Please cite this article in press as: Dubois J et al. The early development of brain white matter: A review of imaging studies in fetuses, newborns and infants. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2013.12.044

Neuroscience xxx (2014) xxx–xxx

REVIEW

THE EARLY DEVELOPMENT OF BRAIN WHITE MATTER: A REVIEW OF IMAGING STUDIES IN FETUSES, NEWBORNS AND INFANTS

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Abstract—Studying how the healthy human brain develops is important to understand early pathological mechanisms and to assess the influence of fetal or perinatal events on later life. Brain development relies on complex and intermingled mechanisms especially during gestation and first post-natal months, with intense interactions between genetic, epigenetic and environmental factors. Although the baby's brain is organized early on, it is not a miniature adult brain: regional brain changes are asynchronous and protracted, i.e. sensory-motor regions develop early and quickly, whereas associative regions develop later and slowly over decades. Concurrently, the infant/child gradually achieves new performances, but how brain maturation relates to changes in behavior is poorly understood, requiring non-invasive *in vivo* imaging studies such as magnetic resonance imaging (MRI). Two main processes of early white matter development are reviewed: (1) establishment of connections between brain regions within functional networks, leading to adult-like organization during the last trimester of gestation, (2) maturation (myelination) of these connections during infancy to provide efficient transfers of information. Current knowledge from post-mortem descriptions and *in vivo* MRI studies is summed up, focusing on T1- and T2-weighted imaging, diffusion tensor imaging, and quantitative mapping of T1/T2 relaxation times, myelin water fraction and magnetization transfer ratio.

This article is part of a Special Issue entitled: The CNS White Matter.

Key words: brain development, white matter bundles, myelination, magnetic resonance imaging, diffusion tensor imaging, fetus and infant.

Contents

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Abbreviations: AF, arcuate fasciculus; ALIC, anterior limb of the internal capsule; CC, corpus callosum; CG, cingulum; CI, linear diffusion anisotropy; CNS, central nervous system; Cp, planar diffusion anisotropy; CS, centrum semiovale; CST, cortico-spinal tract; DEHSI, diffuse excessive high signal intensity; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; EC, external capsule; FA, fractional anisotropy; GA, gestational age; GM, gray matter; HARDI, high-angular resolution diffusion imaging; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; MRI, magnetic resonance imaging; MTR, magnetization transfer ratio; MWF, myelin water fraction; OR, optic radiations; PD, proton density; PLIC, posterior limb of the internal capsule; PTA, post-term age: post-natal age corrected for gestational age at birth considering a term age of 40 weeks; PVWM, peri-ventricular white matter; R1, relaxation rate associated with T1 relaxation time (R1 = 1/T1); R2, relaxation rate associated with T2 relaxation time (R2 = 1/T2); SNR, signal-to-noise ratio; STT, spino-thalamic tract; TBSS, tract-based spatial statistics; TE, echo time; TI, inversion time; TR, repetition time; T1, longitudinal relaxation time; T1w, T1-weighted; T2, transverse relaxation time; T2w, T2-weighted; UF, uncinate fasciculus; VLBW, very low birth weight; WM, white matter; 2D, 2 dimensions; 3D, 3 dimensions; $\lambda_{//}$, longitudinal diffusivity; $\lambda_{\perp}$, transverse diffusivity.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.12.044

INTRODUCTION

Brain development relies on several complex and intermingled mechanisms, such as the maturation and functional specialization of gray matter (GM) regions (cerebral cortex and central gray nuclei) and the establishment and myelination of white matter (WM) connections between the different neural regions. Typical development is the global consequence of interactions between genetic programming, epigenetic and environmental factors (e.g. external stimulations, maternal, nutritional or medical factors). Cerebral changes are particularly intense during the last weeks of gestation and the first post-natal months, as indirectly highlighted by the non-linear increase of the cranial perimeter (by about 14 cm during the two first post-natal years, followed by only 7 cm until adulthood). Although the baby's brain is organized early on into functional networks, it is not an adult brain in miniature: growth and maturation are asynchronous, some regions, like the sensory ones, develop early on and quickly, whereas associative regions, like frontal ones, develop later on and slowly until the end of adolescence (Paus et al., 2001).

