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Ex vivo fetal brain MRI: Recent advances, challenges, and future directions

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1. Introduction – an overview of brain development assessed by structural *ex vivo* MRI

1.1. An overview of major histogenic events that occur during early brain development

Prenatal development of the human brain is a complex process. The fetal telencephalic wall can be roughly divided into five transient zones (by the Boulder Committee; Bystron et al., 2008a,b). Superficial to the ventricle towards the pia, these zones are: i) the proliferative zones (ventricular and subventricular zones, VZ/SVZ), ii) intermediate zone (IZ, i.e. the fetal white matter), iii) subplate zone (SP), iv) cortical plate (CP), and v) the marginal zone (MZ). These zones change during gestation as assessed quantitatively (e.g. thickness and volume) and qualitatively (e.g. changes in histological properties). Such changes in the appearance of transient fetal zones reflect the intensity of neurogenic events such as neuronal proliferation, migration, axonal ingrowth and outgrowth, neuronal differentiation, as well as areal specialization (Fig. 1). Towards the end of gestation, all key structural components are established in the fetal brain, and the brain continues to reorganize postnatally.

Similar to the cerebrum, neuronal proliferation, migration, differentiation, axon growth, synaptogenesis, and pruning also occur during the morphogenesis of the human cerebellum (Sidman and Rakic, 1973; Wang and Zoghbi, 2001; Lavezzi et al., 2006). However, the neurogenic events that occur during cerebellar development continue through the first postnatal year (Altman and Bayer, 1997; Wang and Zoghbi, 2001; Saksena et al., 2008), and occur for longer than those in the cerebrum.

1.2. MRI characteristics of the transient fetal zones

The proliferative zones (VZ, SVZ) contain densely packed cells (neuronal and glial precursors; Rakic, 1972; Kostovic et al., 2002; Radoš et al., 2006). Due to the high density of tightly packed cells, the proliferative zones can be observed from ex vivo MRI as zones with high T_1-weighted (T_1w) or low T_2-weighted (T_2w) signal intensities. On diffusion weighted imaging (DWI), these zones are characterized by high fractional anisotropy (FA) (Kostovic et al., 2002; Huang et al., 2006, 2009; Radoš et al., 2006; Huang and Vasung, 2014). The VZ can be discerned from the SVZ only with MRI examinations that have high spatial resolution (e.g. less than 0.2 mm).

The VZ lines the lateral ventricles. The SVZ is initially a thin zone that

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Abbreviations

CP	cortical plate
CRL	crown–rump length
DTI	diffusion tensor MRI
DWI	diffusion weighted images
FA	fractional anisotropy
GE	ganglionic eminence
GW	gestational weeks
HARDI	high-angular resolution diffusion MRI
IZ	intermediate zone
MR	magnetic resonance
MRI	magnetic resonance imaging
PMI	postmortem interval
SP	subplate
SVZ	subventricular zone
T_1w	T_1-weighted
T_2w	T_2-weighted
TIF	time in fixative
VZ	ventricular zone

continues to thicken during mid-fetal stages (Zecevic et al., 2005). Around 13 GW, the SVZ is divided into the inner (cellular) and outer (less cellular) layers by tangential fibers that course between them. On high-resolution MR images, it is easy to recognize this layer of tangential fibers with a low T_1w MR signal intensity. However, the identification of the exact borders between the SVZ and other zones (i.e. the VZ and the IZ) remains a challenge. The inner part of the SVZ "blends" with the VZ because they both contain tightly packed cells. On the other hand, the outer part of the SVZ "blends" with the IZ because cells are sparse in both zones. Thus, the delineation of the VZ and the SVZ with ex vivo MRI is not possible with a lower spatial resolution than the thickness of the zone(s) of interest (Vasung et al., 2016).

Axonal pathways (i.e. fetal white matter) span the IZ, which is characterized by a moderate T_1w MR signal intensity (Vasung et al., 2016). The IZ is surrounded by the SP zone, which serves as an axonal "waiting compartment" (Kostovic and Rakic, 1990). The IZ and the SP together contain less densely packed neurons, more axonal fibers, and more extracellular matrix compared with the proliferative zones. Compared to the proliferative zones, ex vivo MRI shows that the IZ and SP are characterized by lower or moderate T_1w MR signal intensities and higher or moderate T_2w MR signal intensities (Kostovic et al., 2002; Radoš et al. 2006; Vasung et al., 2017). Although the SP can be distinguished from the IZ with conventional T_1w and T_2w MRI, diffusion MRI (dMRI) is superior for characterizing their microstructural compositions. With dMRI, the IZ (composed of compact fiber bundles) has moderate to high FA values, while the SP (containing a high amount of the extracellular matrix and dispersed axonal fibers) consists of low FA values (Fig. 2; Huang et al., 2006; Huang et al., 2009; Wang et al., 2015; Vasung et al., 2017).

During the first two trimesters, the CP contains tightly packed post-migratory neurons that are arranged into embryonic columns (Rakic, 1988; Jones and Rakic, 2010). During this time, the CP is characterized by high FA values (Fig. 3A), high T_1w and low T_2w MR signal intensities (Huang et al. 2006, 2009, 2012; Kostovic et al., 2002; Radoš et al., 2006). During the last trimester, the dendritic arborizations of the post-migratory CP neurons gradually increase, which results in a gradual decrease of FA values in the CP (McKinstry et al., 2002; Khan et al., 2019; Batalle et al., 2019, Fig. 3B).

Lastly, the MZ is situated directly below the pia. The first synapse formation occurs in the MZ (Molliver et al., 1973). However, it is almost impossible to continuously delineate this zone on MRIs, because the thickness of this zone is often below the typical spatial resolution of ex vivo MRI (e.g. 0.2–1 mm).

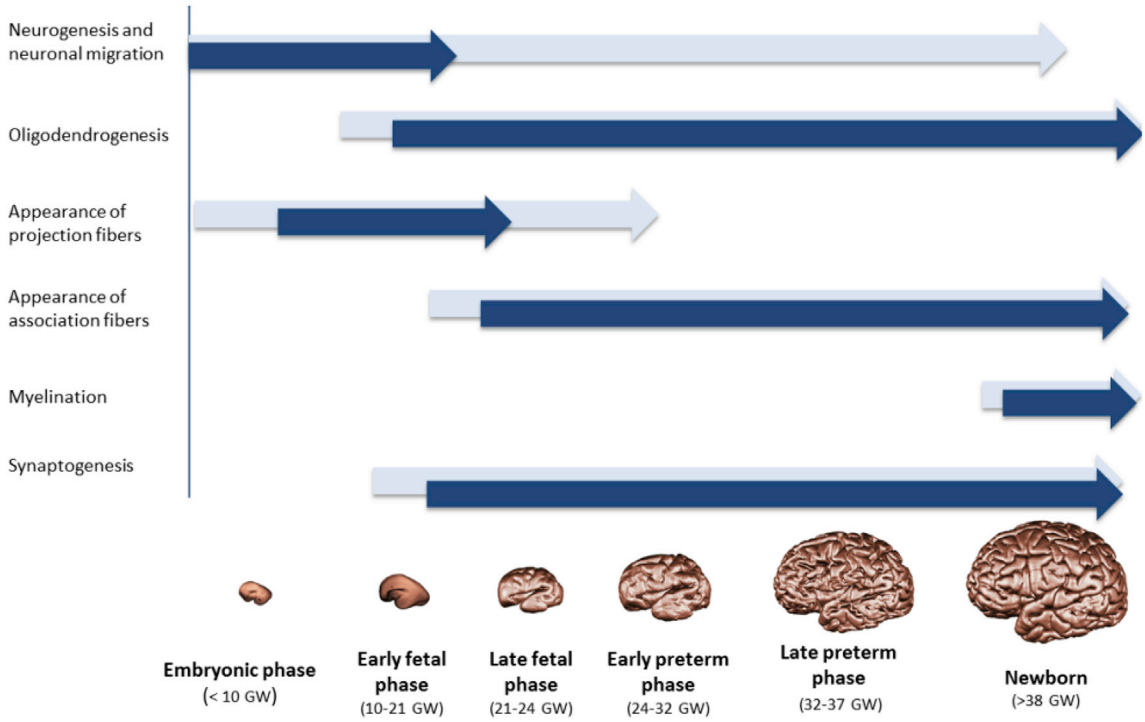

Fig. 1. Summary illustration of the major neurogenic events and their intensities (intensity of the color), which occur during early human brain development. Developmental phases were divided according to classifications of the human brain before 24 GW (https://paperpile.com/c/G7qjz3/LgCb+n2no+MT1Q Ronan and Müller, 2006; Kostovic and Judas, 2009; Sidman and Rakic, 1973) and after 24 GW (Blencowe et al. 2013).

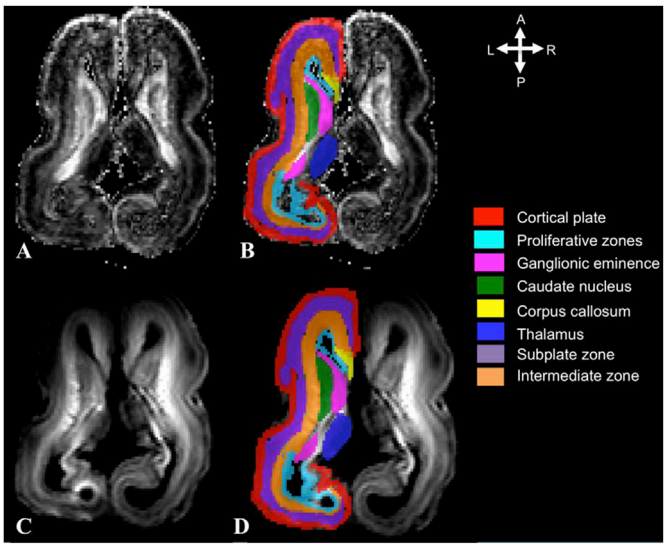

Fig. 2. Example of the semi-automatic segmentation of the transient fetal zones during mid-fetal period. Fractional anisotropy (FA) (A,B) and diffusion weighted MRI (DWI) axial slices (C,D) used for segmentation of the cortical plate (red), proliferative zones (light blue), subplate (purple), intermediate zone (orange), thalamus (dark blue), corpus callosum (yellow), caudate nucleus (green), and ganglionic eminence (GE) (pink). Reproduced from Vasung et al. (2017), with permission.

