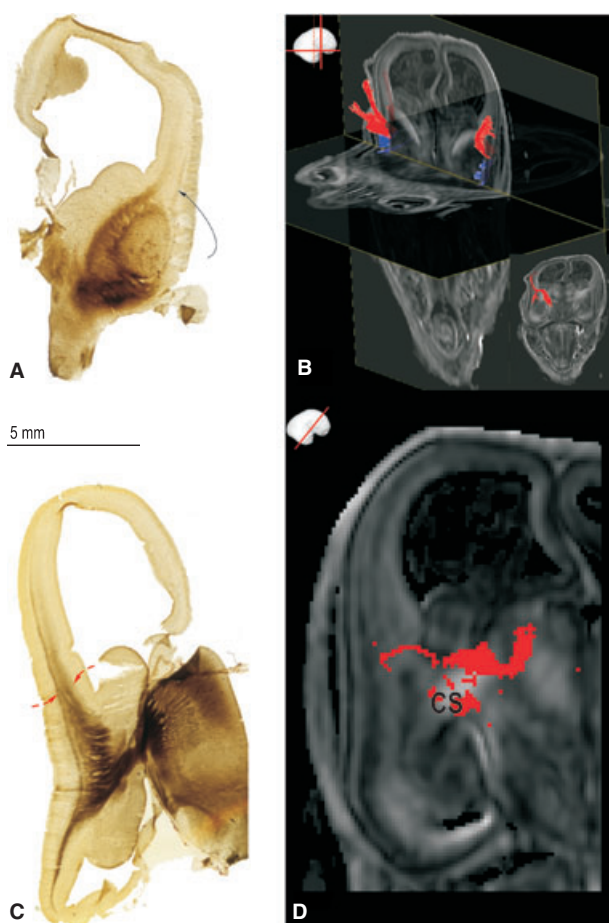
5 mm

Fig. 3 Development of afferent fibres at 11PCW revealed by AChE histochemical staining (A, C) and DTI (B, D). The diencephalo-telencephalic junction (C, red arrows) and external capsule (A, curved arrow) can be seen on AChE stained section. The DTI tractography reconstruction shows bifurcating appearance of external capsule (B) and AChE histochemical staining with DTI reveals thalamocortical fibres passing through the cerebral stalk (C, D, cs) originating from the dorsomedial thalamic complex (C, D). cs, cerebral stalk.

The fibers for the temporal and occipital pallium change their trajectory, bending in the ventrocaudal direction (Fig. 3C). The continuity of the thalamocortical projection from the thalamic nuclei, cerebral stalk and internal capsule fanning out into the early thalamic radiation is obvious only in histochemical preparations. DTI imaging (Fig. 3D) shows only the proximal, thick body of the main thalamocortical fiber system. The thickness of the diencephalic–telencephalic junction has increased significantly (Fig. 3C, red arrows) making the diencephalic–telencephalic border less obvious on coronal images through the fetal brain.

The process of growth of the limbic bundles is more advanced than in neopallial regions. The bundle of fornix has a semicircular shape and shows considerable compactness (Fig. 4C). Projection of the amygdala, the neuroendo-crine pathway of the stria terminalis, which connects the amygdala with the septal area, is very advanced (Fig. 4A). The fibers connected to the amygdala radiate in all directions (Fig. 4B), providing evidence that the amygdala establishes connections to the different parts of the cortex (Fig. 5C) at a very early stage (13 PCW). The early development of the amygdala fiber system is consistent with the early cytoarchitectonic differentiation of the amygdala (Nikolić & Kostović, 1986) and early origin of the amygdaloid nuclear complex of the human and non-human primate brain (Kordower et al. 1992). It is not possible at this early stage of development to attribute individual fibers from ⁄ to the individual nuclei.

Morphogenetic interaction of afferents with the cortical plate (around 13 PCW)

The appearance of thalamocortical (Fig. 5A,B) and basal forebrain afferents in the intermediate zone at an early phase of development raises the question of the developmental and synaptic interactions with the early born and differentiated cortical cells. Before 13 PCW, the cortical plate is composed of densely packed postmigratory neurons, arranged in vertical columns, without significant fibrillar (axonal) content. The fibrillar elements (axons) are distributed in two laminas: the presubplate (below the cortical plate) and marginal zone (above the cortical plate). In these two fibrillar layers the synapses can be found, designating these layers as synaptic strata (Molliver et al. 1973; Kostović & Molliver, 1974; Kostović & Rakic, 1990; Kostović & Judaš, 2007). The prospective postsynaptic elements in the early synaptic strata are the early differentiated presubplate neurons that lie below the cortical plate at the interface with the intermediate zone (Kostović & Rakic, 1990; Meyer, 2007). At around 13 PCW the deep portion of the cortical plate changes dramatically; the cortical cells lose their radial orientation and become constituents of a new layer – the subplate zone. The subplate zone was first described by Kostović & Molliver (1974) (see also Kostović & Jovanov-Milošević 2008). This loose portion of the cortical plate was described as the 'second' cortical plate by Poliakov (Poliakov, 1949; Kostović & Rakic, 1990). The neuropil of the 'second' cortical plate is plexiform, with a random orientation of the axonal and dendritic processes as well as the fast developing synapses (Kostović & Rakic, 1990; Kostović & Judaš, 2002). This phase of cortical development exists in both human and monkey but was not described in the rodent brain (Bayer & Altman, 1990; De Carlos & O'Leary, 1992; Molnar et al. 1998; Del Rio et al. 2000; Smart et al. 2002). Based on the fact that this 'second' cortical plate contains an old neuronal population, randomly oriented neuronal elements and synapses, this event corresponds to the appearance of the thick subplate and was described as the subplate formation stage by Kostović & Rakic (1990). In subsequent phases (15–24 PCW), the cortical