Concurrently with this anatomical evolution of the brain, the infant gradually achieves new psycho-motor and cognitive skills, but how brain maturation explains the often abrupt changes of behavior observed during development is poorly understood. Before the development of non-invasive brain imaging methods, our knowledge on human brain development was relying on (fortunately) rare post-mortem investigations, which are intrinsically limited by the lack of anatomo-functional correlations and by the uncertainty on brain normality. Using myelin staining, most of these studies described whether myelin is present or not in a given WM region at a given age: this information is however not bundle-specific and thus might be misleading at bundles crossings. Advanced post-mortem dissection techniques now enable to follow the trajectory of long-distance bundles (Martino et al., 2010; Maldonado et al., 2013). But absolute measurements of myelin amount are still missing, which prevents the quantitative comparison across WM regions.

Another approach to understand brain development is to study animals, but if such studies enable to test particular hypotheses, they remain largely inadequate because of the specificity of human cognitive functioning and brain development. Mammals are generally classified according to their developmental stage at birth, belonging either to species with early development or to species with immature development. Humans have a special position since brain responses are already observed *in utero* (Draganova et al., 2007), while some high-level functions have a protracted development over two decades. For instance, the fiber myelination in the somatosensory, motor, frontopolar and visual neocortices is delayed in humans compared with chimpanzees, with slower myelination during childhood extending beyond late adolescence (Miller et al., 2012).

The recent development of non-invasive techniques (magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG)) has further enabled to relate maturation of cerebral structures to infants' neurodevelopment and behavior. In particular, several MRI techniques available on clinical scanners (section 'Structural MRI techniques and developmental specificities') enable to investigate and follow longitudinally the brain development and plasticity of healthy and at-risk children (Barkovich, 2000; Paus et al., 2001; Neil et al., 2002; Prayer and Prayer, 2003; Huppi and Dubois, 2006; Yoshida et al., 2013). But when these imaging techniques are applied to babies, many difficulties arise and require adapting data acquisition and post-processing to different developmental periods (fetus, preterm or at-term newborn, infant, toddler, etc.).

With these constraints in mind, we here review the main insights revealed by recent MRI studies on the early development of WM, which is a complex and long-lasting process that plays a crucial role during the human motor and cognitive development (section 'The basic concepts of white matter development'). Two main stages can be delineated: (1) the establishment of long and short

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connections between brain regions during the last trimester of human gestation, leading to an early adult-like organization of neural networks, (2) the maturation of these fibers during infancy and toddlerhood to provide an efficient transfer of information between functional regions. These two processes are consecutively described in the healthy brain by summarizing current knowledge obtained from post-mortem and *in vivo* imaging studies (sections 'Imaging the early organization of white matter' and 'Imaging the maturation of white matter'). Finally, the functional significance of early structural biomarkers of the developing WM is discussed based on studies with behavioral and neurophysiologic evaluations of infants, with a specific focus on preterms without overt brain lesions (section 'Functional correlates of MRI biomarkers of WM maturation').

THE BASIC CONCEPTS OF WM DEVELOPMENT

The early organization of WM

WM organization in adults. WM contains a large amount of glial cells (astrocytes, oligodendrocytes and microglia, which account for around 50% of the total brain volume and nearly 90% of brain cells), but it is mainly studied as the brain compartment of crossing paths that connect different functional regions. Long-distance fibers, generally gathered into bundles, can be classified according to their connection patterns. Commissural fibers connect the two cerebral hemispheres, mostly between homotopic regions (e.g. the corpus callosum (CC)). Projection fibers are bi-directional fibers between the thalamus and the cortex, between the cortex and the brainstem and spinal cord (e.g. the cortico-spinal tract (CST), the optic radiations (OR)). Associative fibers regroup cortico-cortical fibers between intra-hemispheric regions (e.g. the arcuate fasciculus (AF)) and fibers of the limbic system (e.g. the fornix).