1.3. Age-related changes in qualitative MRI characteristics of the transient fetal zones

During prenatal brain development, MR characteristics of the fetal zones (such as FA and MR signal intensities) are not static. Rather, they change with gestational age. It has been suggested that changes in the MR characteristics of fetal zones are related to the intensity of neurogenic events (Kostovic et al., 2002). For example, the high T_1w MR signal intensity of the CP, as well as the high FA decrease during the late preterm period (31–36 GW; McKinstry et al., 2002; Ball et al., 2013; Batalle et al., 2019), which coincides with the gradual increase in dendritic arborization of the post-migratory neurons in the CP (Mrzljak et al., 1988, 1991). Thus, it is likely that the increase in dendritic arborization leads to an increase in the distance between the CP neurons restricting the water displacement more uniformly in all directions and resulting in a gradual loss of FA values within the CP (McKinstry et al., 2002).

With ex vivo MRI, the SP can be detected around 15 GW, and reaches its peak thickness between 26 and 32 GW, but then disappears a few months after birth (Kostovic and Rakic, 1990). During the transition from early (25–30 GW) to late preterm (30–36 GW), the SP cannot be identified as a continuous zone. It has been suggested that this change is most likely caused by a relocation of "waiting" axons from the SP to their final destinations in the CP (Kostovic and Judas, 2002; Kostovic and Jovanov-Milosevic, 2006) by the loss of the extracellular matrix and by the reorganization of the fetal white matter into Von Monakow segments (von Monakow, 1905; Kostovic et al., 2014).

1.4. Age-related changes in quantitative MRI characteristics of the transient fetal zones

Similar to the qualitative changes in MRI characteristics of transient fetal zones that are observed during human fetal development, the thickness and volume of fetal zones also change over time. We can consider developmental trajectories of these zones to better understand basic developmental processes (e.g., cell proliferation, migration, axon extension) that occur during human development (Vasung et al., 2016). For example, the surface of the CP increases almost 50 times from 15 to 42 GW, contrasting a very discrete increase in its thickness (sub-millimeter increase, see Fig. 4; Vasung et al., 2016). By 22 GW, the majority of the migrating neurons already reach their final destinations in the CP except in prefrontal regions (Paredes et al., 2016). Thus, before 22 GW, the arrival of the new neurons in the CP might account for the increase in the surface and the thickness of the CP. After 22GW, an increase in the surface of the CP is most likely accounted for by areal differentiation, dendritic arborization, and the ingrowth of axonal fibers (Vasung et al., 2016). Interestingly, although the cortical surface of each lobe grows at differential rates, the percentage of the total cortical surface occupied by the cortical surface of a specific lobe remains constant across gestational ages (Vasung et al., 2016). As another example, the SP peaks in volume and thickness during the axonal "waiting" period (Fig. 4, Kostovic and Judas, 2002; Vasung et al., 2016). As development progresses, the SP wanes and axons invade the CP (Kostovic and Judas, 2002).

From 15 to 22 GW, the relative volume of the proliferative zones (i.e. the percentage of the hemispheric volume occupied by these zones) decreases exponentially (Vasung et al., 2016), which coincides with the cessation of neurogenesis. Thus, the quantitative and qualitative MRI characteristics of the fetal transient zones most likely reflect the changes in neurogenic events that occur within these zones. However, the detailed information on neuronal migration and axonal

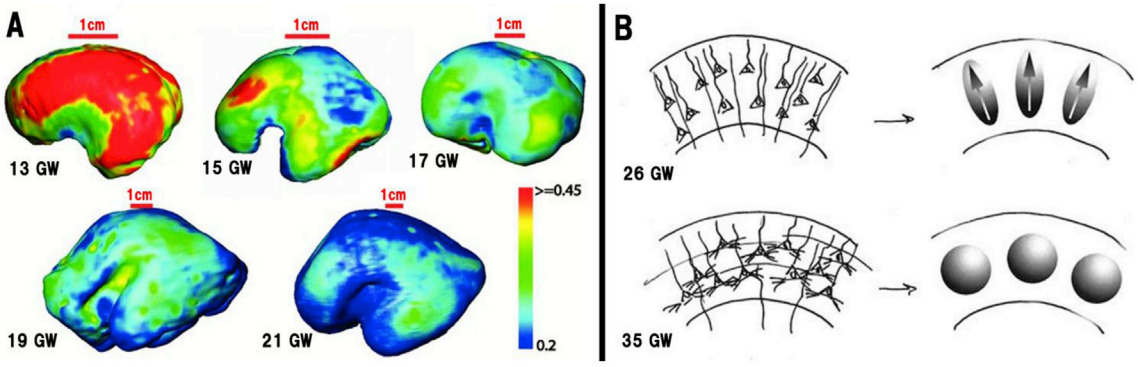

Fig. 3. Changes of FA values of the CP during early (A) and the late (B) prenatal development. (A) FA mapping of the cortical surface of fetal brains at the gestational weeks shown. Color bar indicates FA values in the cortical surface FA maps (Modified from Huang et al., 2012, with permission). (B) A diagram explaining changes in FA values during late prenatal period. Left images are drawings of the cortical structure, while right images are the corresponding diffusion ellipsoids. At 26 GW (upper row), radial glial fibers and pyramidal neurons with prominent, radially oriented apical dendrites are shown. This organization has the effect of restricting water displacement parallel to the cortical surface more than displacement orthogonal to it, resulting in diffusion ellipsoids which are non-spherical with their major axes oriented radially (arrows), which provides high FA values. By 35 GW (lower row), prominent basal dendrites for the pyramidal cells and thalamocortical afferents have been added. This has the effect of restricting water displacement more uniformly in all directions. As a result, the diffusion ellipsoids are spherical, without a preferred orientation, which provides low FA values (Modified from McKinstry et al., 2002, with permission).

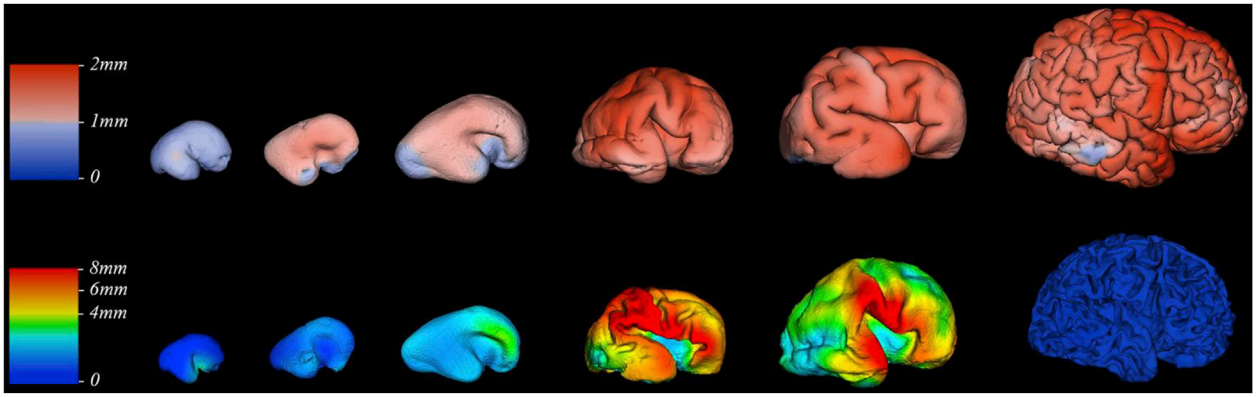

Fig. 4. Thickness of transient fetal zones. Thickness of cortical plate (upper row) and SP (bottom row) measured in millimeters (color coded bars) at 15, 18, 20, 26, 32, and 42 GW (left to right). Reproduced from Vasung et al. (2016), with permission.

outgrowth/ingrowth cannot be characterized with MR measurements of the fetal transient zones. Therefore, we will discuss the potential, advances, and limitations of ex vivo dMRI, dMRI tractography, T_1w, and T_2w MRI, to characterize in detail, the dynamic processes that occur during fetal brain development.

2. Technological considerations of *ex vivo* fetal MRI

2.1. Advantages of the ex vivo MRI compared to in vivo MRI

Ex vivo MRI provides structural and diffusion images of the specimen scanned at high spatial resolution (e.g. 500um or higher) and high signal-to-noise ratio (SNR). The high SNR and spatial resolution are more easily achieved by using high-field strength MRI scanners and using custom-made radio-frequency (RF) coils that more tightly fit the specimen. These coils can be single-channel surface or volume coils (for small specimens) or multi-channel phased-array coils (for large specimens). In addition, compared to *in vivo* MRI where scan times are limited by the subject's ability to remain still during a typical exam of less than 1.5 h long, *ex vivo* MR scan times often take many hours to boost SNR, and are limited almost only by the MR scanner's availability and the costs for its use. Therefore, both structural and diffusion *ex vivo* MRI scans can detect detailed information about tissue properties that go unseen on *in vivo* imaging.