Fig. 4 Development of limbic fibre bundles at 11 PCW revealed by DTI tractography; early formation of subcortical (A, stria terminalis) and cortical (B) amygdala connections as well as the hippocampal pathways (C, fornix).
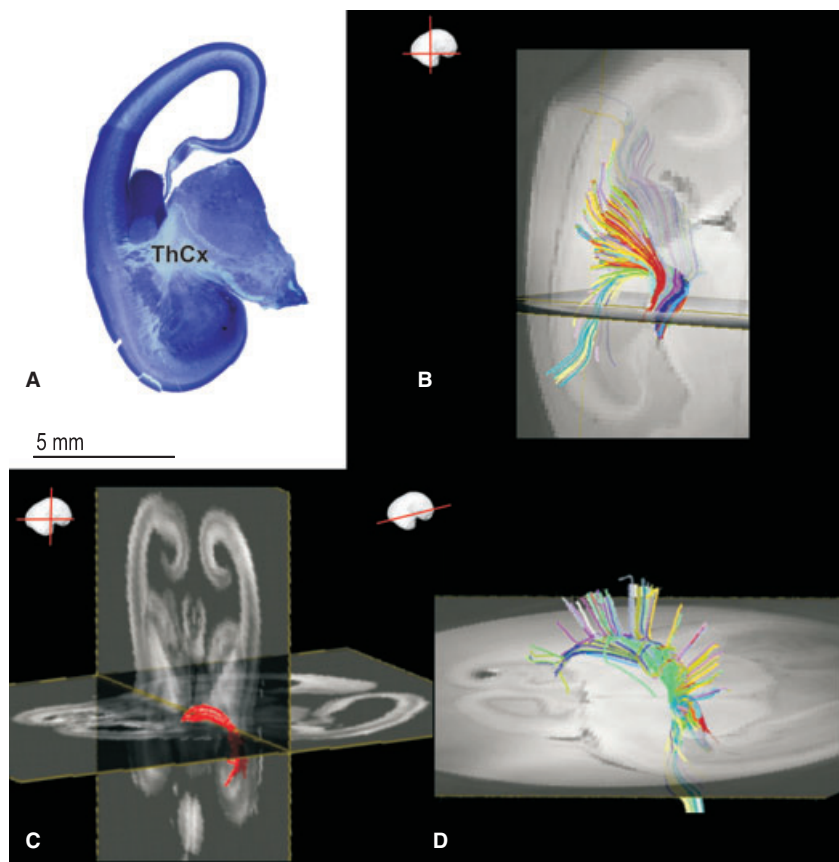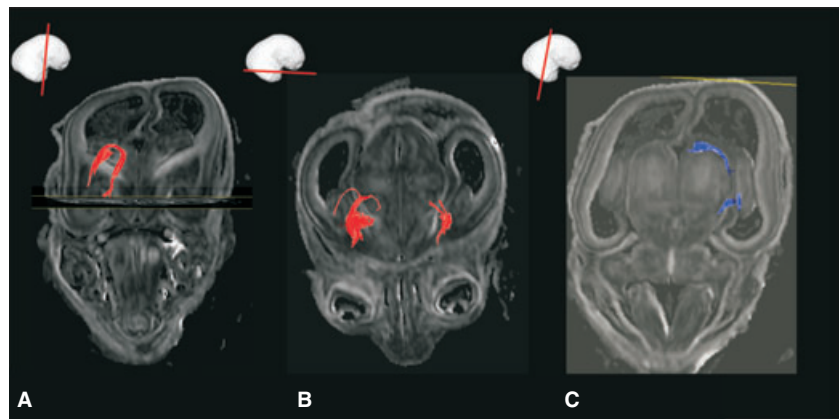

Fig. 5 Development of limbic (uncinate fascicle, C), efferent (periventricular fibre system with subcallosal fascicle of Muratoff and cortico-striate fibres, D) and thalamocortical fibres (ThCx A, B) at 13 PCW revealed by Nissl (A) staining and DTI tractography (B, C, D). ThCx, Thalamo-cortical fibers.

plate again becomes condensed (secondary condensation) and contains no synapses. It is not known what causes this first transient lamination of the cortical plate but the presence of the fibrillar elements in the deep portion of the cortical plate indicates the morphogenetic influence of the afferent system. The mostly likely candidate fiber system is the external capsule radiation because this system is the closest to the cortical plate. The fibers from the cholinergic magnocellular nuclei of the basal forebrain run via the external capsule into the external sagittal stratum (Kostović, 1986). The external capsule–external sagittal stratum is an important border between the intermediate zone and sub-plate (Kostović et al. 2002). The afferents from the external capsule remain permanently at this strategic border between the white matter and cortex. These fibers are closest to the permissive gradients of guidance molecules in the rich extracellular matrix subplate compartment. The beginning of lamination in the cortical plate is the initial step in the establishment of regional differences within the cerebral cortex. Lamination is first observed in the lateral neopallium, external to the angle of the lateral ventricle. The developing subplate is thicker in this midlateral region than in the dorsal neocortical regions. The second cortical plate is thinner in the interhemispheric neopallium and the

formation of the 'second' plate is absent in the limbic inter-hemispheric mesocortex (cingular cortex) (Kostović et al. 1989b, 1993). The interpretation of the subplate zone, presented in the present review, differs from the recent revision of the Boulder Committee where the subplate layer is defined immediately after formation of the cortical plate at around 8 PCW (Bayatti et al. 2008b; Bystron et al. 2008).

In the limbic archicortex, the main fibrillar development is in the marginal zone, which is much thicker than the subplate zone of the limbic cortex.

Efferent pathways

At this early phase of fetal development the presence of all efferent pathways cannot be expected, e.g. pyramidal projection neurons from cortical supragranular layers have not yet been born or are in the process of migration (Rakic, 1974). However, cortical cells from the infragranular layer are already in the cortical plate. There is little data about the development of the corticospinal and corticopontine pathways. Eyre et al. (2000) found that the corticospinal pathway reaches the lower spinal cord as early as 24 PCW. It seems that efferent pathways may be present even in the earliest phases, which we present in this study. Indeed, photographs of serial sections through the developing brain show the presence of crura cerebri at early phases (Fig. 5). However, the material presented in this review does not allow the reconstruction of terminal portions of the corticopontine and corticospinal pathways below the brainstem.

In this period there is progress in the growth of the periventricular fiber systems. According to the classification of Von Monakow (1905), the adult brain periventricular white matter, from segments I and II, forms the first periventricular system (Judaš et al. 2005). In segment 1, the corpus callosum is visible after 11 PCW. The periventricular fiber system is situated along the caudate nucleus (Fig. 5D) and, in this position, there are several fiber systems in transient topographical relationships (Judaš et al. 2004). A great proportion of this contingent of fibers is related to the striatum, i.e. the subcallosal fascicle of Muratoff and other corticostriatal fibers (Schmahmann & Pandya, 2006, Vukšić et al. 2008).

Fetal pattern of axonal distribution: sagittal strata and 'waiting' subplate compartment (15–18 PCW)

The typical fetal pattern of axonal pathway organization is characterized by the distribution of growing axons within the axonal strata of the intermediate zone and the gradual ingrowth into the deep cortical anlage of the subplate zone. Afferents from the basal forebrain, pons and thalamus may be visualized in both histochemical preparations and DTI tractography (Fig. 6A–D).