Growth of fiber connections during the last trimester of gestation. The progressive organization of WM connections has been established with post-mortem studies. Once the neuron has migrated to its final localization, it develops connections with other neurons at both ends: a dendritic tree within the GM, and the formation of an axon running through the WM. At the macroscopic level, the axons formation leads to the formation of long-distance bundles. This wiring occurs mostly during the second part of pregnancy, but its exact temporal progression is still poorly described in humans. It includes processes of neuronal and synaptic overproduction, followed by cellular apoptosis, axonal retraction and synaptic pruning. All these processes of overproduction/elimination are essential to sustain the functional networks plasticity (Stiles and Jernigan, 2010). The early wave of migrating neurons remains in the subplate (underneath the future cortex) and is crucial to establish a first rough blueprint of the cerebral organization, both for the cortex and the WM. On the one hand, they relay thalamo-cortical projections in the late fetal and preterm brain, amplifying sensory signals (Kanold and Luhmann, 2010; Kostovic and Judas, 2010), and on the other hand they send pioneering axons toward the internal capsule to guide axons from the later migrating neurons (McConnell et al., 1989). They also guide inter-hemispheric connections through the CC between 25 and 32 weeks of gestational age (w GA) (deAzevedo et al., 1997).

To reach their target structure, axons grow and are guided by their extremity growth cones, which are attracted or repulsed by positive or negative signals (e.g. contact signals, chemical signals, neuro-transmitters, growth factors). They follow ''pioneering'' axons (process of ''fasciculation''). The initial connection production stage is followed by a pruning stage that aims at suppressing redundant or aberrant circuits and is dramatically sensitive to the environment (Huttenlocher and Bonnier, 1991). This process may be influenced by several factors: e.g. neuron survival, competition for trophic factors, electrical activity of axons, afferent inputs. In particular, in the CC, pruning is a major morphogenetic process between the end of gestation and the first and second postnatal months (Innocenti and Price, 2005). In the rhesus monkey, up to 70% of callosal axons are eliminated in the four first post-natal months (LaMantia and Rakic, 1990). In humans, the number of axons in the CC may be close to a maximum in the newborn brain (with no new axons being formed to cross the midline), and the process of axonal pruning is supposed to occur after birth (Kostovic and Jovanov-Milosevic, 2006).

The maturation of WM

Concurrently and subsequently to the organization of WM networks, fiber connections become progressively mature and functionally efficient through the myelination process that favors the conduction of the nervous impulse (Baumann and Pham-Dinh, 2001; Van der Knaap and Valk, 1995a,b).

Myelin description. In the adult brain, the WM white color is due to the high myelin content (40–50% of dry weight). The myelin sheaths enwrapped around axons are complex bilamellar membranes constituted by lipoproteins (myelin basic proteins (MBP), proteo-lipid proteins (PLP), myelin associated glycoproteins (MAG), 2′,3′-Cyclic nucleotide-3′-phosphohydrolase (CNP), etc.) and lipids (cholesterol, phospholipids, glycolipids, galactocerebrosides, etc.). This ''roll-cake like'' structure is formed by the membrane prolongations of oligodendrocytes in the central nervous system (CNS) (Barkovich, 2000).

The myelin role is to allow a fast conduction of the nerve impulse. Indeed, the action potential propagates along the axon by electrical depolarization of the nervous membrane, continuously when no myelin sheath enwraps the axon, or via saltatory conduction from a Ranvier node to the next (Ranvier nodes are the fiber places between myelin sheath segments). The conduction speed depends on the distance between nodes, on axonal diameter and on the myelin sheath

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thickness: from 2 m s^{-1} in unmyelinated CNS fibers to 120 m s^{-1} in myelinated fibers of the peripheral nervous system.