Aside from the lower spatial resolution, the quality of *in vivo* MR images may be compromised by artifacts due to subject's motion. Strong susceptibility effects are typically observed around ears and nasal cavities (i.e. in areas with air-tissue boundaries). Thus, it is sometimes difficult to identify subtle cortical abnormalities or abnormal fiber pathways from *in vivo* MRI. Ex vivo MRI does not suffer from motion artifacts, and susceptibility artifacts can be mitigated by proper and careful preparation of the specimen (i.e. avoiding the creation of air bubbles). Therefore, careful assessment of high-quality *ex vivo* MR images in combination with histology can provide a basis for detection of subtle cortical abnormalities using T_1w and T_2w MRI, and abnormal development of fiber pathways using dMRI. These findings can be used to guide the detection of cortical abnormalities or abnormal fiber pathways *in vivo*. Similarly, if cortical abnormalities or abnormal fiber pathways are detected *in vivo,* then *ex vivo* MRI studies along with histopathology analyses can be used to confirm these findings. For example, when we see an abnormal fiber pattern *in vivo*, and if *ex vivo* dMRI tractography also detects the same fiber pattern, the *in vivo* pathways would likely correspond to "real" pathways and would not likely be artifacts due to noise and/or dMRI tractography algorithms.

Finally, spatiotemporal changes in anatomy of the human fetal brain as assessed from *ex vivo* MRI results are the product of complex processes that span spatiotemporal changes in gene expression and epigenetic modifications during development (Huang et al., 2013). Spatiotemporal changes in gene expression do vary across species, and it would be of interest to investigate the relationship between spatiotemporal changes in gene expression and diffusion MR tractography to better understand basic developmental processes that occur during human brain development (for review, see e.g. Judaš, 2011; Kang et al., 2011; Pletikos et al., 2014; Charvet et al., 2018). Combining *ex vivo* MRI with genetic and histological analyses is the first step towards a better understanding of the impact that gene expressions can have on regional morphometry and fiber growth/retraction.

2.2. Advances in ex vivo structural MRI

As mentioned above, numerous neurogenic processes occur during prenatal brain development. These processes are under strong genetic influences (Pletikos et al., 2014), and may be associated with MR signal intensity or dMRI measurements (Kostovic et al., 2002; McKinstry et al., 2002; Wang et al., 2015; Lefèvre et al., 2016). The majority of *in vivo* fetal MR imaging protocols use single-shot T_2w MRI sequences (e.g. Prayer et al., 2006), as they are more robust to fetal motion. However, the single-shot T_2w scans tend to be inferior to multi-shot turbo-spin-echo (TSE) scans, which are often performed postnatally. Moreover, direct employment of the TSE protocol used *in vivo* may not be optimal to characterize transient zones found in *ex vivo* fetal brains. This is especially the case during the last phases of fetal development, which is most likely due to differences in tissue properties between *in vivo* and *ex vivo* brains given that *ex vivo* brain are fixed. One way to deal with this issue is to acquire T_2 maps on postmortem samples to infer the best imaging parameters of the TSE that would maximize the T_2 contrast. In this review, we focus on T_1w MRI and dMRI properties of the developing *ex vivo* fetal brain.

2.3. Advances in ex vivo diffusion MRI

dMRI is useful for detecting microstructural diffusion properties in tissue. Using tractography techniques, we can identify pathways in the entire brain mantle in a 3-D manner. High-angular resolution diffusion MRI (HARDI) (Tuch et al., 2002, 2003) with optimal scanning parameters (such as e.g. high b values) theoretically provides exceptional angular resolutions of fiber pathways that traverse long distances throughout the brain, and disambiguating fiber trajectories at points of intersection (crossing fibers). Given that many imaging voxels likely contain multiple fiber orientations, the use of HARDI is an important solution for finding accurate pathways in the brain. However, although limitations have been increasingly reported for traditional diffusion tensor imaging (DTI) tractography, it is still useful depending on the pathways of interest and the goal of the research study (e.g. Song et al., 2017).

Spatiotemporal developmental time courses of the maturation of the

fornix, cingulum bundle, corpus callosal and thalamocortical pathways, inferior longitudinal, inferior fronto-occipital, uncinate, and arcuate fasciculi, as well as insular, cerebellar, and many other pathways in human fetal ages have been described with the use of HARDI (Takahashi et al., 2012, 2014; Song et al., 2015; Wilkinson et al., 2016; Vasung et al., 2017; Das and Takahashi, 2017). Although *ex vivo* dMRI has produced an exceptional resolution of fiber pathways, it is possible to achieve comparable results using *in vivo* imaging (e.g. Xu et al., 2014). Specifically, we imaged *in vivo* and *ex vivo* human fetal brains, and found that radial coherence of the cerebral cortex coincides with the presence of radial glial fibers (Xu et al., 2014). The transformation of these radial glia into astrocytes also coincides with the emergence of cortico-cortical coherence identified with HARDI tractography. Importantly, this transition was viewed in both *ex vivo* and *in vivo* brains at the same timing in the studied brain region. Reproducibility between *ex-* and *in vivo* results were also reported by several groups (Edlow et al., 2012; Wedeen et al., 2012). Such accurate, high-resolution *ex vivo* tractography data provides an excellent reference for *in vivo* tractography. Information regarding the degree to which *in vivo* results can reproduce *ex vivo* results will be important for clinical interpretation of this technique.

The majority of the current diffusion MR tractography studies use a thresholding system based on FA (typically a pre-set FA value, e.g. 0.2) to terminate fibers in the gray matter. However, areas with low myelin and areas that span crossing fibers in the developing brain have low FA values, which may potentially incorrectly terminate pathways in select brain regions. We have reconstructed fibers without setting FA thresholds, and successfully detected immature emerging fiber pathways across a number of studies (e.g. Takahashi et al., 2012, 2014). For example, we reported that the majority of the arcuate fasciculus pathways at 40 GW had low FA values (i.e., FA values lower than 0.2; Fig. 5; Wilkinson et al., 2017). Tractography based on FA values could cause errors in reconstructing the arcuate fasciculus during prenatal and postnatal development. At 3 years old and later, peripheral arcuate pathways showed FA values lower than 0.2 (Fig. 5; Wilkinson et al., 2017). Therefore, it is critical to consider the use of an FA threshold to accurately detect full length/volume of developing pathways.

3. Neuronal migration pathways

3.1. Radial and tangential migration pathways in humans

Two critical processes occur in the second and third trimesters:

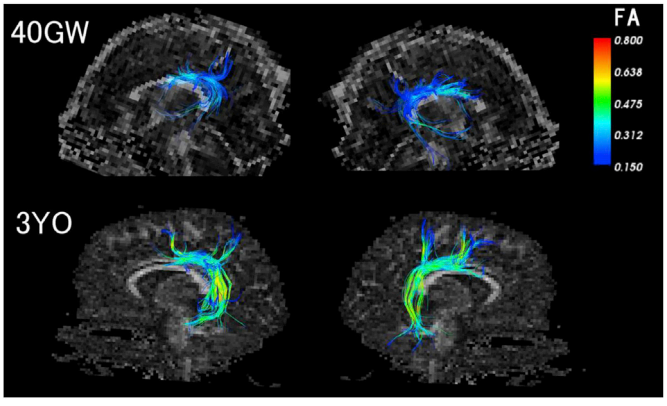

Fig. 5. Color-coded fractional anisotropy (FA) values on arcuate fasciculus in 40 GW and 3 years old subjects. Note that regions with FA values lower than 0.15–0.2 are observed in the majority (40 GW) and peripheral regions (3 years old) of the arcuate fasciculus that cannot be detected with popular DTI analysis methods with an FA threshold (Modified from Wilkinson et al., 2017; with permission). In addition to other technical issues including the quality of MRI scan acquisition and analysis, thresholding parameters based on FA values are important factors when performing tractography.

migration of neurons and development of axonal connections, along with considerable growth of the brain (Rakic, 1972; Caviness et al., 1996; Volpe, 2008). During corticogenesis, neuronal subtypes differ in both their origins and migrational trajectories. Future excitatory glutamatergic projection neurons originate from the proliferative dorsopallial VZ/SVZ, and migrate along radial glial fascicles to the CP (Rakic, 1972, 1988; Bystron et al., 2008a,b). Previous research used vimentin immunohistochemistry to identify radial glial cells in the developing human visual cortex at successive stages of development (i.e., GW 14, 19, 36, and 79: post-term). The authors found that the number of radial glial cells in the visual cortex decreased after 36 GW, and was concomitant with a loss of radial structure (Honig et al., 1996). However, that study had a large sampling gap between 19 GW and 36 GW, an interval of particular interest in the field of normal brain development as well as preterm brain injury. Moreover, their analyses were focused on the primary visual cortex, and it is not clear whether these observations hold across the entire developing cortex. The other, major migratory routes for neurons are mainly from the ganglionic eminence (GE) that course tangential to the CP, containing future inhibitory GABAergic interneurons (Wonders and Anderson, 2006; see also **3.2.**). Altered neuronal migration has been implicated in a range of neurological and psychiatric disorders (e.g. Gressens, 2006; Volpe, 2009; Benes and Berretta, 2001; Marín and Rubenstein, 2001; 2003). Given the clear distinction between murine and primate migratory patterns, and increasing evidence suggesting that certain aspects of neuronal migration are unique to human corticogenesis (e.g. Letinic and Rakic, 2001), there is a clear necessity to investigate migratory patterns directly in the human brain. However, due to limitations inherent to microscopic studies, only small regions of migratory streams can be investigated through histological assessment alone. A systematic assessment of the migratory streams present at any fetal stage is still lacking.