Thalamocortical axons run predominantly through the internal sagittal stratum (Fig. 6C,D). Basal forebrain axons
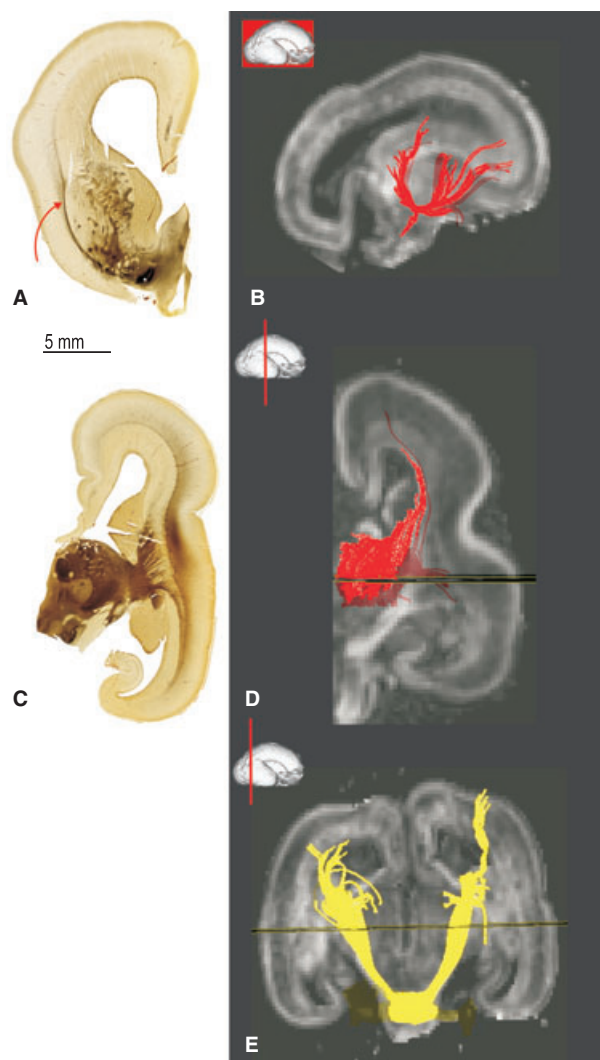

Fig. 6 Demonstration of the basal forebrain fibre bundles running trough the external capsule (A, curved arrow) and external sagittal stratum at 15 PCW (B; tractography reconstruction of basal forebrain fibre system and external capsule). Reconstruction of thalamocortical fibres running trough the internal sagittal stratum at 15 PCW (C) and 17 PCW (D) revealed by AChE staining and DTI tractography. At 15 PCW cortico pontine fibre bundles can be reconstructed using DTI tractography (E).

to the cortex (from the external capsule radiation) run through the most superficial portion of the external sagittal stratum (Fig. 6A,B). The central sagittal stratum contains AChE-negative fibers (Figs 6C and 7C), which are a feature of efferent cortical pathways. All sagittal strata mentioned are part of the intermediate zone fetal 'white' matter. For a description of the layers see Kostović et al. (2002), Huang et al. (2006) and Bystron et al. (2008). The intermediate zone with its sagittal strata is situated between the subplate zone and corpus callosum, which runs into the subventricular zone (Fig. 7A–D; CC). This relationship can be appreciated in the section through the rostral portion of the developing telecephalon (Fig. 7B–D).
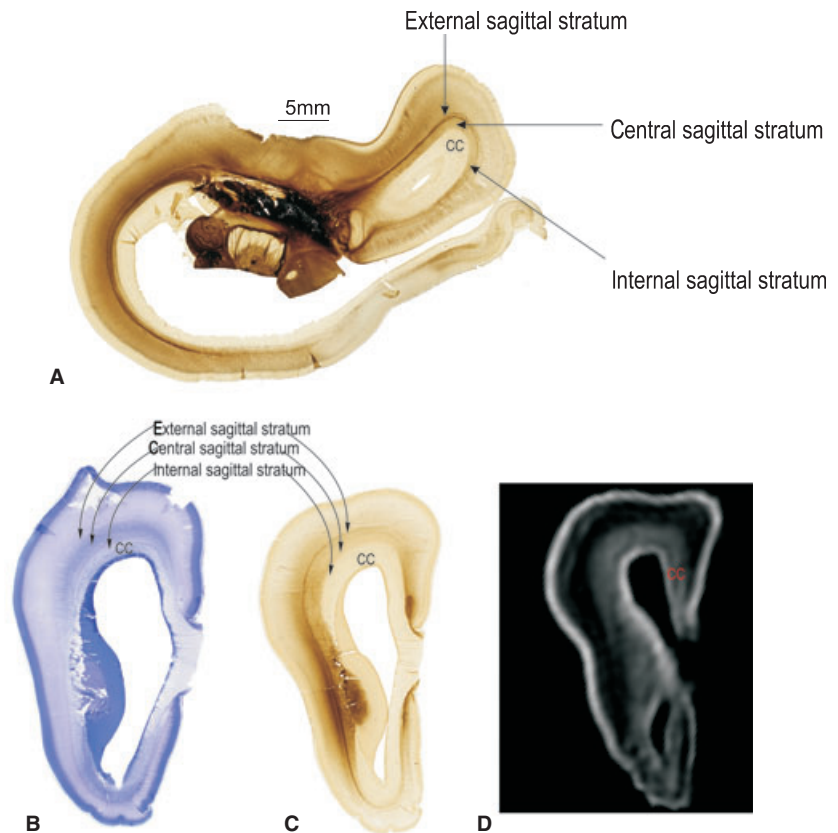
Fig. 7 Demonstration of sagittal strata and corpus callosum (CC) revealed by AChE (A, C) and Nissl staining (B) at 18 PCW as well as the MRI T1 weighted image of the same brain (D). CC, corpus callosum.

The most interesting finding is that the massive fiber system from the corpus callosum occupies the subventricular zone and that these fibers join the deep portion of the intermediate zone (Fig. 7B). This laminar relationship shows that there is continuity in fiber systems from the external sagittal stratum (with the external capsule) to the proliferative periventricular zones. Joint fibers of the intermediate zone and corpus callosum form the fiber corridor situated between the differentiating cortical layers (subplate zone and cortical plate) and periventricular proliferative layers (ventricular and subventricular zone). This is the basic architecture of the fetal telecephalon where a central corridor contains afferent and efferent systems. At present it is unknown whether this fiber corridor contains the same axonal guidance molecules as described for the corticostriatal junction or pallial–subpallial boundary (Lopez-Bendito et al. 2006; Maroof & Anderson, 2006).

In our own material findings, we have found high activity of chondroitin sulphate C, which is an essential portion of glycosaminoglycans (Judaš et al. 2005). In addition, we have found intensive staining of SNAP-25 in efferent fibers from the intermedial zone (see also Ulfig et al. 2000). It is also a matter of debate as to what lamina should be considered as a cortical target at this early phase when the cortex is composed of a thick subplate and thinner cortical plate. According to Kostović & Rakic (1990), the subplate is four times thicker than the cortical plate; it is a part of the fetal cortex and separates the cortical plate from the axons in the intermediate zone. We propose that the main source of axonal guidance molecules for entrance into the cortex is the subplate. The essential component of the subplate zone is the extracellular matrix, which builds up to 70% of the neuropil (Kostović et al. 2002). The extracellular matrix of the subplate contains different attractant and repellent molecules, such as fibronectin (Chun & Shatz, 1988; Tuttle et al. 1995; Pearlman & Sheppard, 1996), semaphorins, ephrins and other molecules (Hoerder-Suabedissen et al. 2009; for reviews see Judaš et al. 2003; Uziel et al. 2006). The possible cellular sources of the extracellular matrix and axonal guidance molecules are subplate cells (neurons or glia).