Myelination of WM fibers. Myelination (i.e. myelin formation around axons) is the last stage of WM development, that begins after the process of axonal overproduction-pruning and follows premyelinating stages including the formation and maturation of oligodendrocytes (Thomas et al., 2000). This process includes several steps (Hardy and Friedrich, 1996; Butt and Berry, 2000; Prayer and Prayer, 2003). Oligodendrocyte precursors proliferate, migrate and form ''initiator'' processes, which align along axons (predominant radial orientation) and identify targeting axons (Volpe, 2008). Spiral ensheathment around the axon starts with an extension of such a process that elongates and wraps around the axon. Afterward, the myelin sheath becomes more compact, through an increasing number of spiral turns that is determined by the axonal diameter (Baumann and Pham-Dinh, 2001).

A single oligodendrocyte myelinates several axons (even of different diameters), suggesting that each axon participates to the regulation of its myelination (Friede, 1972). In the human brain, four stages of oligodendrocyte maturation have been described: early and late progenitor cells, immature and mature oligodendrocytes. The immature oligodendrocytes (which are multipolar cells rich in a lipid called galactocerebroside) account for 30–40% of the entire oligodendroglia population in the preterm period (~28–37 w GA).

The ''pre-myelinating'' state generally refers to the initial period when pre-oligodendroglial cells increase and settle along the axons (Baumann and Pham-Dinh, 2001), and when the cholesterol and glycolipids concentration starts to increase (Poduslo and Jang, 1984; Barkovich et al., 1988). The following ''true'' myelination process corresponds to the ensheathment of oligodendroglial processes around the axons, and to the chemical maturation of the myelin sheath with rising amount of macromolecules (Poduslo and Jang, 1984; Barkovich et al., 1988). At the microscopic level, the myelination induces major changes in water molecules content and compartmentalization (Matsumae et al., 2001) and in protein and lipid contents (Barkovich et al., 1988; Kucharczyk et al., 1994). Notably, a strong correlation exists between myelination and the concentration of galactocerebroside in immature and mature oligodendrocytes (Matthieu, 1993).

Regional asynchrony of WM myelination. Myelination occurs in the human brain from the second part of pregnancy to the end of adolescence. A peak is observed during the first post-natal year. Its progression varies across cerebral regions: it follows a caudo-rostral gradient and progresses from the center to the periphery. Post-mortem studies have detailed this sequence (Flechsig, 1920; Yakovlev, 1962; Yakovlev and Lecours, 1967; Gilles et al., 1983; Brody et al., 1987; Kinney et al., 1988), using a visual ordering from stages 0 to 4 according to staining with hematoxylin and eosin-luxol fast (''mature myelin'' refers to stages 3 and 4). Some myelin is observed microscopically from 20 w GA on at the level of the bulb and pons, which are myelinated at birth. Mature myelin is detected from 37 to 40 w GA in the cerebellum and internal capsule. Between the first and third post-natal months, the posterior limb of the internal capsule (PLIC), the OR and the CC splenium become myelinated. Mature myelin can be found from the 6th month in the anterior limb of the internal capsule (ALIC) and in the CC genu, from the 15th month in the occipital pole, and from the 23rd month in the frontal and temporal lobes (for review (Baumann and Pham-Dinh, 2001).