Traditionally, dMR tractography has been used to detect white matter (axonal) pathways of adult brains. However, since dMRI detects directions of water diffusivity in the tissue, it is likely to also detect glial scaffoldings for neuronal migration in fetal ages. A few groups have imaged diffusion coherence of the migration pathways and changes in the radial organization of the CP by using conventional DTI (e.g. Huang et al., 2009; Huang et al., 2013; Yu et al., 2016; Song et al., 2017). Fig. 6 demonstrates that the HARDI tractography technique (Tuch et al., 2003; Wedeen et al., 2008) can clearly identify pathways likely related to radial neuronal migration (a part of the data shown in Fig. 6 was used in Takahashi et al., 2012). Recently, one of our research studies (Xu et al., 2014) compared HARDI tractography with immunomarkers to identify radial glial fibers, axons, and blood vessels across many developmental time points in human fetuses. We showed that, at mid-gestation, radial coherence is concomitant with the presence of radial glial fibers, At 30–31 GW, the transition from HARDI-defined radial pathways to cortico-cortical pathways began simultaneously with the transformation of radial glial fibers to astrocytes. By term, both radial HARDI pathways and radial glial fibers had disappeared (Fig. 6D). With histology, white matter axons were radial, tangential, and oblique over the second half of gestation, whereas penetrating blood vessels were consistently radial. Thus, we concluded that radial HARDI pathways in the fetal white matter likely reflects a composite of radial glial fibers, penetrating blood vessels, and radial axons of which its transient expression most closely matches that of radial glial fibers (Xu et al., 2014).

We have recently further differentially identified radial pathways between different fetal transient zones (Vasung et al., 2017), as well as pathways likely originating from the VZ to the insular and surrounding cortices (Das and Takahashi, 2017) and the thalamus (Fig. 7; Wilkinson et al., 2016). Yellow pathways in Fig. 7 were identified as pathways from or to the thalamus, which can be seen originating from the VZ. These results are the first to clearly show, in a 3-D manner, tractography streamlines stretching from proliferative zones to subcortical nuclei in humans, which most likely correspond to neuronal migration pathways. In addition, we have also identified tractography streamlines that likely

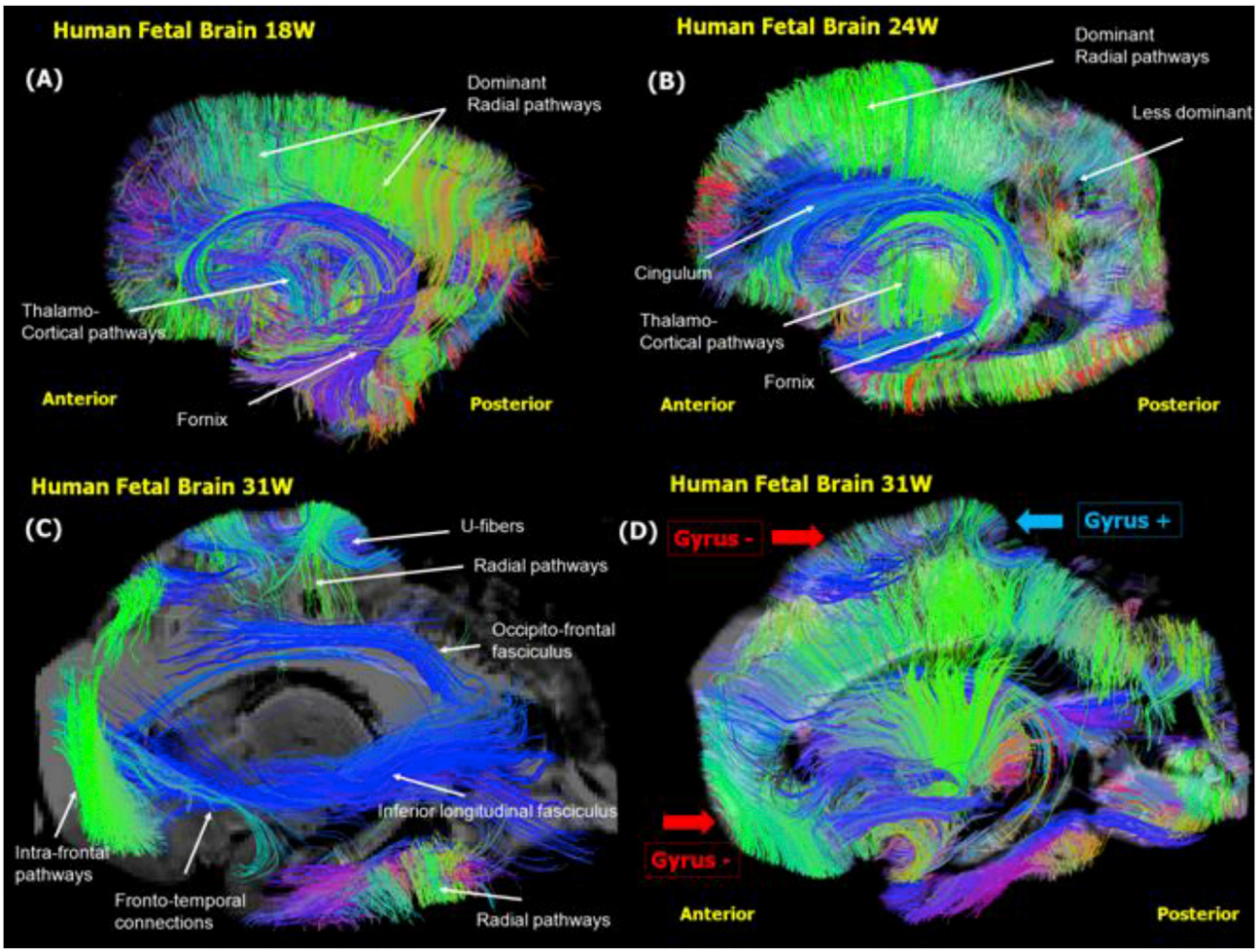

Fig. 6. Radial coherence of the telencephalic fetal wall. Pathways coursing through a sagittal slice at 17 GW (A), 20 GW (B), 31 GW (C), and 40 GW (D) (Modified from Takahashi et al., 2012, with permission).

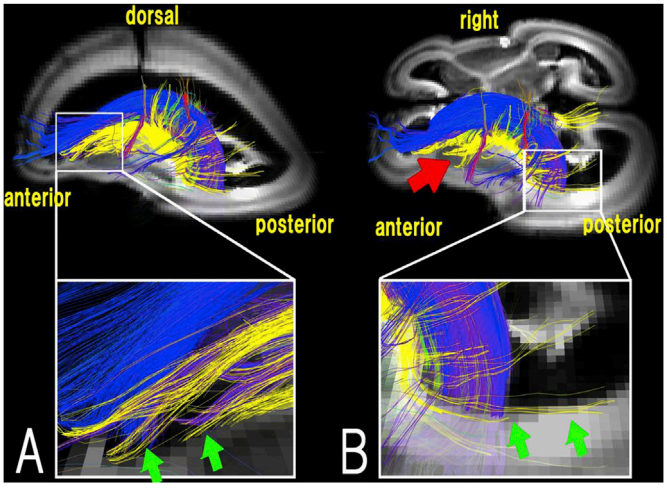

Fig. 7. Thalamic pathways. Oblique sagittal (A) and oblique axial (B) views of a 17 GW old brain. Pathways from/to the thalamus are shown in yellow and pathways linked to the ganglionic eminence (GE) are color-coded based on the standard RGB code to show the spatial locations of terminal regions of each pathway (red: right-left, green: dorsal-ventral, blue: anterior-posterior). Red arrow: pathways from/to the thalamus running vertically from the GE, towards the surface of the brain (Modified from Wilkinson et al., 2016; with permission).

reflect neuronal migration pathways from the GE (Fig. 8; Wilkinson et al., 2016; see also Miyazaki et al., 2016), and those within the cerebellum (Takahashi et al., 2014).

It is possible to resolve cerebellar pathways more accurately using size-optimized coils at higher spatial resolution. Erroneous fiber pathways tend to be detected in the cerebellum when scanned using a large coil for a whole brain with the cerebrum attached (Takahashi et al., 2014). After dissecting the cerebellum from the cerebrum, SNR, spatial resolution and diffusion MR tractography outcomes significantly improved using a size-optimized coil for each cerebellum-only sample (Takahashi et al., 2014), identifying longer, more coherent tractography pathways. Neuronal migration-related radial pathways in the cerebellum at 17 GW were also clearly identified with the size-optimized coils, which disappeared by 38 GW, being replaced by horizontal pathways in the cerebellar cortex (Takahashi et al., 2014).

3.2. *Developmental processes accounting for the expansion of GABAergic and pyramidal neuron numbers in primates*

During brain development, pyramidal neurons and some GABAergic neurons situated in the adult cortex are generated, from distinct regions of the telencephalon (Lavdas et al., 1999; Ang et al., 2003; Letinic et al., 2002; Nery et al., 2002, Fig. 9). Pyramidal neurons arise from the developing cortical proliferative pool and migrate to the CP along radial glia according to the well-known 'inside out' sequence (Rakic, 1974a,b, 2003), which can be visualized with *ex vivo* dMR scans (Takahashi et al., 2011, 2012). In mice and primates, many GABAergic neurons originate

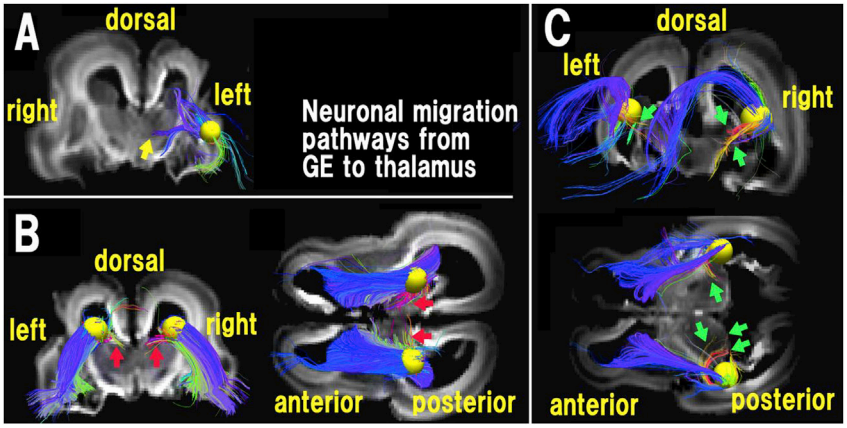

Fig. 8. Three distinct diffusion MR tractography pathways between the GE and the thalami at 18 GW. (A) Pathways running through a yellow sphere placed in an anterior ganglionic eminence (GE) region. The anterior GE region was connected to middle regions of the thalami (yellow arrow). (Modified from Wilkinson et al., 2016). (B) Pathways running through yellow spheres placed in a dorsal GE region. Coronal (left) and axial (right) views are shown. The dorsal GE region was connected to dorsal superficial regions of the thalami (red arrows). (C) Pathways through yellow spheres placed in mid-posterior GE regions. The mid-posterior GE regions were connected to posterior and middle parts of the thalami, corresponding to the ventral complex (green arrows).