Considering the high activity of extracellular markers and guidance molecules in the subplate, this fetal compartment should be called a 'guidance compartment', meaning that afferent axons not only 'wait' but also are guided during the growth through the subplate (Rakic, 1977; Kostović & Rakic, 1990; Kostović & Judaš, 2002; Kostović & Jovanov-Milošević, 2006, 2008). In general, the significance of the subplate compartment for the guidance of axons in the cortex is underestimated (Price et al. 2006). A possible reason for this might be that the rodent brain subplate is very thin and exists for a short time, which does not give sufficient resolution in an experimental rodent model.

Different cellular components of the subplate may influence cellular interaction with afferent axons. The subplate is composed of postmigratory neurons, migratory neurons, radial glia, astroglia and microglia, which have a potential

developmental role in axonal growth. It should be kept in mind that all efferent axons have to pass through the subplate in order to reach the subcortical trajectories and targets. It is very likely that some of the efferent axons in the subplate interact with the afferent axons in early phases of development. This is consistent with the 'hand shake' hypothesis of Molnar & Blakemore (1995). Limbic bundles during the mid-fetal period, fiber pathways for the limbic cortex and limbic subcortical structures are well developed; an angular bundle can be traced from the frontal medial cortex (precingulate, cingulate ventromedial and dorsomedial cortical areas) to the posterior cingulate cortex (Fig. 8). In addition, the cingulum fiber bundle can be well delineated at this phase with the DTI and AChE staining (Fig. 8A). This is the trajectory for most of the cingulate pathways as described in the adult primate cortex (Schmahmann & Pandya, 2006; Petrides & Pandya, 2007). This is also consistent with previous observations in human fetuses (Huang et al. 2006, 2009).

The other aspect of limbic pathway organization that deserves special attention is the extremely rich connectivity of the amygdala, which is connected to the orbital cortex via the uncinate bundle (Fig. 8C, sea green). Another volu-minous fiber system connects the amygdala with the temporal cortex (Fig. 8B, green and red; Fig. 8C, yellow, pink and blue). This fiber system has the shape of a hand with fingers (Fig. 8B, red). We describe it as the amygdalo-temporal (temporo-amygalar) bundle but tractography does not permit determination of the pathway origin and termination. Other pathways that stream out of and into the amygdala (Fig. 8C) form a part of the periventricular crossroad of pathways (temporal crossroad C6) (Judaš et al. 2005). This periventricular crossroad is situated just in front of the rostral tip of the temporal horn of the lateral ventricle. Thus, our observation strongly indicates early development of the cortico–cortical and cortico–subcortical fronto-limbic connectivity (Kostović & Jovanov-Milošević, 2008; Kostović et al. 2008).

Periventricular crossroads

The analysis of DTI images and histochemical preparations (Figs 6D,E and 8C,D) reveals that periventricular territories adjacent to the internal capsule contain intersections (crossing) of the projection, callosal and associative pathways. These crossroads of pathways were described by von
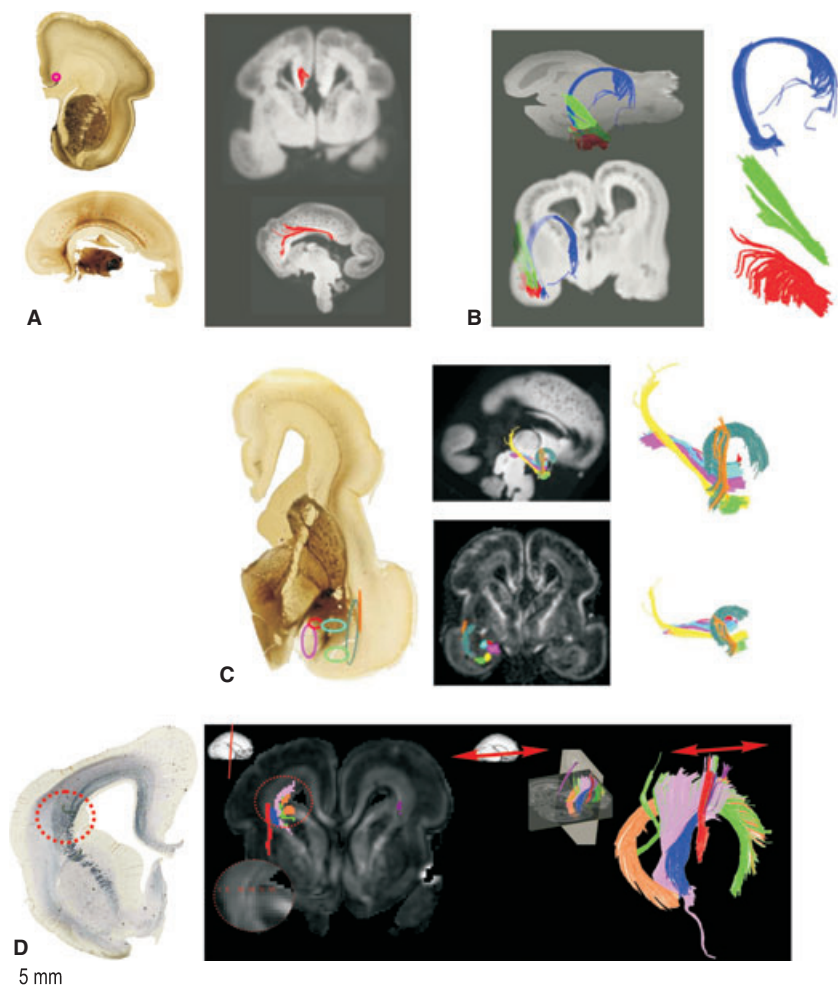

Fig. 8 Development of associative pathways and crossroad formation during mid fetal period. Formation of cingulum bundle at 17 PCW is shown by AChE staining and comparative DTI tractography (A, red colour). During 15 PCW (B) and 17 PCW (C) the amygdala connections and crossroad C6 becomes more complex- as revealed by DTI (C). During 19 PCW crossroad C1 formation can be show by SNAP staining and DTI tractography reconstruction (D). The crossroad area C1 is organized by axonal pathways that run in radial (thalamocortical), sagittal (associative) and transverse (callosal) direction (B, C). In D the different ROIs for the crossroad C1 can be seen (I-VI) and thus reconstructed with tractography (different colours represent different ROIs).