From these post-mortem studies, several rules can be outlined on the myelination progression in the brain (Kinney et al., 1988): it occurs earlier and faster (1) in proximal pathways than in distal ones; (2) in sensory pathways (somatosensory, vision, audition) than in motor ones; (3) in projection fibers than in associative ones; (4) in central regions than in polar ones; (5) in the occipital pole than in the posterior parietal WM and in the temporal and frontal poles. These global schemes cannot be dissociated from one another, and suggest eight sub-groups of maturation, depending on the presence/absence of myelin at birth (sub-groups A/B) and the time periods at which mature myelin is observed (sub-groups 1–4) (Kinney et al., 1988). For example, the middle cerebellar peduncles, the optic tract and chiasm, the PLIC, the CST in the midbrain and pons and the central corona radiata belong to sub-group A1; OR (proximal and mid-distal), auditory radiations (proximal), the CC body and splenium belong to sub-group B1; cingulum (CG), external capsule (EC), the ALIC, the CC rostrum and Heschl's gyrus belong to sub-group B2; fornix and extreme capsule belong to sub-group B4. This asynchrony in the maturation sequence is supposed to depend on the hierarchy of connections between cortical areas (Guillery, 2005): the early maturation of receptive sensory areas (responsible for low-level processing) would enable a stabilization of the information used by integrative areas (involved in high-level processing) which develop later on.

Functional correlates of WM myelination. Beside glial factors, neuronal maturation and electrical activity might control myelination induction (Kinney et al., 1988). Blocking this activity *in vitro* inhibits myelination (Demerens et al., 1996), and the proliferation of oligodendrocytes precursors is influenced by neighboring axonal activity (Barres and Raff, 1993). Electrical activity in the mouse optic nerve influences the triggering of myelination over a short time period (Demerens et al., 1996). This nerve myelination is further delayed in mice kept in a dark environment after birth (Gyllensten and Malmfors, 1963) and accelerated in rabbits whose eyelids have been opened prematurely (Tauber et al., 1980). Astrocytes may act as an intermediary between myelination and electrical impulse activity, through the mediation of a cytokine leukemia inhibitory factor (Ishibashi et al., 2006). Nowadays, the

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inhibitory role of oligodendrocytes and myelin on neuritic growth is also considered, which may partly explain the weak plasticity of the adult brain (Ng et al., 1996).

Since myelination leads to a spectacular increase in the conduction speed of the nerve impulse (Baumann and Pham-Dinh, 2001), it is assumed to improve the functional efficiency of brain networks (van der Knaap et al., 1991). Myelination of the midbrain and spinal cord is actually coupled with behavioral improvement (Langworthy, 1928a,b), but fiber myelination and functional maturation are uncorrelated in different cerebral systems. For instance, the myelination of the CST occurs before birth in several regions (midbrain, internal capsule, central corona radiata) while the newborn motor capacities are weak. On the other hand, the acoustic radiations have an extended myelination until 3 years of age while the infant auditory system is efficient early on.

Such discrepancy may rely on the fact that extending myelination may be necessary in a second step to compensate for brain growth and maintain similar latencies between brain regions across ages (Salami et al., 2003). In the visual system for example, the latency of the first positive wave of response to a stimulus (P1) reaches the adult latency (~100 ms) at around four post-natal months, whereas the distance between the retina and the calcarine fissures still increases by around 6 cm until adulthood. Whereas the transfer of visual information may be efficient early on in 4-month-old infants, an extending myelination may enable to further increase the conduction speed by around 0.6 m s^{-1} in relation with brain growth.

STRUCTURAL MRI TECHNIQUES AND DEVELOPMENTAL SPECIFICITIES

Several complementary MRI techniques can be used to image brain development in healthy infants. Since signal comes from the hydrogen nuclei (the ''protons'') of water molecules, cerebral tissues with different water concentrations and environments demonstrate on MR images different contrasts that change with brain maturation.

Conventional MR imaging and relaxometry

Physical basics. ''Conventional'' MRI generally refers to images whose signal is weighted (noted ''w'') by proton density (PD) or by relaxation times, which characterize how fast the water magnetization returns to equilibrium after the perturbation induced by electromagnetic waves. 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). In the developing brain, T1 weighting is generally obtained with short TR and short TE, or using inversion recovery sequences with long inversion times (TI), while T2 weighting is obtained with long repetition times (TR) and long echo times (TE). Since relaxation times depend on tissue characteristics, T1w and T2w images demonstrate high contrast between cerebral tissues in the adult brain (Fig. 1).