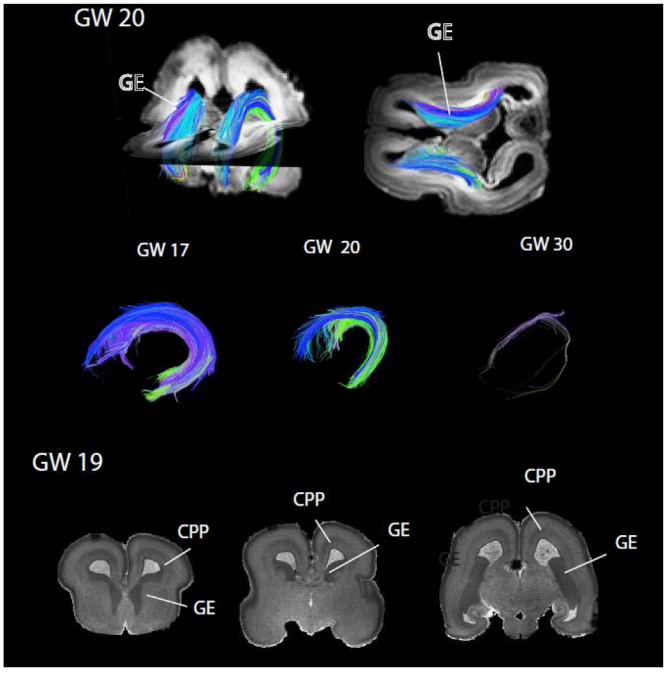

Fig. 9. Diffusion MR tractography of the ganglionic eminence (GE) from gestational week (GW) 17–30 in humans. The GE wanes between GW 20 and 30. Coronal planes from a structural T_1w MRI scans of a human at GW19 show cell dense regions consisting of the GE and cortical proliferative pool (CPP). Comparing the growth of these two proliferative pools throughout development in humans, macaques, and mice permits identifying evolutionary changes in neurogenesis timing across species. The structural MRI scan is made available by the Allen Institute for Brain Science (Miller et al., 2014), and is available at: HYPERLINK "http://download.alleninstitute.org/brainspan/MRI_DTI_data_for_prenatal_specimens/" \o ". Image credit: Allen Institute.

from the GE and migrate to various layers of the developing cerebral cortex (Lavdas et al., 1999; Ang et al., 2003; Letinic et al., 2002; Nery et al., 2002). Interestingly, a recent study showed that the migration of GABAergic interneurons in humans extends into the postnatal period (Paredes et al., 2016). Whether GABAergic neuron migration extends for an unusually long time in humans compared to rodents is an open question. Diffusion and structural MRI scans can be used to track the maturation of future GABAergic and pyramidal neurons during neurogenesis, their migration to the CP (Takahashi et al., 2011, 2012), and compare the timing of neuron production in humans relative to other species (Fig. 9).

The GE and cortical proliferative pool are known to contain proliferative cells in primates as in rodents even though the cortical proliferative pool of primates is expanded relative to rodents (Kriegstein et al., 2006; Lukaszewicz et al., 2005; Workman et al., 2013; Charvet et al., 2017b). Throughout development, progenitor pools grow, peak and wane as the cells exit the cell cycle (Charvet et al., 2017b; Vasung et al., 2016). Mitotic markers are expressed in the GE and cortical proliferative pool throughout development (Lukaszewicz et al., 2005; Charvet and Striedter, 2008; Cheung et al., 2009; Del Bigio, 2011; Chen et al., 2017). In mice, the GE grows and peaks in size at approximately embryonic day (E) 15.5, after which the GE wanes as cells exit the cell cycle and migrate to their final destination. A recent study used single cell RNA sequencing from the mouse medial GE at several stages of embryonic development and showed that the number of immature neurons increased significantly from E15.5 to E17.5 in the medial GE (Chen et al., 2017). The increase in post-proliferative neurons in the medial GE coincides with the decline in GE size in mice (Charvet et al., 2017b). *Ex vivo* diffusion MR scans of human fetuses are instrumental in identifying whether neurogenesis is protracted in humans relative to other mammals.

A comparative analysis of growth trajectories of the GE and cortical proliferative pool requires a comparison of equivalent developmental time points between species given inter-species variation in overall developmental schedules. The timing of maturational milestones can be used to identify equivalent development time points across a broad range of species, including humans, macaques, and mice (Clancy et al., 2001; Workman et al., 2013; Charvet et al., 2017b; Charvet and Finlay, 2018, Charvet et al., 2018, Fig. 10). For instance, the timing of developmental transformations in macaque and humans is plotted against equivalent developmental transformations observed in mice, which permits identifying corresponding ages across species (Fig. 10). Once overall changes in developmental schedules are controlled for, the study showed that the GE and cortical proliferative pool grow for much longer than expected in humans and macaques relative to the timing of other developmental events (Charvet et al., 2017b, Fig. 10). High angular resolution diffusion MR scans confirm the growth trajectories of the GE in a different set of human fetuses (Fig. 9). Accordingly, humans and macaques extend isocortical and GABAergic neurogenesis for longer than expected considering the timing of other developmental transformations. The consequence of extending the duration of neurogenesis is that pyramidal and GABAergic neurons are amplified in the primate cortex. A concomitant increase in the number of pyramidal and GABAergic neurons may be necessary for the cortex to remain functional in primates.

The maturation of the GE and cortical proliferative pool is protracted in primates relative to mice and the timing of post-neurogenetic maturation of GABAergic and pyramidal neurons is conserved in primates as in rodents. The timing of tract formation and the time course in the emergence of genes and proteins expressed by GABAergic and pyramidal

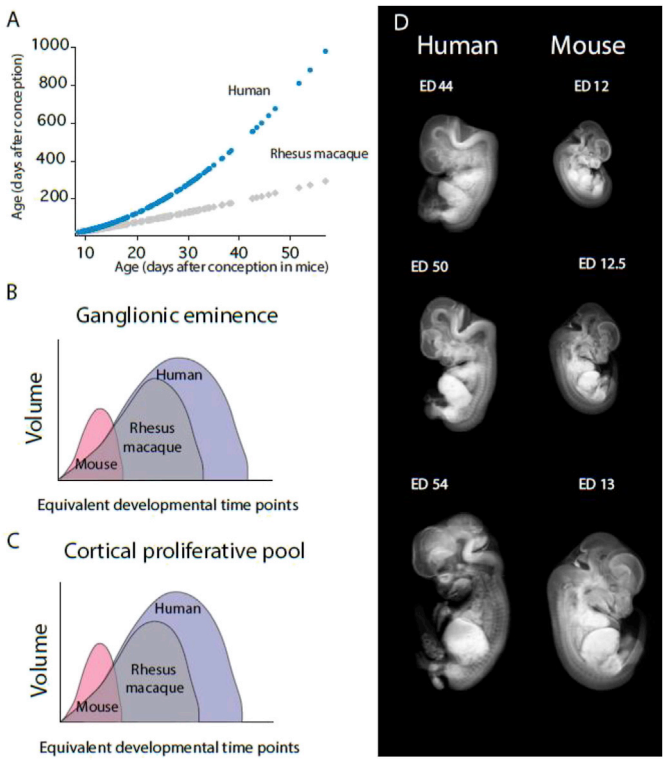

Fig. 10. Extended duration of cortical and GE neurogenesis in primates versus rodents. (A) The timing of developmental transformations (expressed as age in days after conception in macaques and humans) is regressed against equivalent developmental transformations found in mice (Workman et al., 2013; Charvet et al., 2017b, 2018; Charvet and Finlay, 2018). The timing of developmental transformations is instrumental in identifying corresponding ages across species. Such an approach permits identifying variation in the timing of select developmental processes after controlling for variation in developmental schedules across species. Using this approach, Charvet et al. (2017a) found that the ganglionic eminence (GE) (B) and cortical proliferative pool (C) grow for significantly longer in humans and macaques once overall differences in the duration of developmental schedules are controlled for (see Workman et al., 2013; Charvet et al., 2017a; Charvet and Finlay, 2018; Charvet et al., 2018). (D) Examples of equivalent developmental time points are shown from reconstructed structural MRI scans and micro CT-scans. Micro CT-scans of prenatal mice are from Wong et al. (2012). Structural MR scans of prenatal humans are from the multi-dimensional human embryo project (http://embryo.soad.umich.edu/index.html).

neurons show no evidence of a delay in primates relative to the timing of other events (Charvet et al., 2017b). The dissociation between protracted timing of neurogenesis and the conserved timing of post-neurogenetic maturation could facilitate cross-synaptic maturation across brain regions and explain structural differences during brain development between primates and rodents. For instance, it has been suggested that the emergence of tracts coursing between the inner and outer SVZ during fetal development is unique to primates and to some extent carnivores (Smart et al., 2002). Accordingly, the outer SVZ would represent a relatively distinct progenitor pool population in primate evolution. Given that the timing of post-neurogenetic maturation is decoupled from neurogenesis timing, we suggest that the formation of tracts coursing through the inner and outer SVZ in primate development could emerge as a result of the extension in cortical cell proliferation coupled with the conserved timing of tract formation. Tracts coursing between the inner and outer subventricular might appear unusual in primates because neurogenesis extends during the growth of tracts whereas neurogenesis largely wanes during these equivalent developmental time points in mice.