Monakow (1905) and more recently by Judaš et al. (2005). According to Judaš et al. (2005), six crossroad areas can be distinguished in the human telencephalon in fetuses older than 14 PCW. In the crossroad areas, axonal pathways run in radial (thalamocortical), sagittal (associative) and transverse (callosal) directions. The most numerous axonal system in the crossroad areas are projection fibers, which will later form corona radiata. Crossroad areas contain hydrophilic extracellular matrix, which is rich in axonal guidance molecules (Judaš et al. 2005). In addition to thalamocortical fibers, crossroads contain efferent fibers such as the prominent corticopontine fiber system (Fig. 6E). DTI analysis applied in this study allowed visualization of several fiber systems in the periventricular crossroad areas (Figs 6D,E and 8D): thalamocortical, corticopontine, corticocaudate and callosal fiber systems.

Accumulation of the thalamocortical fiber system in the subplate (19–23 PCW)

In a series of studies using AChE histochemistry, Kostović and co-workers (Kostović & Goldman-Rakic, 1983; Krmpotić-Nemanić et al. 1983; Kostović, 1990a,b; Kostović & Rakic, 1990) have shown that thalamocortical fibers accumulate in the superficial subplate after a prolonged 'waiting' period. This event occurs almost simultaneously in neocortical regions. The thalamocortical growing front can be traced to the mediodorsal nucleus (Kostović & Goldman-Rakic, 1983). The intense AChE reactivity of the thalamocortical growing front in the superficial subplate (shown in Fig. 9F and marked with ×) is enhanced due to the overlap with AChE staining in 'cholinergic' fibers from the magnocellular basal forebrain (Kostović, 1986). The hydrophilic extracellu-
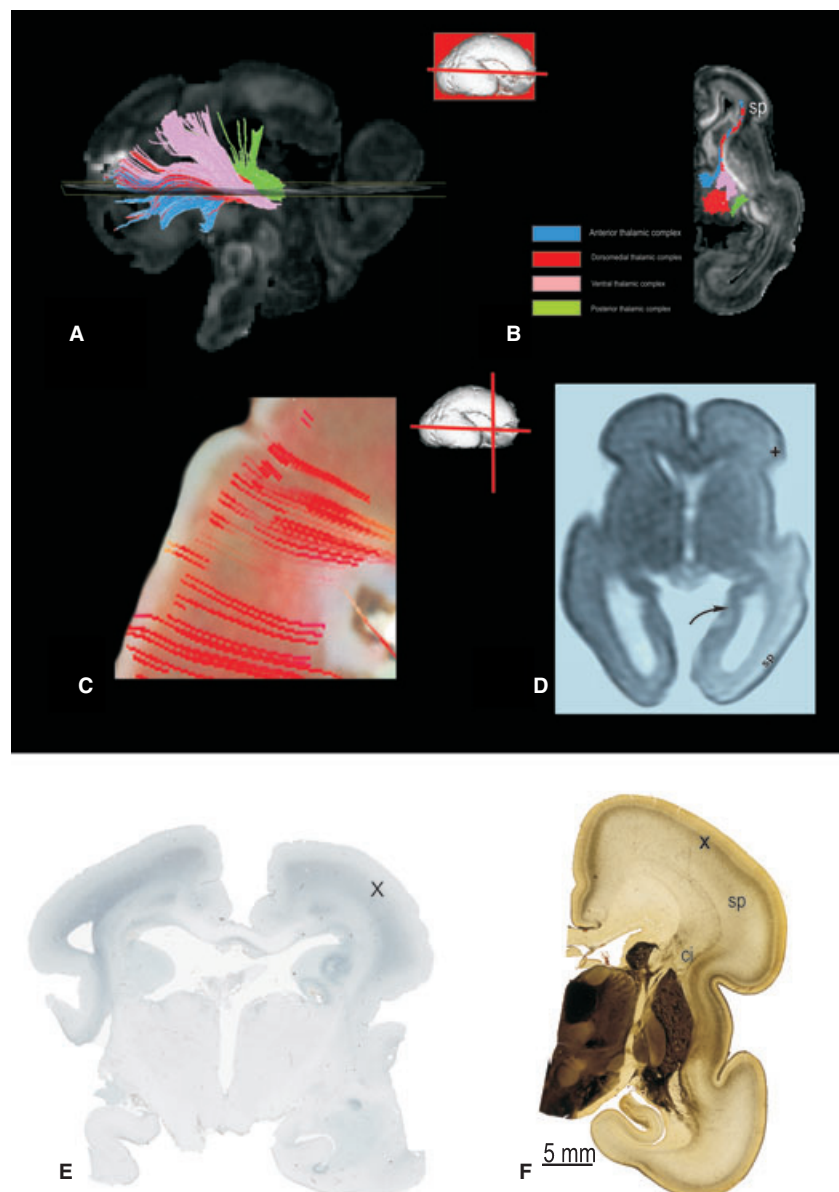

Fig. 9 Development of thalamocortical fibres at mid-fetal period. At 19 PCW fibres from different thalamic nuclei/complex (ROI, B) are taking different routs (anterior, superior and posterior thalamic radiation) towards the 'waiting compartment'-subplate (A) and cortical plate. In C the waiting fibre bundles in subplate, originating from thalamus can be seen by DTI at 24 PCW. For DTI tractography reconstruction in C we have lower the FA threshold level (0.12) due to the highly isotropic subplate in FA images (B). Accumulation of the growing front of thalamocortical fibres in superficial SP is shown by AChE staining (F, X) embedding in ECM rich neuropil shown by fibronectin staining (E, X). In vivo T2 weighted images (D) are also useful in showing subplate (sp) as well as the hiperintense superficial subplate part (D, +) due to the different T2 properties of the fetal laminae. Hippocampus and the enlarged marginal zone are showing similar T2 tissue properties in in vivo T2 weighted images (D, curved arrows). sp, subplate; ci, internal capsule.

lar matrix-rich zone of the subplate can be visualized in conventional T2 *in-vivo/in-vitro* magnetic resonance images as hyperintense zones beneath the cortical plate (shown in Fig. 9D and marked with +) due to the different hydrophilic organization of the subplate. The event of accumulation of afferent pathways cannot be demonstrated convincingly in DTI preparations (Huppi et al. 2001; Maas et al. 2004; Huang et al. 2006, 2009). In DTI images, thalamocortical pathways can be traced within the anterior, superior and posterior thalamic radiations (Fig. 9A,B). Very few individual fiber bundles reach the subplate (Fig. 9C).

