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Delineation of early brain development from fetuses to infants with diffusion MRI and beyond

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Abstract

Dynamic macrostructural and microstructural changes take place from the mid-fetal stage to 2 years after birth. Delineating brain structural changes during this early developmental period provides new insights into the complicated processes of both typical brain development and the pathological mechanisms underlying various psychiatric and neurological disorders including autism, attention deficit hyperactivity disorder and schizophrenia. Decades of histological studies have identified strong spatial and functional gradients of maturation in human brain gray and white matter. The recent improvements in magnetic resonance imaging (MRI) techniques, especially diffusion MRI (dMRI), relaxometry imaging, and magnetization transfer imaging (MTI) have provided unprecedented opportunities to non-invasively quantify and map the early developmental changes at whole brain and regional levels. Here, we review the recent advances in understanding early brain structural development during the second half of gestation and the first two postnatal years using modern MR techniques. Specifically, we review studies that delineate the emergence and microstructural maturation of white matter tracts, as well as dynamic mapping of inhomogeneous cortical microstructural organization unique to fetuses and infants. These imaging studies converge into maturational curves of MRI measurements that are distinctive across different white matter tracts and cortical regions. Furthermore, contemporary models offering biophysical interpretations of the dMRI-derived measurements are illustrated to infer the underlying microstructural changes. Collectively, this review summarizes findings that contribute to charting spatiotemporally heterogeneous gray and white matter structural development, offering

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MRI-based biomarkers of typical brain development and setting the stage for understanding aberrant brain development in neurodevelopmental disorders.

Keywords

diffusion MRI; quantitative MRI; tractography; early development; microstructure; baby brain

1. Introduction

Early brain development, particularly from the mid-fetal stage to 2 years after birth, is probably the most dynamic across the entire lifespan. Striking morphological changes have been observed during fetal development from the 4th post-conceptional week (pcw) to birth during which the brain develops from a tubular structure to a highly complicated yet organized organ with adult-like architecture (e.g. Huang and Vasung, 2014; Silbereis et al., 2016). From birth to 2 years of age, the overall brain size increases dramatically, reaching close to 90% of adult volume by the age of 2 years (Pfefferbaum et al., 1994). The gray matter volume also reaches a lifetime maximum around 2 years of age (Hüppi et al., 1998a; Matsuzawa et al., 2001). These structural changes, in parallel to the brain circuit formation, result from immensely complicated yet precisely regulated molecular and cellular processes (Silbereis et al., 2016), including neurogenesis and neuronal migration (Rakic 1972, 1995; Sidman and Rakic, 1973), synapse formation (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997), dendritic arborization (Bystron et al., 2008; Sidman and Rakic, 1973), axonal growth, pruning (Innocenti and Price, 2005; Kostović and Jovanov-Milosević, 2006) and myelination (Miller et al., 2012; Yakovlev and Lecours, 1967). These cellular and molecular processes shape the structural and functional architecture of the human brain and underlie the varying rates of maturation of functional systems, from the primary sensorimotor to higher-order cognitive regions. The spatial and functional gradients of these major maturational events in the developing brain are described in Figure 1.

Current knowledge of early brain development originated from histological studies. For example, cortical synaptogenesis starts as early as the 18pcw and reaches its peak density in the frontal cortex by the 15th postnatal month, later than synaptogenesis peaks of primary auditory and visual cortices (Huttenlocher and Dabholkar, 1997; Kwan et al., 2012). Similarly, myelination cycles are significantly different across white matter regions and tracts, with varying starting times and durations (Brody et al, 1987; Kinney et al, 1988; Yakovlev and Lecours, 1967). Altered synaptic pruning has been found to be associated with neurodevelopmental disorders such as autism, attention-deficit hyperactivity disorder, and schizophrenia with histological studies (e.g. Feinberg, 1983; McGlashan and Hoffman, 2000; Tang et al., 2014). These major psychiatric disorders have a prominent onset (e.g. Hazlett et al., 2017; Marín, 2016) in early infancy or the fetal period, indicating this early period is likely to be critical to these neurodevelopmental disorders. Despite the significant contribution of histological studies to understanding typical and atypical brain development, such studies are relatively labor-intensive and time-consuming and may not be suitable for surveying the entire brain. Therefore, it is extremely difficult to reveal the global maturation pattern of the white matter or the cerebral cortex with histological approaches alone.

Contemporary magnetic resonance imaging (MRI), capable of surveying the entire brain with usually less than 1-hour scan time, has become a very important tool for understanding the microstructural and macrostructural changes of early developing human brain non-invasively. The MRI images, including diffusion MRI (dMRI), relaxometry MRI (quantitative T1- and T2-maps) and magnetization transfer imaging (MTI), reveal different aspects of gray and white matter microstructural changes as well as myelination processes across the cerebral cortex, subcortical gray matter and major white matter tracts *in vivo*. In this review, we summarize the macrostructural and microstructural findings in the brains of fetuses, preterm and full-term newborns, and infants less than 2 years of age using MRI approaches, especially dMRI. First, we briefly introduce the basic principles of MRI techniques, emphasizing diffusion tensor imaging (DTI), one of the most widely used dMRI models. Next, we consolidate the current understanding of white matter development, including the emergence pattern of white matter tracts and MRI measurement changes of white matter at both tract and tract group levels. Third, we review findings of unique microstructural organization and heterogeneous maturation patterns across the cortical plate and in different subcortical gray matter nuclei. Finally, we discuss the issues and limitations of studying white and gray matter development in the baby brain using MRI techniques, and suggest avenues that could be explored for future research. Without additional description, the fetal and preterm brain age defined in pcw, postmenstrual week (pmw) or weeks of gestation (wg) was directly adapted from the reviewed studies. The standard age terminology of fetal and infant brain can be found in the policy statement by American Academy of Pediatrics Committee (Engle et al., 2004). We hope this review will become a useful reference for investigations using other modalities such as histochemical, electrophysiological and biobehavioral approaches and facilitate detecting important MRI-based biomarkers for prognosis and treatment monitoring of neurodevelopmental disorders.

2. MRI techniques: Diffusion MRI and beyond

With recent unprecedented technical advances in MRI, significant leaps have been made in understanding early brain development using MRI. Diffusion MRI, especially DTI, has become an effective probe to qualitatively and quantitatively characterize brain tissue microstructure, white matter tract anatomy and the structural connectivity of developing human brain. Other MRI-based techniques including T1 weighted (T1w), T2 weighted (T2w) imaging, relaxometry MRI, and MTI have also been extensively used to study brain development in pediatric populations. The shortening of T1 or T2 relaxation time in brain tissues throughout development, particularly in the white matter, is related to decreases in brain water content and increases in the concentration of macromolecules such as myelin (Barkovich et al., 1988). Based on the difference in T1w and T2w contrasts across brain tissues, volumetric and morphological changes of developing brain gray and white matter can be quantified (e.g. Counsell et al., 2002; Hüppi et al., 1998a). Magnetization transfer ratio (MTR), an index of MTI, has been used to characterize the changes in the brain tissue disorganization associated with axonal loss or demyelination. The following sections provide a brief introduction to the principles of these MRI techniques.

2.1 Diffusion MRI

2.1.1 Basics of diffusion MRI—Diffusion is a Brownian motion process, referring to random movement of water and other small molecules due to thermal collisions. In the human brain, diffusion of water molecules is preferentially along the axons rather than perpendicular to them. dMRI, a non-invasive technique, provides a unique opportunity to measure the diffusional characteristics of the human brain. This is particularly important in cases where the contrast from other imaging methods is not sensitive enough to resolve the boundaries between brain tissues. For example, the contrasts of T1w and T2w images of infant brains are relatively weak due to insufficient myelination. By applying a pair of so-called diffusion gradients to the magnetic field, characterized by b value with units of s/mm^2 (LeBihan and Breton, 1985), the diffusion sensitized signal S can be calculated as follows.

$$S = S_0 \exp(-bD) \quad (1)$$

where D is the diffusion coefficient with units of mm^2/s, S and S_0 are the diffusion sensitized and non-diffusion signal. By solving equation (1) in each voxel, the diffusion coefficient (D), known as apparent diffusion coefficient (ADC) in biological tissues, can be obtained. It is noteworthy that one D value reflects diffusion in only one direction, which is along the direction of the appl1ied diffusion gradient.