4. Axonal development

4.1. Axonal pathways in humans

From histological observations, the thalamic afferent fibers grow into the CP at 26–32 GW, while the cortico-cortical pathways grow into the CP around 32–38 GW, i.e. after they "wait" in the SP for an extended time (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2010; see also Fig. 11). Therefore, the majority of the axonal trajectories are already formed prior to these gestational ages. Although the relative timing of development of these pathways is known, we still do not know the regional variation in their development throughout the brain. Conventional structural MRI and DTI have detected projection pathways appearing at 22–26 GW (for review see Kostovic and Jovanov-Milosevic, 2006). DTI has been used to study developing white matter properties in both the animal (Zhang et al., 2003, 2005; Huang et al., 2006, 2008; Kroenke et al., 2007; D'Arceuil et al., 2008; Kuo et al. 2008) and the human fetus (Huang et al. 2009). Some research studies using diffusion MR tractography (Zhang et al., 2003; Huang et al. 2006, 2009; Dubois et al., 2006; D'Arceuil et al. 2008) have shown the development of the major, thick white matter pathways. However, these studies have all used DTI with its limitations. Thus, they could not display the full lengths of fiber pathways and none of these studies were able to describe the precise time-courses of the many brain pathways.

Studying human fetal brain connectivity remains a challenging task. The majority of information describing the development of fetal connectivity is from axonal tracing or histological studies. However, there are only a few studies employing tracing techniques, as these require short postmortem intervals on already limited fetal material. Similarly, standard techniques of histological fiber staining do not stain fibers during the early developmental phases. Therefore, descriptions of fiber development employing histology have relied on the histological staining of neurons (pale areas denote areas of developing fiber pathways, e.g. see Vasung et al., 2010a,b) or histological techniques that stain transient chemical properties of these fibers (e.g Kostovic and Goldman-Rakic, 1983). Lastly, unlike in the adult brain, directionality of fiber growth in the fetal brain can be deducted from histological stained sections, as chemical properties of these fibers change gradually from their origin towards the target.

The first connections that develop in the fetus belong to the major projection pathways (His, 1904; Hochstetter, 1919). Basal forebrain axons, arising from the magnocellular cholinergic neurons (Kostovic, 1986), are observed as early as 10–11 GW as they course through the external capsule. During this time, the thalamo-cortical axons span the telencephalon-diencephalic junction, and are evident by cholinesterase staining (Kostovic and Goldman-Rakic, 1983). Thus, as early as 12 GW, one can reliably identify components of the external and internal capsule in the fetal brain. Aside from projection fiber pathways, the existence of the fornix, most likely containing septo-hippocampal fiber pathways (Kostovic et al., 1980), has also been reported at this stage (His, 1904; Hochstetter, 1919). At this stage, pyramidal neurons, whose axons will form association fibers, have not yet migrated (Rakic, 1974a,b).

Thirteen GW marks an important phase in the developing fetal brain. At this time, the SP can be identified in histological sections (Molliver et al., 1973; Kostovic and Rakic, 1990). However, SP can be detected on high-resolution structural MRI within 15 GW (Kostovic et al., 2002). During the following weeks there is increased growth of the efferent fiber pathways as some of the lower layer neurons of the cerebral cortex might have already reached their destinations. There are several DTI-based findings during this period. The largest fiber pathway at this stage seems to be the corpus callosum (Vasung et al., 2010a,b). In addition, thick cortico-pontine pathways, as well as limbic fiber pathways (Vasung et al., 2010a,b), are evident from tractography reconstructions.

From 20 to 26 GW the volume of the SP zone, axonal "waiting compartment" (Kostovic and Rakic, 1990; Kostovic et al., 2014), continues to increase with age. This period is marked by the massive growth

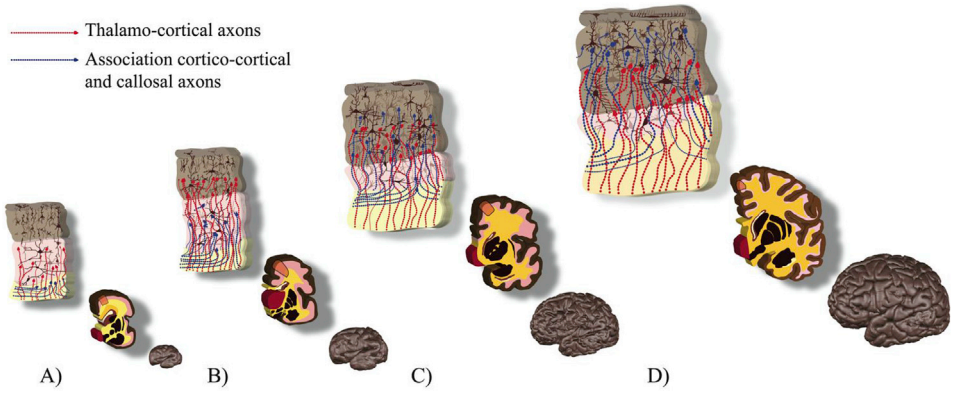

Fig. 11. Summary illustration of transient fetal zones at 27 (A), 32 (B), 36 (C) and 42 (D) GW. Upper and middle row: the cortical plate in brown, the subplate in pink, the intermediate zone in yellow. Major histogenetic events (upper row) are orange insets from the middle row: neurons in brown, thalamo-cortical axons in red, cortico-cortical and callosal axons in blue. Associated changes in cortical morphology (gyrification and surface growth) can be seen in the bottom row. Dendritic arborization of cortical and subplate neurons is painted according to (Mrzljak et al., 1988, 1991). Development of cortical connectivity was illustrated according to the work of Kostovic and group (for reviews see (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2009; Vasung et al., 2010a,b)). Upper and middle rows were painted using the template coronal slices of the brains used in Vasung et al. (2016).

of the axonal bundles that span the cortex. Using DTI and HARDI, our own (Takahashi et al., 2012; Wilkinson et al., 2016; Vasung et al., 2017) and another (Huang et al., 2006, 2009) group has successfully identified the following projection fiber pathways: cortico-ponto-cerebellar and fibers related to pons, basal ganglia fibers (belonging to the fasciculus subcallosus-Muratoff bundle or external capsule), thalamic, and basal forebrain fibers. However, at this stage these fibers are seen mostly approaching or terminating within the SP (Vasung et al., 2017). The fetal telencephalon also displays strong radial coherence at this stage (Takahashi et al., 2012; Vasung et al., 2017). In parallel to the ongoing process of neurogenesis, some of the association fiber pathways, which are still in formation, can be recognized at these ages (e.g. inferior longitudinal fasciculus, fronto-occipital fasciculus, middle longitudinal fasciculus, and vertical occipital fasciculus) (Takahashi et al., 2012; Song et al., 2015; Vasung et al., 2017; e.g. Figs. 6 and 11).

From 26 GW onwards, the thalamic afferent fibers that were "waiting in the SP", relocate to the CP (Kostovic and Jovanov-Milosevic, 2006). This thalamo-cortical relocation has been confirmed by a DiI tracing study in the fetal brain (Hevner, 2000). This period is also marked by an exponential increase in white matter volume (Vasung et al., 2016), which is most likely caused by rapid outgrowth of long and short associational cortico-cortical pathways (Huang et al., 2006; Huang et al., 2009; Takahashi et al., 2012; Vasung et al., 2017; e.g. Figs. 6 and 11). Similarly, during this period the corpus callosum continues to grow and develop (Vasung et al., 2017), while the telencephalon gradually loses its radial coherence (Takahashi et al., 2012; Vasung et al., 2017).

Although we are on the verge of identifying the spatio-temporal sequence of gradual maturation in fibers of the fetus, it should be noted that most of these findings come from DTI imaging which suffers from numerous limitations (Jones et al., 2013; Maier-Hein et al., 2016). Thus, until we have a "ground truth" for diffusion and tractography models (i.e. polarized light imaging, Palm et al., 2010), we should be cautious in interpreting these results, and should rely on knowledge from histology.

4.2. Evolutionary changes in cortical connectivity patterns across mammals: what is special about primates?

There are a number of differences in brain connectivity patterns between primates and other mammals. For instance, diffusion MR scans and tract-tracers have identified cross-cortical projections between auditory and frontal regions of the cortex called the arcuate fasciculus in primates (Deacon, 1992; Rilling et al., 2008; Schmahmann and Pandya, 2009). The arcuate fasciculus has been observed in Old World monkeys, apes, and humans but has not been observed in other mammals (Schmahmann and Pandya, 2009). Notably, the arcuate fasciculus is expanded in humans relative to other primates, which suggests that the arcuate fasciculus evolved within the primate lineage, and that it may have been expanded to process information related to language. Species differences in gene expression patterns can also be used to identify evolutionary changes in connectivity patterns (Hof et al., 1995; Zeng et al., 2012; Krienen et al., 2016; Charvet et al., 2018) because neurons can be classified according to the genes that they express. This approach is indirect in that it provides no information as to the precise terminations of cell types. Thus, there are a number of complimentary venues through which to study evolutionary changes in connectivity patterns.

For the most part, evolutionary changes in connectivity patterns have been challenging to identify because of the difficulty in quantifying connectivity patterns, and resolving the precise terminations of tracts. Combining results from diffusion MR tractography of *ex vivo* brains, gene expression, and stereological methods across cell types can be used to identify evolutionary changes in cross-cortical connectivity patterns in adulthood and the developmental processes that generate them (Charvet et al., 2018). A focus on human as well as non-human primates is especially valuable because the study of the non-human primate brain yields insight into the evolutionary history and the context in which the human brain evolved.