Developmental specificities of T1w and T2w contrasts. Because of brain tissues immaturity and high water content, T1w and T2w contrasts are very different in the infant brain from what is described in the adult brain, and contrasts evolve with brain maturation (Fig. 1). Considering the brain as a whole, successive maturational stages are described (Paus et al., 2001): (1) the infantile pattern (0–6 months), showing a reversal of the normal adult contrasts (T1w: lower WM intensity than GM intensity; T2w: higher WM intensity than GM intensity); (2) the iso-intense pattern (8–12 months), characterized by a poor contrast between GM and WM; and (3) the early-adult pattern (> 12 months) (T1w: higher WM intensity than GM intensity; T2w: lower WM intensity than GM intensity). Actually, the specific time-course of these patterns depends on brain regions because of maturation asynchrony (see Section 'Imaging the maturation of white matter').

As a consequence, the delineation between the GM and WM is often not obvious on infant images, contrarily to the clear border observed on adult T1w images. T1 weighting is mostly used during the preterm and perinatal periods, but the contrast becomes poorer with age until it recovers during the second post-natal year. T2 weighting transitorily enables a better contrast between term and 4–6 months post-term (Leroy et al., 2011b). The second post-natal semester is actually the most difficult period to image, with a weak delineation of the GM/WM border.

To identify myelinated WM regions from unmyelinated regions, T1w contrast is generally preferred during the first 6–8 post-natal months, and T2w contrast between 6 and 14 months because changes in WM contrasts are observed on T1w images before T2w images (van der Knaap and Valk, 1990; Barkovich et al., 1992).

Mapping T1 and T2 relaxation times during WM maturation. The changes observed on T1w and T2w contrasts can be used to understand maturation processes, but T1w and T2w signals cannot be directly compared across individuals because of the variability between exams related to technical tunings. To provide such inter-individual comparisons, either signals may be normalized for each subject in reference to a given tissue (e.g. the cerebro-spinal fluid) (Leroy et al., 2011a), or T1 and T2 relaxation times may be quantitatively measured (Fig. 1) by recording signals from dedicated MRI acquisitions with different sequence parameters (e.g. different inversion times TI to compute T1, different echo times TE to compute T2).

In the developing brain, T1 and T2 decrease more strongly in WM than in GM because of myelination processes (Fig. 4a) (Barkovich, 2000; Prayer and Prayer, 2003). At least two distinct pools of water molecules are supposed to contribute to MR signal in the WM: water located within the myelin sheath (with relatively short T1 and T2 relaxation times) and intra-