2.1.2 Diffusion tensor and other advanced diffusion MRI models—A diffusion profile composed of D value measurements along multiple orientations can be obtained by applying a sufficient number of diffusion gradients along varying directions. We can characterize this diffusion profile with a mathematical model. DTI (Basser et al., 1994) is most widely used among all dMRI models, despite certain limitations (e.g. Jones and Cercignani, 2010; Tournier et al., 2011). DTI characterizes the magnitude, anisotropy and orientation of the diffusion by a three-dimensional ellipsoid, or a rank-2 diffusion tensor, with the underlying assumption that water molecular diffusion follows a Gaussian distribution. After the tensor fitting process, the properties of the three-dimensional ellipsoid such as the length of the longest, middle and shortest axes (called eigenvalues, λ_1, λ_2, and λ_3 respectively) and their orientations (called eigenvectors, ν_1, ν_2 and ν_3, respectively) can be obtained. Once the eigenvalues and eigenvectors are estimated at each image voxel, several DTI-derived metrics can be calculated. Specifically, fractional anisotropy (FA) (Pierpaoli and Basser, 1996), a measurement that characterizes the shape of the three-dimensional ellipsoid, can be calculated with its value ranging from 0 to 1. FA is sensitive to white matter microstructural changes (Beaulieu, 2002). Specifically for the fetal and baby brain, the FA is also sensitive to cerebral cortical microstructural changes. FA is probably the most widely used metric in dMRI studies of baby brains. The orientation of the longest axis of the estimated ellipsoid (primary eigenvector, ν_1) can be converted to a color at each pixel (Makris et al., 1997; Pajevic and Pierpaoli, 1999). By combing the intensities of the FA map, a color-encoded orientation map can be obtained. In addition, axial diffusivity (AD), the primary eigenvalue (λ_1) of the tensor, quantifies the water diffusion parallel to the primary eigenvector of the diffusion tensor. AD has been thought to describe the axonal integrity of the white matter fiber bundle. Radial diffusivity (RD), usually calculated as the average of the second and the third eigenvalues of the tensor, quantifies the magnitude of diffusion orthogonal to the principal diffusion direction. RD has been thought to reflect the extent of white matter myelination (Song et al., 2005). Although AD and RD have been used to infer these microstructural changes, caution needs to be taken for their interpretations (Wheeler-Kingshott and Cercignani, 2009). Mean diffusivity (MD), calculated as the average of all three eigenvalues, quantifies the average magnitude of water diffusion along all directions. Figure 2 shows DTI-derived maps of fetal and infant brains from the mid-fetal stage to 2-years-old. Furthermore, advanced diffusion MRI models, including but not limited to diffusion kurtosis imaging (DKI) (Jensen et al., 2005) and neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012), have been proposed to characterize brain microstructure.

2.1.3 Diffusion MRI based tractography—Tractography based on dMRI has been used to reconstruct white matter pathways three-dimensionally and map the structural connections of the human brain. The results are highly dependent upon the dMRI models and parameters used. DTI-based deterministic tractography refers to the techniques of connecting the primary eigenvectors to reconstruct the pathways of white matter bundles. Streamline propagation methods (Mori et al., 1999; Jones et al., 1999) have been widely used. Since DTI only reveals one dominant fiber orientation in each voxel, it oversimplifies the underlying complex neural structures at voxels containing crossing or kissing fiber bundles. More advanced dMRI tractography methods, including Q-ball (e.g. Tuch et al., 2002), diffusion spectrum imaging (DSI in e.g. Wedeen et al., 2008), constrained spherical deconvolution (CSD in e.g. Tournier et al., 2012), and ball and stick (e.g. Behrens et al., 2007), have been proposed to resolve complex fiber architecture in a given voxel. It is beyond the scope of this review to describe these advanced tractography methods in depth. Reviews of dMRI-based tractography can be found in the literature (e.g. Behrens and Jbabdi, 2009; Jbabdi and Johansen-Berg, 2011).

2.2 Beyond Diffusion MRI: Other quantitative MRI approches

2.2.1 Approaches of quantifying myelination based on T1 and T2 relaxometry —The longitudinal relaxation time (T1) characterizes the proton interactions with its environment (“spin-lattice” interactions), while the transverse relaxation time (T2) characterizes the interactions between protons (“spin-spin” interactions). Both T1 and T2 are sensitive to local chemical and magnetic environment. Although sensitive to relaxation times, anatomical T1w and T2w images only provide qualitative information on their variations across brain tissues. Indeed it is challenging to compare T1w and T2w signal intensities across individuals because of the variability of exams related to scan acquisition settings, head size and positioning within the coil. And it is challenging to compare T1w and T2w signal intensities across brain regions of individual subject too because of B0 and B1 field inhomogeneity, particularly when phased-array surface coils are used. Recently, computing the ratio between T1w and T2w image intensities has been proposed to map myelination differences across cortical areas (Glasser and Van Essen, 2011). This strategy enables one to benefit from the anatomical images that are routinely acquired in the clinical setting, and to improve the localization of heavily myelinated regions in contrast to lightly myelinated ones. The contrast to noise in the ratio between T1w and T2w image is increased because the myelin content covaries with T1w and T2w intensity, but in opposite directions. The ratio between T1w and T2w image is also more reliable than T1w or T2w image alone, as some aspects of spatial inhomogeneity in signal intensity can be ameliorated. Specifically, the bias related to the sensitivity profile of the radio frequency receiver coil (B1−) can be corrected with the ratio, since it is the same in T1w and T2w images. Variations due to transmit field (B1+) biases are not corrected but minimized as they are correlated between (but not the same in) both images, and these variations might be less problematic in scanners with good B1+ homogeneity (Glasser and Van Essen, 2011).

Nonetheless, the best approach to measure reliable differences across individuals (e.g. in infants during development) or across brain regions within the same individual is to map T1 and T2 relaxation time constants quantitatively. This requires the acquisition of several images with different parameter settings (different inversion times to compute T1, or different echo times to compute T2), and the estimation of absolute T1 and T2 values by fitting the model of the expected signal to the actual measurements in each voxel.

Maps of the fraction of water related to myelin, sometimes called the "myelin water fraction" (MWF), can be obtained with T1 and T2 measurements. T1 and T2 strongly depend on the water concentration. At least two distinct pools of water molecules contribute to the MR T1 and T2 signal in brain tissues: water located within the myelin sheath (showing relatively short T1 and T2 relaxation times), vs intra-axonal, intra-cellular and interstitial water (i.e. water outside of the myelin sheath, showing longer T1 and T2). Approaches based on "multi-component relaxation" (MCR) analyses further provide direct information about the myelin content, by modeling different pools of water molecules in each voxel (Spader, et al. 2013). These pools can be distinguished from measured MR signals, on the basis of different relaxometric properties (T1 and/or T2) and of specific exchange relationships (Beaulieu, et al. 1998; Menon, et al. 1991; Whittall, et al. 1997). Such decomposition is supposed to provide valuable information about tissue microstructure. Although the exact number of pools to be modelled is still debated (Deoni, et al., 2012), a consistent pool of water related to myelin is the MWF. Unlike relaxation times, MWF is independent of the magnetic field strength, but its computation is highly sensitive to both the acquisition protocol and the post-processing model, making direct comparisons across studies challenging. An example of T1w, T2w, quantitative T1 and T2 time constant maps, and MWF in representative baby brains at 1.5-, 4.5- and 8-months-old is illustrated in Figure 3.

2.2.2 Approaches based on magnetization transfer—Other MR quantitative parameters relying on myelin amount have been proposed in the recent years. The MTR, an index of MTI, informs about the ratio between free water and water with restricted motion bound to macromolecules such as proteins and lipids (McGowan, 1999). This technique appears to be sensitive to myelin-associated macromolecules, but also to the macromolecular density of axonal cytoskeleton components such as microtubules and neurofilaments (Nossin-Manor, et al. 2013). While MTR is generally thought to directly reflect the myelin amount (Kucharczyk, et al. 1994), it might also depend on the tight organization and close package of non-myelinated fibers (Nossin-Manor, et al. 2013).