The developmental shifts in histochemical properties and fibrillar organization (Fig. 9E) within the subplate show that this cellular compartment permanently changes in its fibrillar and cellular content. This concept is further supported by the shifts in molecular markers (Bayatti et al. 2008a,b). The molecular identification of subplate neurons was the research goal for multiple groups (Chun & Shatz, 1988; Meinecke & Rakic, 1992; Delalle et al. 1997; Kwan et al. 2008; Ayoub & Kostović, 2009; Hoerder-Suabedissen et al. 2009; McKellar & Shatz, 2009; Osheroff & Hatten, 2009). Zečević and colleagues have shown that glial cells also show differential distribution within the subplate (Jakovcevski & Zecevic, 2005).

Limbic cortex and limbic bundles

It is not known whether the limbic axonal pathways, related to the cingular, entorhinal and hippocampal cortex, display a waiting period and accumulation phenomena before the penetration of cortical or subcortical targets. In the archipallium of the hippocampus the enlarged marginal zone (Fig. 9D) shows the same histological properties as the subplate zone of the neopallium: enlarged thickness, fibrillar content, extracellular matrix-rich neuropil and intensive synaptogenesis (Kostović et al. 1989b). These basic features were also observed in the marginal zone of limbic (ventral) portions of the cingular cortex (Kostović & Krmpotić-Nemanić, 1976; Kostović & Judaš, 2002) and entorhinal cortex (Kostović et al. 1993).Thus, it is very likely that the marginal zone serves as a 'waiting' compartment for limbic axonal pathways. However, in contrast to the neocortical pathways in the subplate, the period of growth of the limbic pathways is shorter and growth trajectories are well delineated. As stated before, the limbic pathways form well-delineated bundles that are different from the neopallium where fibers are arranged in sagittal strata. In addition, limbic pathways grow in the cortical target zones tangentially (Kostović et al. 1989b).

Penetration of the cortical plate (after 24–26 PCW)

The major event in the axonal pathway development is penetration of the thalamocortical and basal forebrain fibers into the cortical plate (Fig. 9C). This event takes place after 24 PCW although some fibers may enter the cortical plate several weeks earlier (Kostović & Goldman-Rakic, 1983) as demonstrated in the AChE preparations. Histochemical activity gradually invades the lower third of the cortical plate (Fig. 10A). At around 28 weeks, the reactivity occupies the deep two-thirds of the neocortical plate (Fig. 10B) with an evident columnar distribution (see also Kostović, 1990a,b). During later development the AChE reactivity of the cortical plate becomes less dense (Fig. 10C). The ingrowth of thalamocortical fibers into the cortical plate (Counsell et al. 2007) was not directly illustrated in DTI structures. However, the decrease in fractional anisotropy in the frontal cerebrum after 24 PCW (Trivedi et al. 2009) and the decrease of the directionally averaged water apparent diffusion coefficient after 30 PCW (McKinstry et al. 2002) are very likely to be caused by the ingrowth of the afferent fibers (Kostović & Jovanov-Milošević, 2008; Kostović et al. 2008) and reorganization of embryonic columnar organization (McKinstry et al. 2002; Huang et al. 2006). Innervation of the cortical plate with the thalamocortical afferents is a crucial event in the histogenesis and functional organization of the cortex. Thalamocortical afferents cause visible lamination of the cortical plate (Kostović & Judaš, 2002). The ingrowth of thalamocortical fibers is guided with permissive influence or attraction by complex molecular interactions (Molnar & Blakemore, 1995; Molnar et al. 1998; Sestan et al. 2001; Price et al. 2006). The establishment of the first synapses in the human telencephalon after 24 PCW (Molliver et al. 1973) marks possible functional interactions between the thalamic afferents and cortical plate cells. This interaction may induce functional differentiation of cortical layer IV (Wilkemeyer & Angelides 1996; Catalano & Shatz 1998; Anderson & Price 2002) and can be studied by optical recording and current source density analysis (Molnar et al. 2003; Higashi et al. 2005). The most significant event related to the establishment of thalamocortical connectivity is the appearance of somatosensory evoked potentials (Molliver, 1967; Kostović & Jovanov-Milošević, 2006; Vanhatalo & Kaila, 2006; Kostović & Judaš, 2007; Milh et al. 2007). The thalamocortical pathways conducting impulses for pain sensation mature in the same period (Slater et al. 2008; Lagercrantz & Changeux, 2009).

Long corticocortical pathways (commissural) and development of the corona radiata (26 PCW and older)

The callosal corticocortical pathways develop very soon after the thalamocortical fibers. This sequential callosal growth is several weeks behind the thalamocortical fiber growth. The most massive fiber system in the brain after 24 weeks is the corpus callosum. At the septal (rostral) levels callosal fibers build the massive callosal plate (Fig. 10A,B) (Kostović & Judaš, 2002), which almost fills the
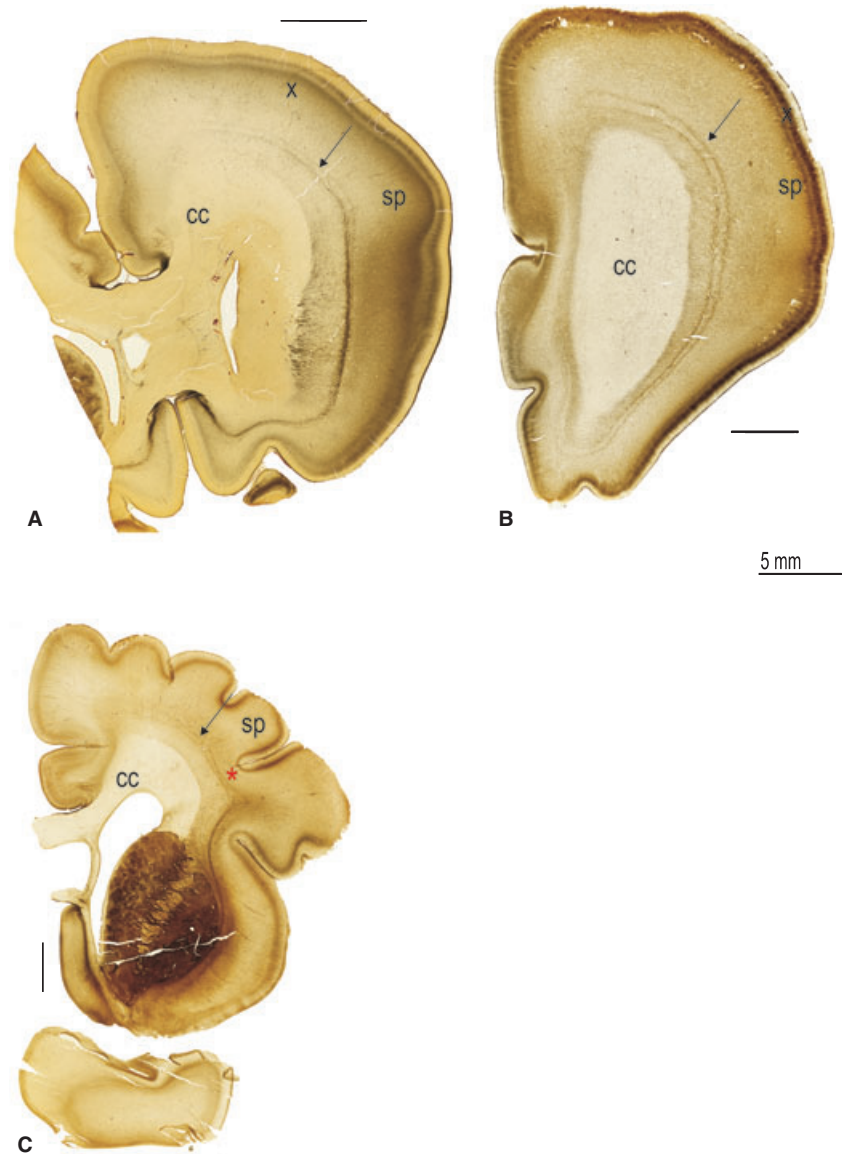
Fig. 10 Histochemical demonstration of thalamocortical penetration into the cortical plate. At 26 PCW the histochemical activity gradually invades the lower third of the cortical plate (A; X). Around 28 PCW the same reactivity occupies deep two third of the neocortical plate (B; X) and during the later development (36 PCW) the AChE reactivity of the cortical plate becomes less dense (C). After 24 PCW the most massive fibre system is corpus callosum building the massive callosal plate that can be well seen at the coronal sections of the AChE histochemistry (A, B, C; CC). After the 36 PCW the resolution of subplate (SP) can be seen (C) but the external sagittal stratum can be still well delineated (A, B, C; arrows). sp, subplate; CC, corpus callosum.