Cortical neurons exhibit stereotypical patterns of projections, which vary according to their position across the depth of the cortex and the genes that they express (DeFelipe et al., 2002, 2013; Hevner et al., 2003; Molnár and Cheung, 2006; Molyneaux et al., 2007). Tract-tracing studies have shown that superficial layers (i.e., layers II-III) preferentially project within and across cortical regions (Fitzpatrick and Imig, 1980; Foster et al., 1981; Joschko and Sanderson, 1987; Coogan and Burkhalter, 1990). Layer IV neurons preferentially project locally whereas many layer V-VI neurons preferentially project to subcortical structures (Jones and Burton, 1976; Kawamura, 1973a, b, c; Barbas, 1986; Striedter, 2005; Schmahmann and Pandya, 2009). Within each of these layers, cortical neurons can further be classified according to the neurotransmitters that they express (DeFelipe et al., 2013). Many cortical pyramidal neurons project over long distances through the cortical white matter to target cortical or subcortical structures. In contrast, cortical GABAergic neurons are inhibitory and typically form local circuits within the gray matter of the isocortex. The position of a neuron across the cortical depth can be used to predict its projection patterns and the suite of genes that it expresses.

There is extensive conservation in stereotypical projection patterns across mammals though there are notable differences in the population of these cell types. For example, primates exhibit a well-defined layer IV and relatively thick upper layers compared with many other mammals (Hutsler et al., 2005, Fig. 12). A previous study compared layers II-IV neurons across a broad range of primate (e.g., Old World, New World,

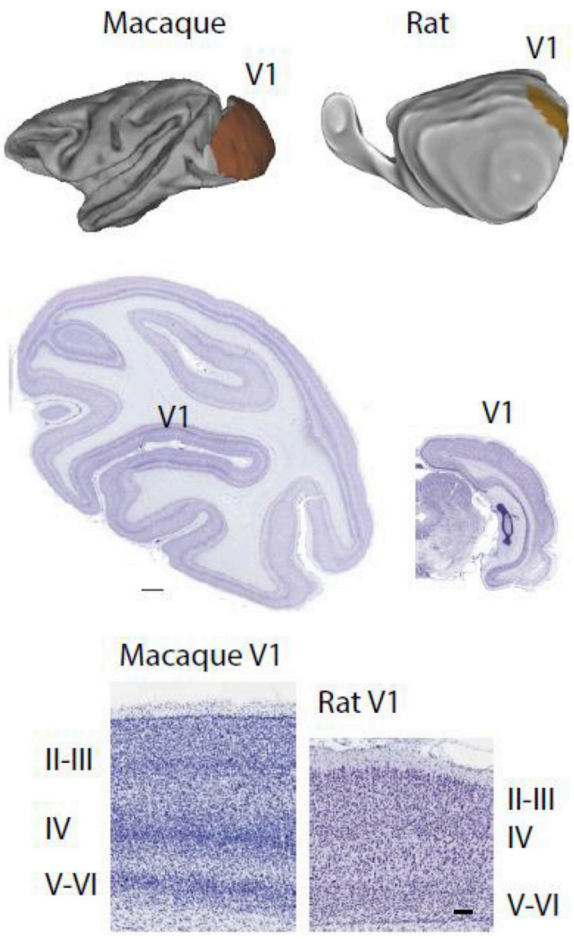

Fig. 12. Structural differences between the primary visual cortex of macaques and rats. Top panel shows the cortex of a macaque and a rat, and the primary visual cortex is highlighted in both species. Coronal sections through the cortex of a macaque and rat show that the primary visual cortex of the macaque possesses a well-defined layer IV and relatively thick upper layers compared with rats. Images of Nissl-stained sections were taken from brainmaps.org. Scale bar of the middle panel: 1 mm. Scale bar of the lower panel: 100 μm.

lemurs, prosimians) and non-primate species (e.g., rodents, carnivores, and Afrotheria). After controlling for brain size, primates possess disproportionately more layer II-IV neurons compared with rodents and other mammals (Charvet et al., 2017a). There is only a slight relative increase in the percentage of GABAergic interneurons in the cortex of primates relative to rodents such that the amplification of layers II-IV neurons in primates is concomitant with an absolute increase in GABAergic interneuron and pyramidal neurons relative to many other mammals (Beaulieu et al., 1992, 1993; Džaja et al., 2014). Given that layers II-IV consist of GABAergic and pyramidal neurons, the human and non-human primate cortex should show major differences in cortico-cortical circuits relative to other species.

Ex vivo diffusion MR scans can be used to visualize tracts across the entire brain of any species (Takahashi et al., 2010; Wedeen et al., 2012; Calabrese et al., 2015; Feng et al., 2017). In the white matter of the cortex, diffusion MR scans show projections of pyramidal neurons, but not those of locally projecting GABAergic interneurons that remain within the gray matter of the cortex. Tracts within the white matter of the cortex might relay information within the cortex or between subcortical and cortical structures. The direction/orientation of a diffusion MRI-based tract can be used to distinguish projections that relay information within the cortex from those that relay information between the cortical and subcortical structures. In the white matter, tracts coursing across the dorsal to ventral direction have a tendency to form projections between cortical and sub-cortical structures (e.g., corticocpsinal tract, thalamo-cortical tracts) and to some extent cross-cortically. In contrast, pathways coursing along the anterior to posterior direction in the cortical white matter have a strong tendency to project cross-cortically (Mori et al., 2002). Concomitant with an increase of neurons in layers II-IV, primates possess an increase in anterior to posterior cortico-cortical tracts compared with rodents and other mammalian species (Charvet et al., 2017a, Fig. 13). That is, the human and non-human primates cross-cortical connectivity patterns differ from that of other examined mammals.

Previous studies have examined species differences in gene expression across cortical layers of primates and rodents. Some genes are expressed primarily by long range projecting neurons in the cortex (Hof et al., 1995; Voelker et al., 2004). For instance, humans possess a relative increase in Neurofilament heavy polypeptide (*NEFH*) expression and other synaptic-related genes in layers III of the primary visual cortex compared with mice (Zeng et al., 2012). The observation that *NEFH* is preferentially expressed in long range projecting neurons, and that its expression is amplified in layers III of the human primary visual cortex suggests that humans possess an amplification of long-range cortico--cortical projecting neurons (Hof et al., 1995; Zeng et al., 2012; Charvet et al., 2018). Interestingly, a relative increase in *NEFH* expression is also observed in layer III of macaques compared with mice, suggesting that the increase in layer III *NEFH* expression may be a feature shared among human and non-human primates (Bakken et al., 2016). Combining comparative analyses of neuron numbers, diffusion MR tractography, and gene expression patterns across species demonstrates that humans and non-human primates deviate from other mammals in possessing increased long range cross-cortically projecting neurons.

5. Limitations

Ex vivo MRI allows us to visualize fiber pathways with extremely high-resolution tissue structures. *Ex vivo* structural MRI provides a means to identify detailed morphological changes whereas *ex vivo* diffusion MRI provides an unprecedented perspective with which to study the development of fiber pathways. However, we are still not able to directly

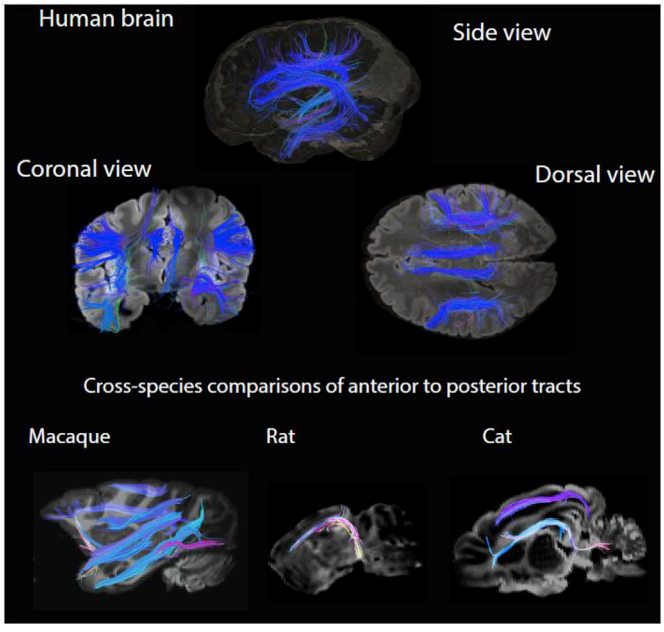

Fig. 13. *Ex vivo* high angular resolution diffusion MR tractography of a human, macaque, rat, and cat brain. The human brain possesses an extensive number of anterior to posterior cross-cortically projecting tracts. Other primates such as the rhesus macaque also possess many anterior to posterior cortical tracts compared with other mammals such as rats and cats (Charvet et al., 2017b).

distinguish which tractography pathways represents axons, glial fibers, or aligned cell components, because the current structural and diffusion MRI techniques do not produce direct measures of the tissue. To overcome this limitation, integrating analyses from MR methods with histology or gene expression data improves our understanding of the basic developmental processes occurring during human fetal brain development. However, histology has a different type of limitation, which precludes the study of global fiber connections, and therefore, direct correlation of high-resolution diffusion MRI and histology to determine what tractography can and cannot detect and to what extent it is currently informative when assessing MRI results.

Since the presence of any microscopic neuropathology cannot be determined prospectively before scanning, pathology of MRI-scanned cases should be carefully assessed after the scans to better correlate MRI and histopathology findings. Neurologically healthy brain specimens are valuable not only as controls, but also because there is still a significant lack of knowledge about typical human brain development. One obvious problem is that "normal" infants do not die, and natural disease in autopsied cases may introduce some error when interpreting normal human brain development.

Postmortem interval (PMI) and the time in fixative (TIF, e.g. 4% formalin) are potential factors that could affect results from *ex vivo* MRI examinations. Specimens with shorter PMI and TIF are thought to be better to minimize confounding variables. In fact, the potential for *ex vivo* MRI techniques to detect fine tissue properties including reconstructed fiber pathways has at the same time the potential to detect false positives. This problem is typically prominent when the condition of imaged specimens is not optimal as a result of long PMI and/or TIF. However, we have experience in the use of specimens with long PMI and TIF, and have obtained results with high spatial resolution and SNR (e.g. Wang et al., 2015).