3. Maturation of white matter from middle fetal stage to 2-years-old

The brain can be divided into white and gray matter. Gray matter can be regarded as information processing hubs, and white matter acts as a long-range communication and transmission system. For several decades, the architecture of white matter has been delineated with histology of postmortem brains. The recent advances of MRI of developing brains shed light on important questions such as when and how certain connections emerge at the beginning of life and what are the maturational trajectories of white matter tracts in typical development. Especially with dMRI, the emergence and maturation processes of fetal and infant brains' white matter tracts have been elucidated (e.g. Dubois et al., 2006, 2008; Huang et al., 2006, 2009; Hüppi et al., 1998b; Kasprian et al., 2008, 2013; Kolasinski et al., 2013; Miller et al., 2014; Neil et al., 1998; Partridge et al., 2004; Takahashi et al., 2011; Xu et al., 2012).

3.1 Delineating emergence of white matter tracts with DTI tractography

The major white matter tracts in the human brain can be categorized into five functional categories: limbic, commissural, projection, association and brainstem tract groups (Wakana et al., 2004, 2007). Figures 4a–4e show the emergence of these developing white matter tracts of the five tract groups in the baby brain from the mid-fetal stage to 2-years-old. As all tracts were three-dimensionally reconstructed with DTI tractography, it is noteworthy that Figure 4 only demonstrates the timeline from the perspective of DTI tractography and is restricted by factors that limit DTI tractography (see e.g. Jbabdi and Johansen-Berg, 2011 for review). Thus, Figure 4 may not accurately reflect the exact emergence time of white matter tracts. Histological delineation is complementary to DTI tractography, but is restricted by the factors such as local coverage with small blocks and difficulty for three-dimensional reconstruction. In addition, it is labor-intensive. With fetal brain DTI studies (e.g. postmortem brain in Huang et al., 2006, 2009, Ouyang et al., 2015, Song et al., 2017, Takahashi et al., 2011; *in utero* fetuses in Kasprian et al., 2008, 2013), a heterogeneous emergence pattern of white matter across different tracts and tract groups was observed. Specifically, in the limbic tract group, the fornix (FX) probably emerges earlier than 13 weeks of gestational age (wg), and the cingulum bundle in cingulate gyrus (CGC) and cingulate bundle in hippocampus (CGH) appear around 19wg. In the commissural tract group, the body of the corpus callosum (BCC) emerges around 15wg, followed by the genu (GCC, before 19wg) and splenium (SCC, after 19wg) of the corpus callosum. In the projection fiber tracts, the anterior corona radiata (ACR) probably emerges before 13wg, followed by the superior portion (SCR) around 15wg and the posterior portion (PCR) after 19wg. In the association tract group, the external capsule (EC) emerges before 13wg, followed by the appearance of the uncinate fasciculus (UNC) around 15wg, and the inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFO) around 19wg. The exact time for the emergence of the superior longitudinal fasciculus (SLF) is not clear. The observations from dMRI tractography suggest that the SLF may emerge during the third trimester (Huang et al., 2006, 2009; Miller et al., 2014; Takahashi et al., 2011). Histological studies show such long-range cortico-cortical fibers emerge around 33–35pcw (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Rakic, 1990), although the SLF is not prominently visible with dMRI-based tractography even at birth using current techniques. The white matter tracts that emerge earlier (e.g. the brainstem tracts) may play important roles in supporting the basic functions for life. Conversely, the later emerging tracts such as the SLF may contribute more to higher-level brain functions. Playing a critical role in language function, the SLF has been demonstrated to mature late (e.g. Zhang et al., 2007). The approximate emergence pattern of white matter tracts from a suite of dMRI tractography studies (Huang et al., 2006, 2009; Kasprian et al., 2008, 2013; Kolasinski et al., 2013; Miller et al., 2014; Takahashi et al., 2011; Xu et al., 2012) and histological atlases (Bayer and Altman, 2004, 2005) is summarized in Figure 4f.

3.2 The heterogeneous microstructural changes of white matter tracts and tract groups with DTI measurements

Significant microstructural changes of white matter tracts take place during the fetal stage (Kersbergen et al., 2014) and the first two years of life (Geng et al., 2012; Hermoye et al., 2006; Mishra et al., 2013; Mukherjee et al., 2001; Yu et al., 2014). A general pattern of age-dependent FA increase and diffusivity (i.e. MD, AD and RD) decrease has been found in most baby brain white matter tracts (e.g. 28–43wg in Berman et al., 2005; 30–40wg in Kersbergen et al., 2014; 1–4 month in Dubois et al., 2008; 0–2 year in Geng et al., 2012). Within this general pattern, the maturational rates of different white matter tracts are spatiotemporally heterogeneous. Linear (Berman et al., 2005; Dubois et al., 2006, 2008), exponential (Lebel et al., 2008; Mukherjee et al., 2001; Yu et al., 2017) and logarithmic (e.g. Yu et al., 2014) curves have been used to fit the age-dependent changes of DTI-derived metric measurements of white matter tracts based on the studied age range. Linear curves were usually used for characterizing white matter microstructural changes in a relatively short period while exponential or logarithmic curves were used in longer developmental periods. Schematic maturational curves of FA values for the five white matter tract groups from the mid-fetal stage to 2-years-old are illustrated in Figure 5a based on previous studies (28–43wg in Berman et al., 2005; 30–40wg in Kersbergen et al., 2014; 1–4 month in Dubois et al., 2008; 0–2 year in Gao et al., 2009; Geng et al., 2012; Hermoye et al., 2006; Mukherjee et al., 2001, 2002; Yu et al., 2017). The increasing FA values in all tract groups probably indicate the widespread myelination process across white matter regions. The maturational pattern of different tract groups is heterogeneous (Figure 5a). As shown in the sketch plot in Figure 5a, during the age from 20pmw to 2-years-old the FA values of commissural tracts are the highest among the five tract groups, while the association tracts are the lowest. These high FA values in commissural tracts could be due to the higher level of axonal density, and the low level of fiber orientation dispersion, while the lower FA value in association tracts may be related to lower axonal density and greater fiber orientation dispersion, as shown by NODDI (Chang et al., 2015), as well as the crossing fibers in these regions. To further characterize the temporal changes of the white matter tracts in the early developing brain, a three-stage maturational pattern from 0 to 3 years: an initial rapid maturation stage, a relatively slow maturation in the middle, and a final plateaued maturation stage, was proposed in a cross-sectional study (Yu et al., 2017). Based on this three-stage pattern, it was found that FA percentage increases of the commissural and brainstem tract groups from 0 to 2 years were higher than those of the projection, limbic and association tract groups in the same developmental period. In addition, it was found that the association tract group is the last one to reach the plateau stage, suggesting the maturation of the association tracts continues for a longer time than other tract groups. Developmental asynchrony across different white matter tracts has also been confirmed by a longitudinal study (Sadeghi et al., 2013) of the early developing brain with measurements of FA, MD, AD and RD.

White matter microstructural changes are governed by a suite of complicated but synchronized developmental processes. Strongest correlations between homologous tracts in the left and right hemispheres were found with correlation analysis of tract-based measurements of MD, FA, AD and RD in the normal adult brain (Wahl et al., 2010). The differences of inter-tract correlations between neonates and children around puberty were investigated using hierarchical clustering analysis (Mishra et al., 2013). It was suggested that inhomogeneous but organized myelination processes may contribute to a reshuffled inter-tract correlation pattern and strengthening of the correlation of homologous tracts from neonates to children around puberty. In a different developmental age range of 7 to 25 years, synchronous changes of cortical thickness and corresponding white mater microstructure has also been observed (Jeon et al., 2015). Although DTI-derived measurements of white matter microstructure may offer significant information about brain development, caution needs to be taken when interpreting the results. FA and diffusivity measurements are at most indirect indicators of myelination (Beaulieu, 2002; Song et al., 2005), axon packing (Mädler, et al., 2008) or axon density (Klawiter et al., 2011). For example, a high FA value in the corpus callosum that is already observed in the preterm brain may reflect the higher level of axonal packing than other white matter regions and a low FA value in the EC may reflect its fanning geometry.