periventricular surface of the dorsal telencephalon. This callosal relationship outlines the adult topographical position of the corpus callosum. The massive size of the callosal periventricular plate indicates the initial phase in overgrowth events (Innocenti & Price, 2005). In the early postnatal phases there is a significant decrease of callosal fibers (LaMantia & Rakic, 1994; Innocenti & Price, 2005) and callosal morphogenetic zones (Jovanov-Milošević et al. 2009), which occurs before the period of myelination.

The DTI reconstruction of callosal fibers during late gestation demonstrates an elaborated callosal radiation in all segments of the corpus callosum (Maas et al. 2004; Huang et al. 2006, 2009; Counsell et al. 2007; Kasprian et al. 2008; Ment et al. 2009). These studies did not prove whether/when the callosal fibers actually innervate the cortical plate and did not even show if the callosal fibers pene-

trate/innervate the subplate. Kostović & Rakic (1990) have proposed that the callosal fibers are the main constituent of the subplate after the thalamocortical fibers have already grown into the cortical plate. Some of the callosal fibers probably never reach the cortical plate. (Schwartz & Goldman-Rakic, 1991).

Classical neuroanatomical studies have encountered serious difficulties in demonstration of the growth of the long associative fibers due to the fact that the glutamatergic axons could not be stained with standard immunocytochemical or histochemical techniques. These fibers are also negative for the cholinesterase. Some of the deep associative pathways, most notably the fronto-occipital fascicle (visualized with SNAP-25), were shown early in midfetal brain by Judaš et al. (2005). According to Huang et al. (2006) the inferior longitudinal fascicle and inferior fronto-occipital fascicle
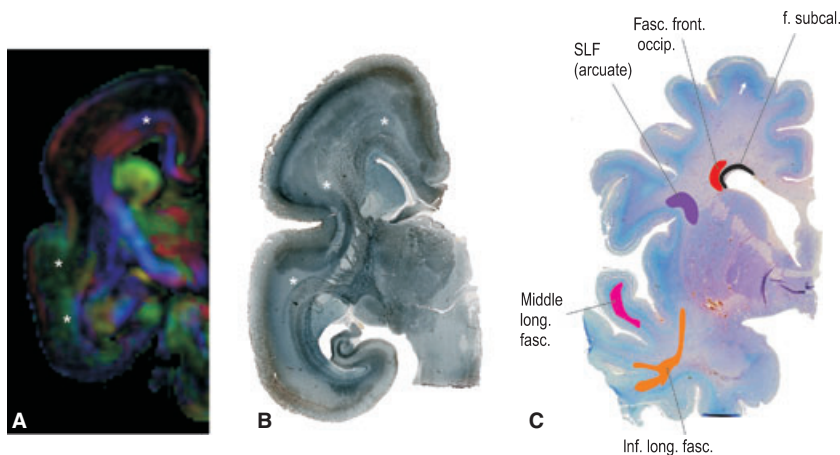
Fig. 11 Development of associative fibre bundles revealed by DTI colour coded map (A), GNG staining (B) and PAS staining (C). The prospective trajectories of the associative pathways were indicated by asterisks (A, B) or outlined by colours (C). f. subcal, subcallosal fasciculus; middle long. fasc., middle longitudinal fasciculus; SFL, superior longitudinal fasciculus; inf. long. fasc., inferior longitudinal fasciculus.

were seen around 17 PCW but do not undergo a significant development during the second trimester. The superior longitudinal fascicle is not prominent even at birth (Huang et al. 2006; Zhang et al. 2007). Our preliminary observations showed different properties of the extracellular matrix at the locations of the associative pathways (Fig. 11).

We have interpreted the position of the superior crossroad (Judaš et al. 2005) as a prospective trajectory of the superior longitudinal fascicle in our postmortem MRI study.

During the late fetal period there is a major change in the orientation and distribution of the projection fibers. The projection fibers elongate, changing tangential fiber stratification into the corona radiata system. According to Judaš et al. (2005), 'the transformation of fiber architectonic pattern from predominantly tangential in fetuses to predominantly radial in preterm infants occurs concomitantly with several other events: (i) the development of distal portions of the corona radiata and the centrum semiovale proper, (ii) the dissolution of the transient fetal subplate zone, (iii) the relocation of cortical afferents from the subplate zone into the cortical plate, and (iv) the onset of gyrification (Kostović & Rakic, 1990; Kostović & Judaš, 2002)' (Fig. 10C).

The individual projection fibers in the corona radiata seem to pass even the border of the subplate (compare with Fig. 8.3.d in Huang et al. 2006). The subplate is still well developed in the cortical gyri, whereas it is reduced in the bottom of the sulci. The presence of the subplate at late fetal age (Kostović, 1990a,b; Kostović & Rakic 1990; Kostović et al. 2002; Judaš et al. 2005) is the main marker of immaturity of the fetal white matter.

In late preterm, the white matter consists of the following segments: segment 1, with the callosum and periventricular fibers; segment 2, the foot of the corona radiata with the periventricular crossroads; segment 3, the centrum semiovale; and segment 4, the gyral white matter. Segment 5 [the (intra)cortical white matter] is not developed (Judaš et al. 2005). The subplate zone interrupts the continuity of the white matter and gyral cortex (Kostović et al. 2002; Judaš et al. 2005; see also classification in Von Monakow, 1905).