In addition, as a common issue both in *in-* and *ex vivo* fetal MRI, the age of the fetuses and prematurely born infants is most commonly estimated on the basis of their crown–rump lengths (CRL) (O'Rahilly and Müller, 1984) and pregnancy records. In order to provide accurate and unbiased age estimation of fetuses and of prematurely born infants, it is common in the field of anatomy to express the age as weeks from conception (post-conceptional week [PCW], typically gestational weeks [GW] minus 2 weeks) (Olivier and Pineau, 1962), if available. However, given that the majority of researchers in neuroimaging use gestational weeks, for the purpose of this article we have reported major histogenic findings using GW for age.

6. Future directions

6.1. Large-scale data analyses

Pattern recognition technologies are emerging as important techniques for the analysis of *ex vivo* fetal MRI examinations. MRI has been shown to have the potential to play an important role in the analysis of post mortem fetuses, as some conditions are easier to identify from *ex vivo* MRI than through traditional autopsy (Thali et al., 2003). Previous work analyzing the potential of post mortem MRI for the assessment of the cause of fetal death has demonstrated that MRI can potentially play an assistive role (Thayyil et al., 2013). This post-mortem analysis was normally performed manually (i.e. in the absence of advanced pattern recognition tools) which puts considerable burden on the radiologists and pathologists involved in the research. Pattern recognition technologies can potentially play an important role in these types of studies by facilitating histological validation and automating the extraction of anatomical measurements from both MRI and microscopic resected tissue.

The majority of pattern recognition technologies developed for fetal MRI to date have focused on *in vivo* imaging (Clouchoux et al., 2012; Dittrich et al., 2014; Gholipur et al., 2017; Habas et al., 2010; Kuklisova-Murgasova and Aljabar, 2011; Serag et al., 2012; Wright et al., 2015; see also Levman and Takahashi, 2015), using a variety of registration and regression technologies in order to establish a baseline atlas of expected development of the fetal brain. Reviews of this specific topic are available (Clouchoux et al., 2012b; Makropoulos et al., 2017). Although the main research thus far has focused on *in vivo* imaging, such contributions have considerable potential towards being adapted for applications in *ex vivo* MRI. Considerable research has focused on *ex vivo* MRI based modeling of the medial temporal cortices and associated structures, as summarized in a review article (Augustinack et al., 2013), analysis of which demonstrates the potential to support probabilistic brain mapping based on *ex vivo* MRI contrast, validated to histology and subsequently aligned to *in vivo* imaging. Related work has demonstrated the feasibility of using such technologies for *ex vivo* brain analysis and has demonstrated that myelin and Nissl staining relate to contrast in *ex vivo* MRI (Augustinack et al., 2014).

Recent work has demonstrated the feasibility of adapting the types of technologies relied upon in automated *in vivo* brain imaging analysis to post mortem fetal brains (Zhan et al., 2013). In this application, 34 *ex vivo* brain specimens were imaged with a 7T MRI scanner, with samples ranging in gestational age from 15 to 22 GW. The technology developed incorporated automated morphometrics, tensor-based morphometry and surface modeling techniques for data analysis. These techniques support the assessment age-specific shape changes during gestation, including the development of the lateral ventricles, the Sylvian fissure and local surface measurements, which help to inform researchers as to the natural patterns of brain growth. Previous work has also demonstrated the feasibility of measuring cortical folding from *ex vivo* fetal MRI examinations (Batchelor et al., 2002), research that has demonstrated sensitivity to anatomical variability as well as the quantification of differences between normal and abnormal fetal brains.

Ex vivo technologies have the potential to not only support autopsies that otherwise would be performed manually (Thayyil et al., 2013), but investigations that make use of such technologies have the potential to identify abnormal trajectories of brain growth that may be associated with extremely early stage development of neurological disorders, such as autism. However, there are many challenges to overcome when making such pattern recognition technologies widely available and useful, including the need for reliable data analysis techniques that can handle the large-scale deformation differences observed in *ex vivo* specimens relative to that observed *in vivo*, contrast differences (Augustinack et al., 2014), challenges associated with *ex vivo* ventricular bleeds without dilation (Thayyil, 2011; Thayyil et al., 2013) and more.

Although the majority of the related work in this field has been focused on *in vivo* fetal MRI, pattern recognition technologies are developing towards playing an important role in *ex vivo* imaging of the fetal brain with MRI. It is anticipated that with time, such techniques will play a crucial role in histological validation, automated distributed measurement extraction, identification of anatomical abnormalities associated with neurodevelopmental disorders, as well as towards providing assistance in pathological analyses (by providing automated quantified measurements from MRI (e.g. Levman et al., 2017) to support microscopic cellular analysis), including diagnostic decision support systems for pathologists.

6.2. Translation of ex vivo results to in vivo application

Some human brain banks (Kretschmann et al., 1979; Kostovic and Rakic, 1990; Judaš et al., 2011) offer an indisputable source of information on histological correlates of these neuroimaging findings, which are in turn, often challenging to interpret. Nevertheless, the only systematic correlation and co-registration of histology and MRI images exist only for the adult human brain (Amunts et al., 2013). Moreover, the definition of transient fetal zones on MRI images relies on scattered published histological slices that do not cover the entire brain (Kostovic and Goldman-Rakic, 1983; Kostovic and Rakic, 1990; Kostovic et al., 2002; Radoš et al., 2006; Kostovic and Judas, 2009), or on several

available atlases covering the entire brain but relying on descriptions that are appropriate for the developing rodent brain (Bayer and Joseph, 2005; 2005). Thus, to our knowledge, there is no study that systematically investigates the MRI-histological correlation of the human fetal brain across the entire telencephalon.

Ex vivo assessment of MR signal intensities, DTI parameters, and tractography-reconstructed pathways of the transient fetal zones are crucial for translation on *in vivo* subjects. However, only a correlation between *ex vivo* histology and MRI can provide sufficient information to offer proper biological interpretation of the *in vivo* MRI findings. Despite its lower resolution compared to *ex vivo* MRI, and despite unpredictable fetal motion, researches have already successfully captured *in vivo* structural and diffusion MRI of the fetal brain (Girard et al., 1995; Garel et al., 2001; Glenn and Barkovich, 2006a,b; Glenn and Barkovich, 2006a, b; Rutherford, 2009; Habas et al., 2010; Gholipour et al., 2014; Jakab et al., 2014; Mitter et al., 2015). Therefore, with new MR image acquisition and reconstruction techniques (e.g. Alexander et al., 2017; Hamilton et al., 2017; Liu et al., 2017; Poser and Setsompop, 2018), a detailed high resolution histological and MRI *ex vivo* atlases of the developing fetal brain (Kostovic et al., 2002; Huang et al., 2006, 2009; Vasung et al., 2010a,b, 2016; 2017; Takahashi et al., 2012; Xu et al., 2014; Wang et al., 2015; Wilkinson et al., 2016; Das and Takahashi, 2017) can offer valuable information for interpretation of *in vivo* fetal MRI findings, and can identify areas where technical improvements in MRI acquisition, reconstruction, or analysis are still necessity.

Advances in techniques and interpretations of *in vivo* fetal MRI directly contribute to progress in fetal treatments such as fetal surgeries (Moon-Grady et al., 2017, Moldenhauer and Adzick, 2017) and gene therapies (Witt et al., 2017; Massaro et al., 2018). Quantitative MRI analysis is crucial for early diagnoses and assessment of therapeutic effects as well as treatment side effects, especially when targeting neurological disorders. Since neuronal migration and cortical gyrification during brain development are closely associated with spatiotemporal gene expression patterns (Meyer, 2007; Huang et al., 2012), especially in gene therapies, we need to pay attention to potential risks to the modulation of brain morphology due to unexpected alteration of gene expression patterns. Detailed *ex vivo* fetal MRI observations could assist interpretations of atypical morphological findings in various *in vivo* fetal MRI scans including these fetal therapies.

In recent years, advances in neonatal care led to increased survival of prematurely born infants. The level of prematurity and the degree of severity of identifiable brain lesions have been associated with smaller brain volumes, smaller volumes of the gray and white matter at term equivalent age, childhood and adolescence (for review see Ment et al., 2009; Ferriero, 2016; Malhotra et al., 2017). Imaging biomarkers are starting to serve as a useful tool for identification of cognitive disabilities that these children display later in their life (Kwon et al., 2014). However, we are still far from accurate neurobiological interpretation of these biomarkers. Moreover, as the regional trajectories of human fetal brain growth during preterm development remain unknown, it is difficult to assess to what extent these trajectories are altered following preterm birth. To this end, the failure of brain maturation following preterm birth (Kinney and Volpe, 2018) indicates that the maturation trajectories of certain transient fetal zones might be altered. Therefore, comprehensive *ex vivo* MR and histological analyses dedicated to the assessment of transient fetal zones following premature birth are needed.

7. Conclusion

Ex vivo fetal brain MRI has great potential to resolve detailed tissue structures such as tissue properties that reflect various neurogenic processes including neuronal migration and emergence of axonal pathways in fetal transient zones. Depending on the condition of postmortem brain specimens, MRI scan protocols and data processing procedures (e.g. no FA thresholds), it is possible that *ex vivo* MRI provides false positive results. However, careful assessments with histopathology techniques and large-scale scans/analyses would minimize the effect of such confounders. In fact, current *in vivo* MRI examinations have a greater risk of false positives, and *ex vivo* MRI results with careful consideration will likely be able to serve as a great reference to *in vivo* MRI findings on fetal brain development and disorders.

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(http://download.alleninstitute.org/brainspan/MRI_DTI_data_for_prenatal_specimens/).

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