3.3 Advanced dMRI techniques to assess white matter maturation

As introduced in section 2.1.2, a variety of advanced dMRI techniques have also been used to characterize white matter maturation. In addition to the single “shell” of diffusion-weighted orientation measurements needed for DTI at b values typically ranging from b=600–1300 s/mm^2, these more advanced dMRI methods require one or more additional shells at higher b values to probe the non-Gaussian component of water diffusion in biological tissues. Specifically, DKI uses this multi-shell dMRI acquisition to characterize white matter tract development in the infant brain from 0 to 5 years old with an exponential curve (Paydar et al., 2014)., Similar to FA change patterns, the mean kurtosis (MK) values, defined as the average kurtosis over all diffusion directions in DKI, of the commissural tracts (SCC and GCC) were higher than the MK of the projection (PLIC and ALIC) and the association tracts (EC). Age-dependent increases of both FA and MK may reflect the myelination of white matter. However, MK was detected to continue to change even as FA has reached its plateau in some white matter regions, suggesting that MK may be a more sensitive measurement to quantify certain microstructural changes of biological tissues (Paydar et al., 2014). DTI and DKI are statistical descriptions of the diffusion-weighted signal, with DTI encompassing the second moment (Gaussian variance) with a rank-2 tensor and DKI including also the fourth moment (non-Gaussian kurtosis) with a rank-4 tensor. This sets them apart from biophysical compartment modeling approaches such as AxCaliber (Assaf et al., 2008), NODDI (Zhang et al., 2012) and white matter tract integrity (WMTI; Jelescu et al., 2015) that explicitly use the multi-shell dMRI data to estimate biologically meaningful properties of the tissue such as the relative volume fractions of free water (CSF), extracellular space and intracellular space, as well as the overall geometry of neurite orientations. These NODDI metrics have been applied to differentiate myelinated fibers (e.g. PLIC) from not yet myelinated ones (e.g. ALIC) in neonate brains (Kunz et al., 2014). With WMTI and NODDI metrics from the multi-shell dMRI acquisition also used for DKI (Fieremans et al., 2011), non-linear increases in both intra-axonal volume fraction and tortuosity of the extra-axonal space were found in GCC, SCC and PLIC in infants from 0 to 3 years old (Jelescu et al., 2015). These increases likely result from active myelination combined with the known asynchrony of fiber development.

3.4 Other quantitative MRI approaches to assess white matter maturation

3.4.1 Approaches based on T1 and T2 relaxometry—T1 and T2 decrease with developmental processes, more strongly in white matter than in grey matter because of the myelination (Barkovich, 2000; Prayer and Prayer, 2003). Assessing the maturation of regions is first possible based on visual inspection of T1w and T2w images, which show an abrupt increase in myelinated white matter in preterm brain between 35 and 41pcw (Hüppi et al., 1998a). To identify mature from immature regions, T1w contrast is generally preferred during the first 6–8 postnatal months, when brain images show an “infantile pattern” (with a reversal of the normal adult contrasts), while T2w contrast is preferred between 6 and 14 months, when images show an iso-intense or early-adult pattern (Barkovich et al., 1992; van der Knaap and Valk, 1990; Paus et al., 2001; Dubois et al., 2014a).

The age-related decreases in T1 and T2 values might be further quantified in the developing brain. Both T1 and T2 values of brain tissue drop in parallel with the decrease in water concentration, nevertheless their time courses are different, and two distinct mechanisms can be distinguished: the change in water compartmentalization (Matsumae et al., 2001), and the increase of protein and lipid content (Barkovich et al., 1988; Kucharczyk et al., 1994). T1 shortening starts during the “pre-myelination” state, while T2 shortening correlates temporally with the chemical maturation of the myelin sheath (Barkovich et al., 1988; Baumann and Pham-Dinh, 2001; Poduslo and Jang, 1984). T1 and T2 drops are particularly rapid over the two first years (Engelbrecht et al., 1998; Haselgrove et al., 2000), and age-related changes are generally modelled with exponentials functions (Leppert et al., 2009). Because of differences in the maturation timeline, the specific time-course of these patterns is brain-region dependent.

Regarding measurement of the myelin water fraction, a strong increase is observed during infancy (Kulikova et al., 2016), and follows a nonlinear growth pattern until toddlerhood (Dean et al., 2014; Deoni et al., 2012). Consistent with histological studies of myelination, the spatiotemporal pattern of myelination progression is demonstrated (Deoni et al., 2011, 2012), showing successive increases in the cerebellum, pons, and internal capsule, caudo-cranially from the splenium of the corpus callosum and optic radiations, to the occipital and parietal lobes, and then to the genu of the corpus callosum and to the frontal and temporal lobes.

Altogether MRI parameters provide complementary information on multiple maturational processes (Deoni et al., 2013; Lancaster et al., 2003) and it is only by comparing these parameters that one can hope to outline comprehensive patterns of white matter microstructure (Dubois et al., 2014a, 2016b; Qiu et al., 2015). This makes it possible to differentiate bundles based on their maturation patterns, as recently highlighted during the preterm period (Nossin-Manor et al., 2013, 2015). Furthermore, DTI-derived measurements might be combined with T1 and T2 by considering an original measure of maturation based on the computation of the Mahalanobis distance comparing infants' individual data with a group of adults, taking into account the possible correlations between MRI measurements (Kulikova et al., 2015). This measure confirms the asynchrony of white matter maturation in infants between 3 and 21 postnatal weeks, and provides a quantitative evaluation in weeks of the developmental differences between white matter bundles. Clustering brain voxels over a group of infants on the basis of T1, T2 and DTI-derived measurements, has also uncovered four white matter regions with different compactness and maturation (Lebenberg et al., 2015). The spatial distribution of these clusters was anatomically relevant while the approach was free from any anatomical hypothesis.

3.4.2 Magnetization transfer—MTR increases during white matter maturation (Kucharczyk et al., 1994, Nossin-Manor et al., 2013, 2015) with an exponential time course (Engelbrecht et al., 1998; van Buchem et al., 2001). Differences across regions are observed, with a relatively mature stage at around 13 months and 16 months in the occipital and frontal white matter respectively, and at 18 months and 19 months in the splenium and genu of the corpus callosum (Xydis et al., 2006).

The different MRI measurements seem to capture different properties of white matter maturation, even if some studies have suggested some developmental relationships such as relative inverse correlations between MTR and T2 (Engelbrecht et al., 1998) or MTR and T1 (Nossin-Manor et al., 2013). Notably, a study using the cuprizone mouse model of demyelination has shown that the bound pool fraction (f) from MTI is the best indicator of the myelin sheath fraction, while T1 relates to the fraction of myelinated axons, and AD from DTI relates to the fraction of non-myelinated cells (Thiessen et al., 2013). These latter two measurements might thus characterize the tissue micro-architecture rather than myelination.

Complementary to myelin-sensitive and dMRI techniques, a composite framework has been proposed recently to estimate the g-ratio (Stikov et al., 2015), i.e. the ratio between the inner and outer diameters of the myelin sheath, which is thought to be a fundamental characteristic of white matter fibers. In the adult brain, the approach relies on MTI to estimate the myelin content and on NODDI to assess the intra-axonal fraction. Similar approaches using MWF instead of MTI have been tested to quantify myelination in the developing brain of newborns (Melbourne et al., 2016), infants and children (Dean et al., 2016). However, like other MRI measurements, MWF is a voxel-wise aggregate index that merges the properties of distinct fibers that may be crossing or fanning at the voxel level.

3.5 Biophysical models to interpret DTI measurement changes

To better understand the cellular processes underlying white matter maturation in terms of axonal growth, organization and myelination, biophysical models have been proposed to link these cellular processes to the DTI-derived measurement changes during early brain development. For example, a model including different major maturational changes taking place in the tissue (fiber organization, membrane proliferation and fiber myelination as shown in Figure 5b) was proposed as a biophysical interpretation for the changes of DTI-derived measurements (i.e. FA, MD, RD and AD) during white matter development (see details in Dubois et al., 2008; Nossin-Manor et al., 2015). Specifically, the axonal or fiber organization stage would be expected to be associated predominantly with an increase in AD without affecting RD, leading to an increase in both FA and MD. The membrane proliferation or "pre-myelination" stage, characterized with an expansion of immature oligodendroglia cells and their processes, would be expected to be associated with a reduction in all three diffusivity indices due to the increased membrane density and the decreased water content in brain tissue; meanwhile FA would increase. The third stage, myelination of white matter fibers, is associated with a decreasing RD and a little changed AD, which drive FA increases and MD decreases. In places where different tracts are crossing, the situation may require more complex interpretation if these tracts mature with different timelines (Dubois et al, 2014, 2016b). These DTI-based models could be tested with the newer multi-shell dMRI-based models (e.g. DKI and NODDI) that may measure free water content, axonal density and fiber orientation dispersion (see section 7 for details).