Discussion on development of fiber pathways in the cerebral cortex of the fetus

The data about the initial outgrowth, path-finding, trajectories, waiting compartments and target distribution indicate that the fetal part of gestation is the most important for the growth of long projection, associative and commissural pathways in the human cerebrum. It is evident that the neocortical fiber pathways show a different pattern of fiber growth than the limbic fiber systems. The main projection pathway of the limbic nuclei and cortex grows in the form of the compact axonal bundles along the midline (fornix, stria terminalis and cingulum). These bundles elongate and curve parallel to the growth of the hemispheres. However, neopallial fiber pathways change their trajectory at the level of the lateral angles of the ventricles, forming the crossroads, embedded in a rich extracellular matrix with axonal guidance molecules (Molnar & Blakemore, 1995; Molnar et al. 1998; Molnar & Butler, 2002; Judaš et al. 2005; Price et al. 2006). This junction area was described (Molnar & Butler, 2002) as a crucial junction point for the pathway selection of the most commonly demonstrated cortico–subcortical and subcortico–cortical pathways. The involvement of guidance molecules in thalamocortical pathway formation was, among others, most convincingly demonstrated for the Slit/Robo (Bagri et al. 2002), EphRTK/ephrins (Dufour et al. 2003), Nrg1/ErbB4 (Lopez-Bendito et al. 2006) and Semaphorin/Neuropilin1 (Wright et al. 2007) families of proteins. At present it is not known whether the same molecules guide corticostriatal and telencephalo–diencephalic junction fibers in the intermediate zone and sagittal strata. The current evidence is insufficient to form a conclusion about the guidance within the external capsule. The evidence presented in this review clearly shows that the external capsule is a complex system that contains projection fibers from the basal forebrain (Kostović, 1986; Mesulam et al. 1992), associative cortical and corticostriatal pathways. The presence of basal forebrain pathways is not described in the current imaging literature (Makris et al.

1997) and in experimental studies (Schmahmann & Pandya, 2006). The basal forebrain projections through the external capsule were shown to be the earliest modulatory input to the neopallium. The significance of this early afferent modulatory input for the early endogenous (Kostović, 1986; Kostović & Judaš, 2007), oscillatory activity of the cortex was stressed in recent experimental studies (Hanganu & Luhmann, 2004; Hanganu et al. 2009; Luhmann et al. 2009; Yang et al. 2009). The other modulatory inputs arriving at the telencephalon at very early ages are from the monoaminergic nuclei in the brainstem (Nobin & Bjorklund, 1973; Olson et al. 1973; Molliver & Kristt, 1975; Zecevic & Verney, 1995). These earliest afferent pathways, visualized by fluorescent techniques, do not form distinct bundles, and are formed by extremely fine fibers. Therefore, these pathways cannot be demonstrated by a tractography or by the histological techniques presented in this review. The only possible trajectory where these early monoaminergic afferents can be eventually visualized is the medial forebrain bundle in the lateral hypothalamus (Nauta, 1971; Nobin & Bjorklund, 1973; Olson et al. 1973).

The evidence presented in this review supports the concept of the 'waiting' period and 'waiting' compartments. As presented above, all of the thalamocortical afferents and basal forebrain afferents invade the subplate after 13-14 PCW and 'wait' in the subplate compartment for a prolonged period, until after 23 PCW. The concept of the waiting period was introduced by Rakic (1977) and was further corroborated in a series of articles on the development in thalamocortical projection in human and monkey brain (Kostović & Rakic, 1984; Kostović & Goldman-Rakic, 1983; Kostović & Jovanov-Milošević, 2006; Kostović & Judaš, 2002, 2007, 2010). Within this period the tractography can trace long pathways within the trajectories but not the ramification within the subplate. This may be explained by the plexiform isotropic nature of the fibrillar network 'embedded' within the fluid rich extracellular matrix of the subplate. It is only after 19 weeks, during the accumulation of the thalamocortical fibers, that some of the fibers can be traced across the subplate. However, the histochemical cholinesterase method was shown to be efficient in the demonstration of the ingrowth of the afferents into the cortical plate.

The indirect evidence for the accumulation of the thalamocortical circuitry within the cortical plate is lamination (Kostović & Judaš, 2002) and changes in isotropy of the cortical plate (Huppi et al. 2001; McKinstry et al. 2002).

Another observed phenomenon of the developmental cerebrum is the axonal distribution and growth in sagittal strata. This stratified pattern of distribution is the predominant pattern in the early development of the cerebral hemisphere (Altman & Bayer, 2002; Bayer & Altman, 2002, 2004, 2005, 2006, 2008; Judaš et al. 2005). The crucial period of the change in stratified development occurs after 28 PCW when the thalamocortical afferents, together with other

projection pathways, develop the corona radiata (thalamic radiation, Stabkrantz, Von Monakow, 1905). After this period, the sagittal strata remain well delineated only in the occipital and frontal pole (Judaš et al. 2005).

In the current literature we have found different descriptions and terminology for the classification of the sagittal strata (Makris et al. 1997; Schmahmann & Pandya, 2006). The results presented in this review suggest that the minimum subdivision of the sagittal compartment is into the three sagittal strata (external, central and internal stratum) as suggested by Von Monakow (1905). From the evidence presented in the previous paragraph it is obvious that the data on the development of the sagittal strata are very scanty. Because of this, further studies are needed to describe the content of the individual sagittal strata. This is a very interesting problem for the neuroimaging community because these strata can be easily demonstrated by the tractography method due to the fact that the fibers run in a predominantly anterior–posterior direction.

Significance

The great significance of the prenatal growth of the cerebral pathways is widely accepted in the developmental and prenatal neurological literature. The growing white matter is considered to be the most vulnerable cellular compartment in the preterm brain (Counsell et al. 2007; Leviton & Gressens, 2007; Mathur & Inder, 2009; Ment et al. 2009; Miller & Ferriero, 2009; Volpe, 2009). Lesions of the white matter lead to cognitive impairment in 30–60% of very preterm children, whereas 40% display a mild motor deficit (Mathur & Inder, 2009). A high percentage of very preterm infants have a sensory deficit (Johnston et al. 2001). The most vulnerable locus in the developing white matter of preterm infants is the periventricular crossroads of pathways, which can be damaged by focal leukomalacia (Judaš et al. 2005; Volpe, 2009). As presented above, these loci contain the associative and commissural pathways, which may explain the complex neurodevelopmental and cognitive deficits seen after periventricular lesions in preterm infants (Evrard, 2001; Johnston et al. 2001; Volpe, 2003, 2009; Judaš et al. 2005; Mathur & Inder, 2009; Ment et al. 2009; Miller & Ferriero, 2009).

Acknowledgements

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