4. Microstructural maturation of gray matter from middle fetal stage to 2-years-old

Gray matter also develops rapidly in the fetal and infant stages. It has been shown with structural MRI that the cortical gray matter volume in the human brain increases more than 4-fold in the short period of the 3rd trimester (Hüppi et al., 1998a; Limperopoulos et al., 2005) and around 1.5-fold in the first two years of postnatal life (Knickmeyer et al., 2008). Because of its sensitivity to microstructural changes of organized cortical tissue unique in the fetal and infant brain, dMRI offers insight into the development of not only white matter but also cortical cytoarchitecture. With spatiotemporal mapping of FA of the cerebral cortex, dMRI also sheds light on the dynamics of neuronal processes across the early developing cerebral cortex.

4.1 Microstructural organization in the cortical plate in fetal and preterm human brain and its DTI quantification

In the fetal and preterm human brain, the cerebral wall is characterized by a laminar organization (e.g. Kostović et al., 2002; Kostović and Vasung, 2009) with some transient compartments lacking their direct counterparts in the adult brain. The outermost layer of this cerebral wall is known as the cortical plate. During cortical development, the majority of cortical neurons are generated near the cerebral ventricles and migrate towards the cortical surface along a radially arranged scaffolding of glial cells. They arrive at their final destination in the fetal cortical plate and assume a well-defined columnar structure (Rakic 1972, 1995; Sidman and Rakic, 1973). In this immature cortex, water molecules preferentially diffuse along the radial glial scaffold and radially oriented apical dendrites instead of perpendicular to them. The highly organized radial architecture of the immature cerebral cortex of fetal and preterm brains is characterized by high FA values as well as by an organized radial orientation of diffusion tensor primary eigenvectors. Unlike the adult human brain, where the FA of the cerebral cortex is low, the FA values of the cortical plate are high in fetal and preterm development (indicated by yellow arrows in Figure 2). With high-resolution postmortem DTI, the cerebral wall of fetal of 13–21wg has been subdivided into cortical plate, subplate and inner layer (Huang et al., 2009, 2013). During 13–21wg, FA values of the cortical plate are much higher than those of the subplate, a transient compartment located beneath the cortical plate. Compared to the cortical FA of the adult brain, relatively high FA values (0.2–0.3) were also found in cortical regions of preterm neonates in the 3rd trimester using *in vivo* DTI (e.g. 26wg in McKinstry et al., 2002; 25–27pmw in Maas et al., 2004; 25wg in deIpolyi et al., 2005; 27pcw in Ball et al., 2013). Figure 6 shows the cortical FA maps during the 2nd (13–21pmw) and the 3rd (32–41pmw) trimesters. It is clear from Figure 6 that the FA distribution across the cortical regions at a given fetal or preterm age is heterogeneous. A relatively high FA at the frontal cortex compared with primary sensorimotor cortex can be appreciated. This distribution (e.g. Ball et al., 2013; Huang et al., 2013; deIpolyi et al., 2005; Yu et al., 2016) suggests that the frontal cortex is relatively more immature, having less dendritic arborization, synaptic formation, or cellular differentiation in the fetal and preterm brains. Visualization of the primary eigenvectors of the diffusion tensor also demonstrates radial (orthogonal to the cortical surface) organization in the immature cerebral cortex (Huang et al., 2009, 2010; McKinstry et al., 2002; deIpolyi et al., 2005).

4.2 Heterogeneous microstructural changes across the cortical regions assessed by DTI during fetal and preterm development

The maturation pattern of the developing cortical plate is characterized by a reduction in both FA and MD, in contrast to the increase in anisotropy and decline in MD of white matter during early development. From 13 to 21wg, the FA measurements of the overall cortical plate undergo a significant decrease as shown in Figure 6a, with the highest value being more than 0.5 at 13wg dropping to around 0.25–0.3 in most cortical areas at 21wg (Huang et al., 2013). Cortical FA decrease has been reported in the developing brain in the 3rd trimester with *in vivo* DTI of preterm neonates (e.g. 27–38pcw in Ball et al., 2013; 25–38wg in deIpolyi et al., 2005; 27–42wg in Eaton-Rosen et al., 2017; 32–41pmw in Jeon et al., 2016; 26–36wg in McKinstry et al., 2002; 26–40pmw in Smyser et al., 2016, 20–35pmw and 35–40pmw in Yu et al., 2016). For slightly older neonates (38–45pcw in Ball et al., 2013; 36–41wg in McKinstry et al., 2002), no significant FA changes were found in any cortical areas. Cortical FA maps in 32–41pmw are demonstrated in Figure 6b. While neuronal migration is essentially complete by 26pcw (Kostović et al., 2002; Sidman and Rakic, 1973), the subsequent cortical maturation processes involving synaptogenesis and synapse pruning, dendritic arborization, myelination of intracortical white matter, and axonal growth (i.e. Bystron et al., 2008; Huttenlocher and Dabholkar, 1997; Kostović and Jovanov-Milosević, 2006; Marin-Padilla, 1992) disrupt the pronounced radial organization of radial glial scaffold and result in the FA decrease (Figure 7a) (McKinstry et al., 2002). Such cortical FA decreases have also been documented in early developing animal brains (e.g. Huang et al., 2008; Kroenke et al., 2007, 2009; Mori et al., 2001; Sizonenko et al., 2007; Takahashi et al., 2010; Thornton et al., 1997). Besides reductions in FA, a continuous reduction of MD values was found in the cortical regions of neonates from 26–46pmw (27–

46pcw in Ball et al., 2013; 26–40pmw in Smyser et al., 2016). The steady decrease of cortical MD could be associated with a dramatic decrease in water content and an increase in tissue density of the cortex secondary to increases in neurite number, cellular complexity, and synapse formation (Dobbing and Sands, 1973). As water content decreases and tissue density increases, barriers to motion move closer, leading to a decrease in MD values.

Though both FA and MD decrease globally during cortical maturation, the rate of maturation is asynchronous across cortical areas, with the maturation of primary motor and sensory regions preceding that of the association and prefrontal areas, as summarized in the sketch plots in Figure 7b. A sharper FA decrease was found in the frontal cortex than the perirolandic and occipital cortices from preterm brains of 27 to 38pcw (Ball et al., 2013). Similar findings were reported in preterm brains during 35–40pmw, with FA decreasing in the frontal cortical regions faster than in primary cortices (Yu et al., 2016). This differentiated developmental pattern of cortical microstructure among various regions is consistent with neuroanatomical, physiological and functional findings, including regional cerebral glucose utilization with positron emission tomography (PET) (Chugani and Phelps, 1986; Chugani et al., 1987), regional cerebral blood flow (CBF) with arterial spin labeling (ASL) MRI (e.g. Ouyang et al., 2017a) and cortical functional connectivity with resting-state functional MRI (e.g. Cao et al., 2017; Doria et al., 2010). An exploratory correlation between the cortical microstructure and blood flow demonstrated that a sharper FA decrease in the frontal cortex was significantly correlated with a more rapid CBF increase in the same region in the preterm brains of 32 to 45pmw (Ouyang et al., 2017a). This study provides preliminary evidence on the association between cortical microstructural changes and elevated regional CBF. From a microscopic view, synaptogenesis and synaptic elimination have been observed to have distinct regional variations with an earlier beginning in the primary sensorimotor regions, and later start in association regions such as the prefrontal cortex (Huttenlocher and Dabholkar, 1997). From a macroscopic-connectomic view, the rapid increase of functional connectivity in preterm neonates aged 31–41pmw was predominantly found in the primary sensorimotor and visual regions (Cao et al., 2017). Taken together, the regionally asynchronous pattern of cortical microstructural changes observed with DTI during fetal and infant brain development may interact with functional and physiological maturational processes in the cortex observed with other approaches. The heterogeneous maturation pattern of cortical FA and MD may be used to infer the complicated but precisely organized cellular and molecular processes during cortical maturation.

4.3 Other quantitative MRI approaches to assess the maturational changes across cortical regions during the preterm period and infancy

A few studies have aimed to characterize maturational changes in the developing cortex throughout infancy. Based on T2w signal, differences are observed across regions of the linguistic network from 1 to 4 months old, with delayed maturation of the ventral superior temporal sulcus when compared with Heschl gyrus, planum temporale and the inferior frontal region (Leroy et al., 2011). In 12- to19-months-old infants, the T1w intensity and contrast significantly increase with age in the left lateral temporal regions involved in lexico-semantic processing, suggesting that neurophysiological processes supporting cognitive behaviors may develop before microstructural maturation is complete within associative cortices (Travis et al., 2013). So far, the T1w/T2w ratio has only been computed from 8 years of age, showing that intra-cortical maturation is ongoing until the late 30s (Grydeland et al., 2013).

Regarding multi-parametric approaches (DTI and relaxometry), a recent study evaluating the cortical microstructural properties in preterm born infants scanned at term equivalent age, suggested differential maturation across regions (Friedrichs-Maeder et al., 2017). At term, MD and T1 are lower in the primary sensorimotor cortices than in secondary processing areas, which in turn are lower than in higher order tertiary areas (Friedrichs-Maeder et al., 2017). From 1 year of age, T1 decreases while MWF increases in most cortical regions; however the developmental pattern still varies across primary and associative cortices (Deoni et al., 2015). All these microstructural changes observed within the infant cortical regions with distinct MRI measurements probably reflect a complex interplay between several mechanisms, such as the development of dendritic arborization, the proliferation of glial cells, and/or the myelination of intra-cortical fibers.

4.4 Developmental changes in deep grey matter assessed by DTI and other quantitative MRI approaches during the preterm period

Marked microstructural changes are also observed in central grey nuclei throughout development. Pioneering DTI studies have shown that MD values strongly decrease in preterm brains with age between 30 and 40wg (Neil et al., 1998) and in infant brains from 1 day to 4 years (Mukherjee et al., 2001), while anisotropy in the central grey nuclei increases but to a lesser extent than in white matter tracts (Mukherjee et al., 2001). Much like the cortical regions, the maturational pattern differs across nuclei (e.g. the caudate head and lentiform nucleus vs the thalamus) (Mukherjee et al., 2001). More specifically in the thalamus, RD decreases with age in all substructures from 36 to 43pmw, while AD decreases in all except the right thalamo-postcentral and parietal and occipital substructures (Poh et al., 2015). In the basal ganglia (caudate, putamen, globus pallidus), AD and RD decrease while FA increases over the same period (Qiu et al., 2013). These microstructural changes observed with DTI suggest that membrane proliferation and fiber myelination are intense in the developing deep grey matter of the baby brain.

A few additional studies have used other quantitative approaches to characterize the maturation of the central grey nuclei. During the preterm period, T1 measures decrease gradually with age in the thalamus and lentiform nucleus, simultaneously with white matter regions (Schneider et al., 2016). Comparing T1, MTR and DTI measures seem particularly relevant to fully characterize the microstructural properties and the maturational patterns of deep grey matter regions such as the globus pallidus, putamen, thalamus and ventolateral thalamic nucleus (Nossin Manor et al., 2013). For instance, this latter structure shows a high concentration of myelin-associated macromolecules and a low water content (high MTR and low T1), low diffusivities (low MD and RD), and low directionality and coherence (low FA and AD). During the first post-natal months, T2 strongly decreases in the thalamus, caudate nucleus and putamen (Bültmann et al., 2017). Finally, combined observations from 27 to 58wg have shown that the intra-axonal fraction from NODDI and the fraction of water related to the myelin increase in the thalamus while T2 decreases, suggesting that these microstructural changes are not solely due to myelination (Melbourne et al., 2016). Taken together, these studies suggest that disentangling microstructural processes, and studying maturational patterns across white matter, cortical and deep grey regions, requires the consideration of multi-parametric MRI approaches.

5. Connectome of early developing brain

In addition to studies of gray and white matter microstructure, it is also important to understand the connectivity between maturing brain regions in order to elucidate the development first of sensory and motor processing and subsequently of higher-order cognitive and behavioral functions. Exciting new advances in defining the developmental changes of whole-brain connectivity have been achieved by applying graph theory to diffusion tractography of white matter, the "structural connectome", and resting state fMRI of gray matter, the "functional connectome". In network analysis of the structural connectome, the gray matter regions represent the "nodes" and the white matter connections between different nodes represent the "edges". It is beyond the scope of this article to comprehensively review this rapidly evolving field, but the studies thus far demonstrate dramatic increases in the strength, efficiency and integration of the structural and functional brain networks during fetal (Jakab et al., 2014; Thomason et al., 2014, 2015; Schopf et al., 2012; Song et al., 2017; van den Heuvel and Thomason 2016) and neonatal (Ball et al., 2014; Brown et al., 2014; Cao et al., 2017; Fransson et al., 2007; Huang et al., 2015; Smyser et al., 2010; Tymofiyeva et al., 2012, 2013; van den Heuvel et al., 2015) development using traditional graph metrics, with both "small-world" and "rich club" organization already established at the earliest gestational ages investigated. Recent studies of the anatomic embedding of the structural connectome in adults show the highest density of connectome edges within the periventricular white matter (Owen et al., 2015, 2016), which may overlap with the "periventricular crossroads" of crossing commissural, association and projection fiber pathways that have been identified in studies of fetal development (Judas et al., 2005). A promising new advance is the discovery that the structural connectome can be decomposed into canonical spatial eigenmodes that characterize information transmission throughout the network and that are perturbed in neurodevelopmental disorders (Wang et al., 2017). These eigenmodes of the white matter network can explain functional activity and functional connectivity (Abdelnour et al., 2014; Robinson et al., 2016) and can thereby reproduce the known resting state fMRI networks (Atasoy et al., 2016). Brain network eigenmodes therefore provide a natural bridge between the structural and functional connectomes. Their development during fetal and neonatal life remains an area for future investigation.

6. Current issues and limitations

There are several issues arising from studying the structural development of white and gray matter of the fetal and infant brain using MRI techniques. First, motion-induced artifacts are probably the most prominent among all of the unsolved problems in baby MRI. In general, MRI scans require the subject to remain still in the scanner. In certain clinical settings, this issue can sometimes be circumvented with sedation. However, sedation is not preferred by either the clinicians or the parents, as it involves cumbersome setup, careful monitoring of the baby, and has potential complications related to sedation. In research of typically developing infants, the subjects are usually scanned during natural sleep. However, even small motion during the sleep can make it very challenging to acquire MR images without any motion artifacts. A few techniques (e.g. Gholipour et al., 2010; Kim et al., 2010; Dubois et al., 2014b; Cordero-Grande et al., 2018) have been developed to correct motion retrospectively based on the post-processing of the images. While the retrospective analysis plays an important role, research on prospective aspects of fetal and infant brain MRI during acquisition, including adopting novel MR sequences (i.e. self-navigated MR sequences, see Tisdall et al., 2012) and specific hardware devices (e.g. KinetiCor device for monitoring motion), could potentially further improve motion correction. Second, given the smaller size of the baby brain, higher resolution of MR images compared to that of adult brains is needed to delineate brain structures with similar anatomical detail to that of adult brains. This higher resolution imaging entails lower signal-to-noise ratio, making it more difficult to reduce the scan time and the likelihood of subject motion. Advances in data acquisition using simultaneous multiple-slice acquisition (Sotiropoulos et al., 2013) could dramatically improve the resolution to isotropic 1–1.5mm in DTI. Third, dMRI has its complications and intrinsic limitations. The advanced dMRI sequences with multiple shells and many diffusion-encoded directions make it more difficult to reduce the scan time and minimize motion. The artifacts from dMRI acquisition (e.g. those related to magnetic gradient imperfections, eddy currents, etc.) and complications associated with various non-DTI models are not elaborated here. The prominent limitations related to the most widely used DTI model for fetal and infant populations must be recognized when interpreting DTI-related results. As DTI-derived measurements can be only used to infer the microstructure and cannot directly quantify the axonal density, axonal packing or myelin level (Wheeler-Kingshott and Cercignani, 2009), caution needs to be taken when interpret age-dependent or pathology-related DTI parameter value changes. FA is also affected by crossing-fiber issues at imaging resolution of isotropic 2mm widely used in most fetal and infant DTI research. By retrospectively processing the diffusion weighted images, the approach towards correcting lower FA at the crossing-fiber regions (e.g. Mishra et al. 2015) could alleviate the bias of FA measurements at these regions. A well-known limitation associated with DTI tractography is the potential false-negative tractography results as DTI tractography is not able to resolve fiber topography in regions of crossing fibers (see e.g. Jbabdi and Johansen-Berg, 2011; Jones et al., 2013 for review). This limitation directly affects the interpretation of the emergence of certain white matter tracts using dMRI tractography (e.g. Huang et al., 2009, Miller et al., 2014; Takahashi et al., 2011).

7. Conclusion and future directions

We have consolidated the findings on early brain development from fetuses to infants using MR imaging techniques, focusing especially on dMRI. First, the maturational process of major white matter fiber bundles in most of the period from mid-fetal to 2-years-old is characterized by an increased FA and a decreased MD, whereas that of cortical gray matter is characterized by a decrease in both FA and MD. Second, maturation patterns of DTI-derived measurements reflect the cellular and molecular processes. For example, the increase of FA of white matter is related to myelination and axonal packing, whereas the decrease of FA of cortical gray matter is related to synaptogenesis and dendritic arborization that disrupt the radial organization of the developing cortex. Alternative quantitative MRI approaches could provide complementary information to the dMRI findings and open the door for future multi-modality studies. Third, the early development of white and gray matter is spatiotemporally heterogeneous Specifically, myelination begins earlier in projection and commissural fiber tracts than that in the association fiber tracts, and the multi-modal associative cortices (e.g. prefrontal regions) are shown to mature later than uni-modal associative cortices, which in turn mature later than primary sensory and motor cortices, consistent with past histologic studies.

Future research could include development of novel MR imaging techniques in both data acquisition and post-processing for motion correction in baby MRI. More sophisticated diffusion models (e.g. DKI, NODDI) are needed to overcome the limitations of the diffusion tensor model. After comprehensive validation of these models, they may provide information about microstructural changes in white matter and cortical regions in addition to those discovered through DTI. Further, complementary to the current literature which mostly focuses on long-range white matter fiber development, more investigations are expected to improve our understanding of how short-range white matter fibers mature in this early brain developmental period (see e.g. Ouyang et al., 2016; Phillips et al., 2013; and Ouyang et al., 2017b for review). Methodologies for performing reliable tractography of short-range white matter fibers or white matter bundles across different maturational stages are needed (Dubois et al., 2016a, 2016b). Another interesting direction for future research would be to investigate the relationships between brain structural and cognitive/behavioral development, which would particularly benefit from longitudinal studies that allow tracking of developmental trajectories of white matter and/or gray matter. Establishing normative developmental charts of structure, function and behavior is not only essential for understanding the complicated and rapid early development, but also critical for revealing alterations caused by neuropathology for early diagnosis and intervention. Finally, data sharing could significantly facilitate the understanding of the complicated structural and functional dynamics during the fetal and infant stages. The recent release of multi-modality neonate MRI from ERC-sponsored developing human connectome project (dHCP) (www.developingconnectome.org) and NIMH-sponsored fetal brain development (www.brainmrimap.org) could potentially expand our knowledge of baby brain development.

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Highlights

- Dramatic microstructural changes take place in developing fetal and infant brain
- Diffusion and other MRI modalities effectively quantify these developmental changes
- Emergence of different white matter tracts were delineated with dMRI tractography
- Cerebral cortical microstructural changes were quantified with dMRI metrics
- 4D spatiotemporal patterns of brain structural development were delineated

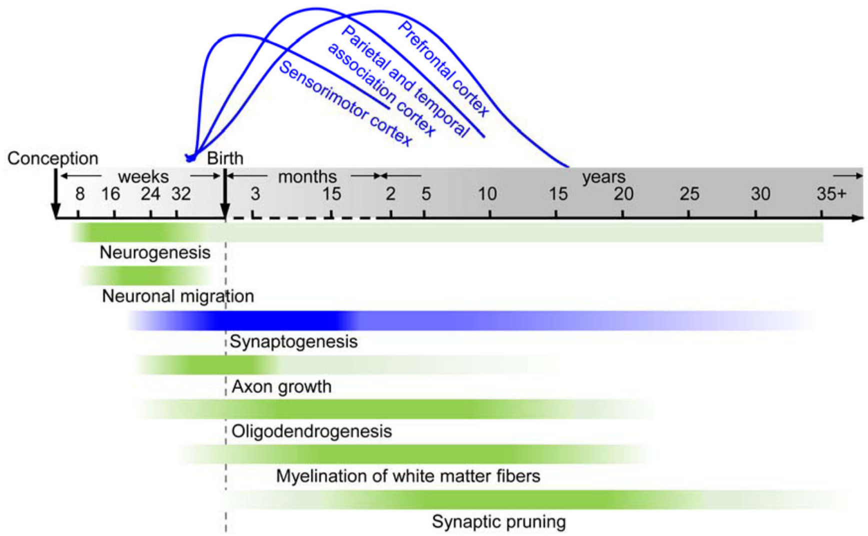

Figure 1.

Timeline of spatiotemporally distinctive human brain maturational processes, including neurogenesis, neuronal migration, synaptogenesis, axon growth, oligodendrogenesis, myelination of white matter fibers and synaptic pruning. Time axis is in post-conceptional weeks (before birth), postnatal months (until 24 months), and postnatal years (after 2 years). The color intensity in each bar corresponds to the rate of developmental changes. The spatial progression across brain regions is illustrated using synaptogenesis (blue bar) as an example. Specifically, the spatial progression of synaptogenesis from primary sensorimotor cortex to higher-order prefrontal cortex is illustrated by the blue curves above the time axis.

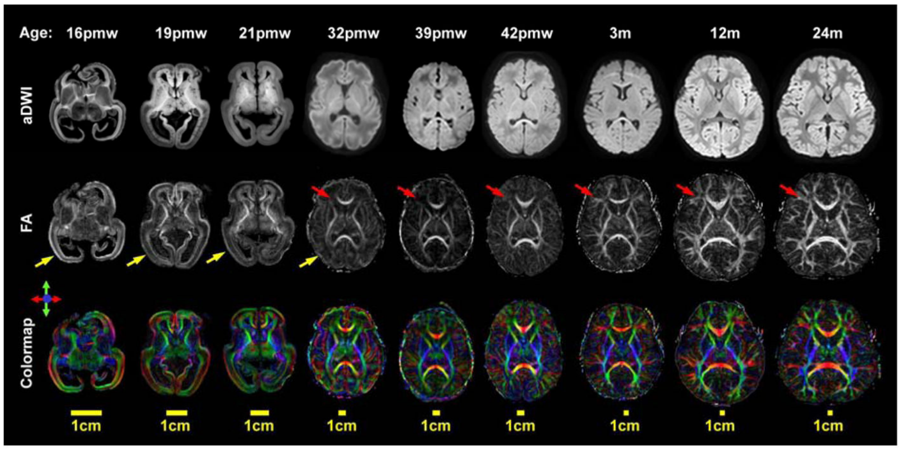

Figure 2.

Diffusion MRI (dMRI) contrast in the fetal and infant brain from 16 postmenstrual weeks (pmw) to 2 years (24 months) of age. From top to bottom, axial slices of the averaged diffusion weighted images (aDWI), fractional anisotropy (FA) maps and color-encoded diffusion orientation maps are shown. Yellow arrows indicate high FA values in the cortical plate, and red arrows indicate high FA values in the white matter regions during this early developing period. This figure is generated with the data from Huang lab.

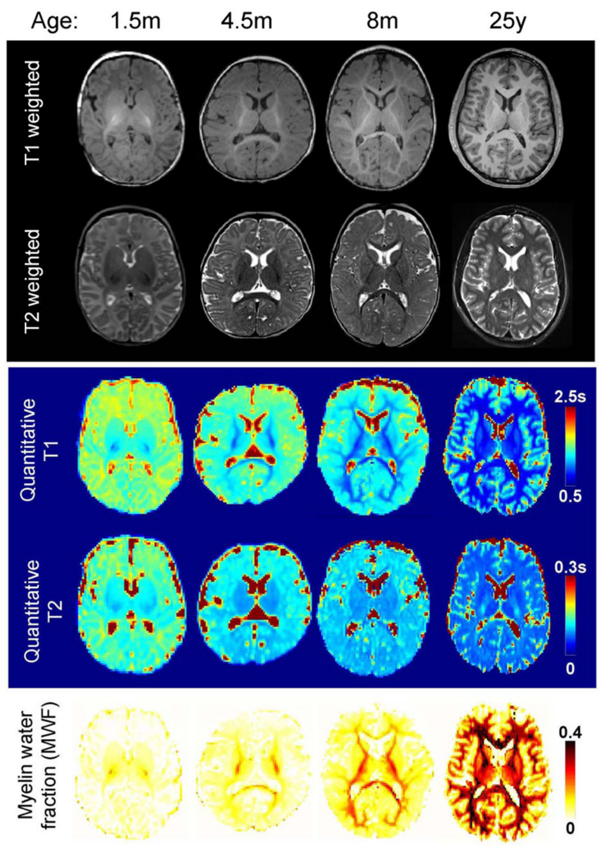

Figure 3.

Anatomical images of the developing brain. From top to bottom, T1 weighted, T2 weighted images, quantitative maps of T1, T2 relaxation times (in seconds) and myelin water fraction (MWF) of representative subjects at different ages, infant of 1.5 month (m), 4.5m and 8m and a young adult (25 years), are shown.

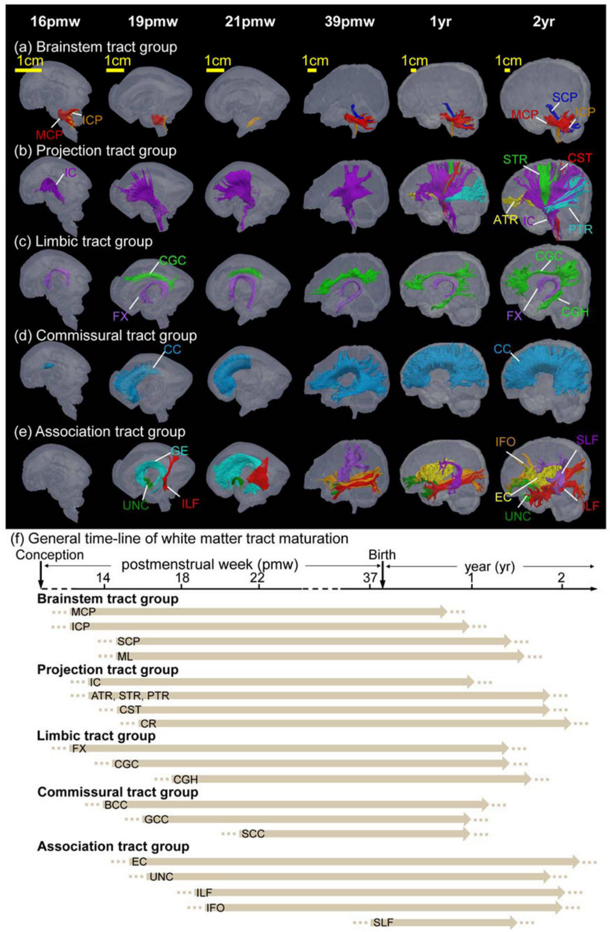

Figure 4.

Diffusion MRI tractography of the white matter tracts in developing fetal and infant brain from 16 postmenstrual weeks (pmw) to 2 years. (a) Brainstem tracts including inferior, middle, superior cerebellar peduncle (ICP, MCP and SCP) and medial lemniscus (ML); (b) Projection tracts including interior capsule (IC), corona radiata (CR), corticospinal tract (CST), anterior, superior and posterior thalamic radiation (ATR, STR and PTR); (c) Limbic tracts including cingulum bundle in the cingulate cortex (CGC), cingulum bundle in the temporal cortex (CGH) and fornix (FX); (d) Commissural tracts including body, genu and splenium of corpus callosum (BCC, GCC and SCC); (e) Association tracts including fibers in external capsule (EC), inferior longitudinal fasciculus (ILF), inferior occipitofrontal fasciculus (IFO), superior longitudinal fasciculus (SLF) and uncinate fasciculus (UNC). Ganglionic eminence (GE), a transient fetal brain structure and well traced with DTI tractography, is also included in this tract group. (f) General timeline of white matter maturation across different tracts and tract groups. Dotted lines indicate that white matter tracts emerge at these ages, though to a relatively minor degree, and arrows indicate that overall white matter tracts are formed with continuous maturational processes such as myelination and axonal packing thereafter. This figure is generated with the data from Huang lab.

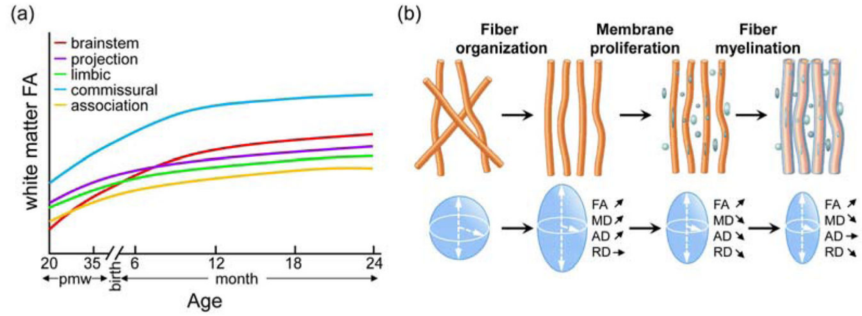

Figure 5.

Developmental trajectories of fractional anisotropy (FA) across white matter tracts from the mid-fetal stage to 2 years (a) and the biophysical model of white matter maturation (b). In (a), sketch plots show age-dependent white matter FA changes in five tract groups, namely, brainstem, projection, limbic, commissural and association tract groups from 20 postmenstrual weeks (pmw) to 2 years. Time axis in (a) is in postmenstrual weeks (pmw) before birth and postnatal months until 24 months. In (b), the biophysical model interprets the changes of DTI-derived metrics (i.e. FA, mean/axial/radial diffusivity: MD, AD and RD) (adapted with permission from Dubois et al., 2008 and Qiu et al., 2015).

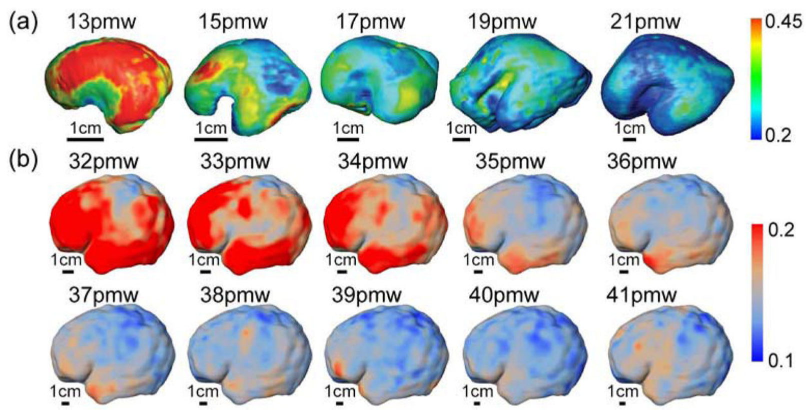

Figure 6.

Mapping of FA onto the cortical surface from 13 to 21 postmenstrual weeks (pmw) in the 2nd trimester (a) (adapted with permission from Huang et al., 2013) and the cortical surface from 32 to 41pmw in the 3rd trimester (b) (adapted with permission from Jeon et al., 2016).

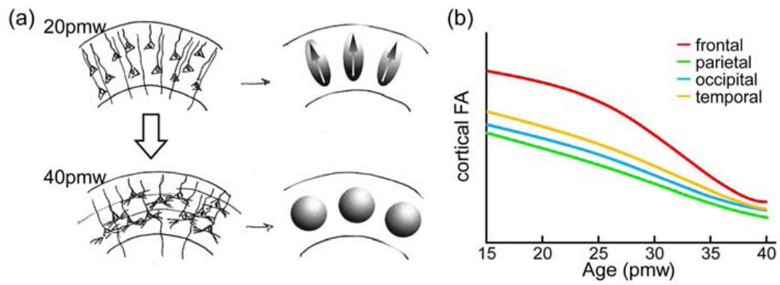

Figure 7.

Biophysical model of disruption of radial glial scaffold and associated fractional anisotropy (FA) decrease (a) and distinctive spatiotemporal FA decreases across different cortical regions from 15 to 40 postmenstrual weeks (pmw) (b). In (a), upper left panel demonstrates highly organized radial glial fibers, pyramidal neurons with prominent, radially oriented apical dendrites in a 20pmw brain cortical plate, resulting in the diffusion ellipsoids with high FA values and the primary axes oriented radially (upper right panel); lower left panel demonstrates prominent basal dendrites for the pyramidal cells and thalamocortical afferents disrupting the organized radial organization in a 40pmw brain cortical plate, resulting in the diffusion ellipsoids with low FA values (adapted with permission from McKinstry et al., 2002).