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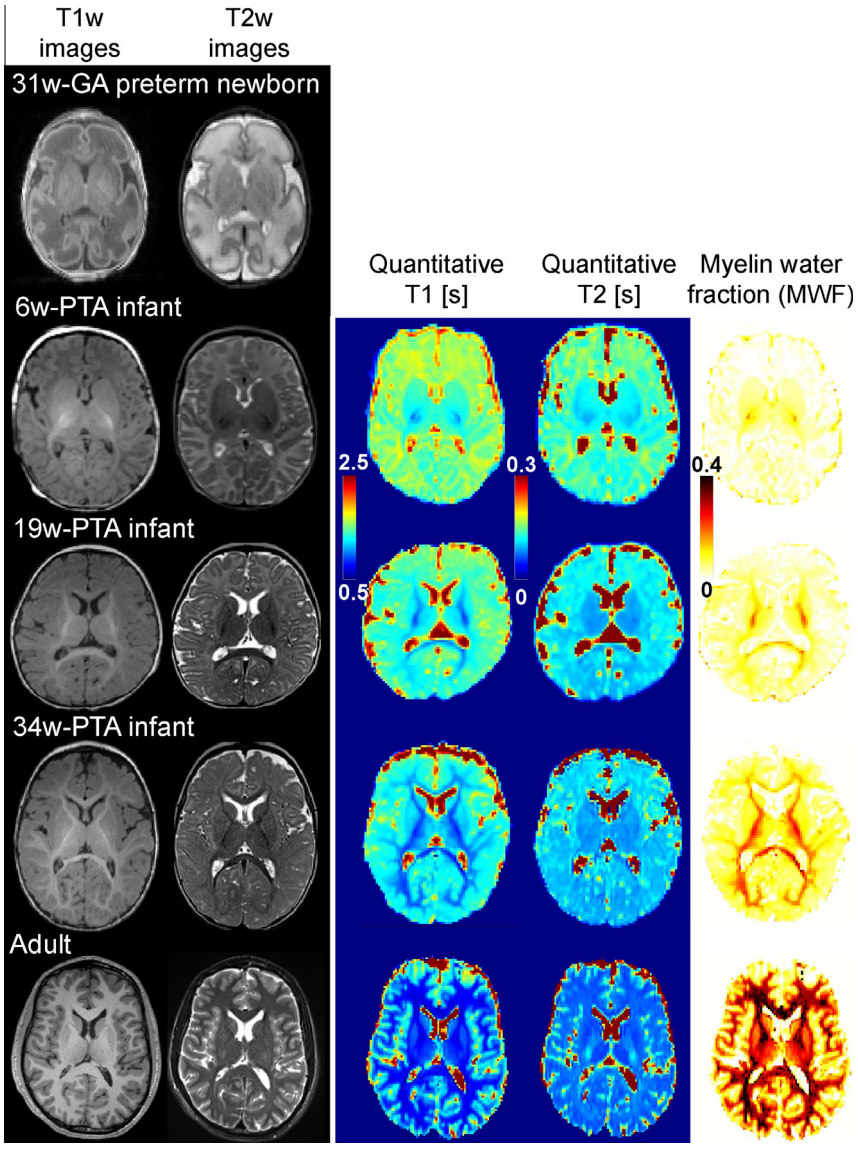

Fig. 1. Anatomical images of the developing brain. T1w and T2w images are presented for subjects of different ages: a preterm newborn of 31 weeks of gestational age (GA), term-born infants at a post-term age (PTA) of 6 weeks, 19 weeks and 34 weeks (PTA: post-natal age corrected for gestational age at birth, considering a term age of 40 weeks), and a young adult. Note the contrast inversion between GM and WM during the first post-natal year. For the infants and adults, quantitative maps of T1 and T2 relaxation times (in seconds), and of myelin water fraction (MWF) are also presented. Within the white matter, T1 and T2 decrease with age, while MWF increases. Preterm images were acquired on a 1.5-T MRI system, the other images on a 3-T system.

axonal, intra-cellular and interstitial water (i.e. water outside of the myelin sheath, with longer T1 and T2). Both T1 and T2 decreases parallel the decrease in water concentration, nevertheless their time courses are different, and two distinct mechanisms can be distinguished: the change in water molecules compartmentalization (Matsumae et al., 2001), and the increase of protein and lipid contents (Barkovich et al., 1988; Kucharczyk et al., 1994). T1 shortening starts already during the ''pre-myelinating'' state, while T2 shortening correlates temporally with the chemical maturation of the myelin sheath (Poduslo and Jang, 1984; Barkovich et al., 1988; Baumann and Pham-Dinh, 2001) (Fig. 4c).

Diffusion imaging

Physical basics and post-processing strategies. Another recent approach to assess WM maturation is diffusion-weighted imaging (DWI) which measures the natural motion of water molecules. The diffusion in cerebral tissues is not ''free'' (Le Bihan, 2003). Microscopic displacements may be restricted within multiple physical compartments, or hindered by cell and organelle membranes: this results in tortuous pathways around these obstacles. Imaging diffusion at the macroscopic scale thus enables to explore the tissue microstructure non-invasively (Le Bihan et al.,

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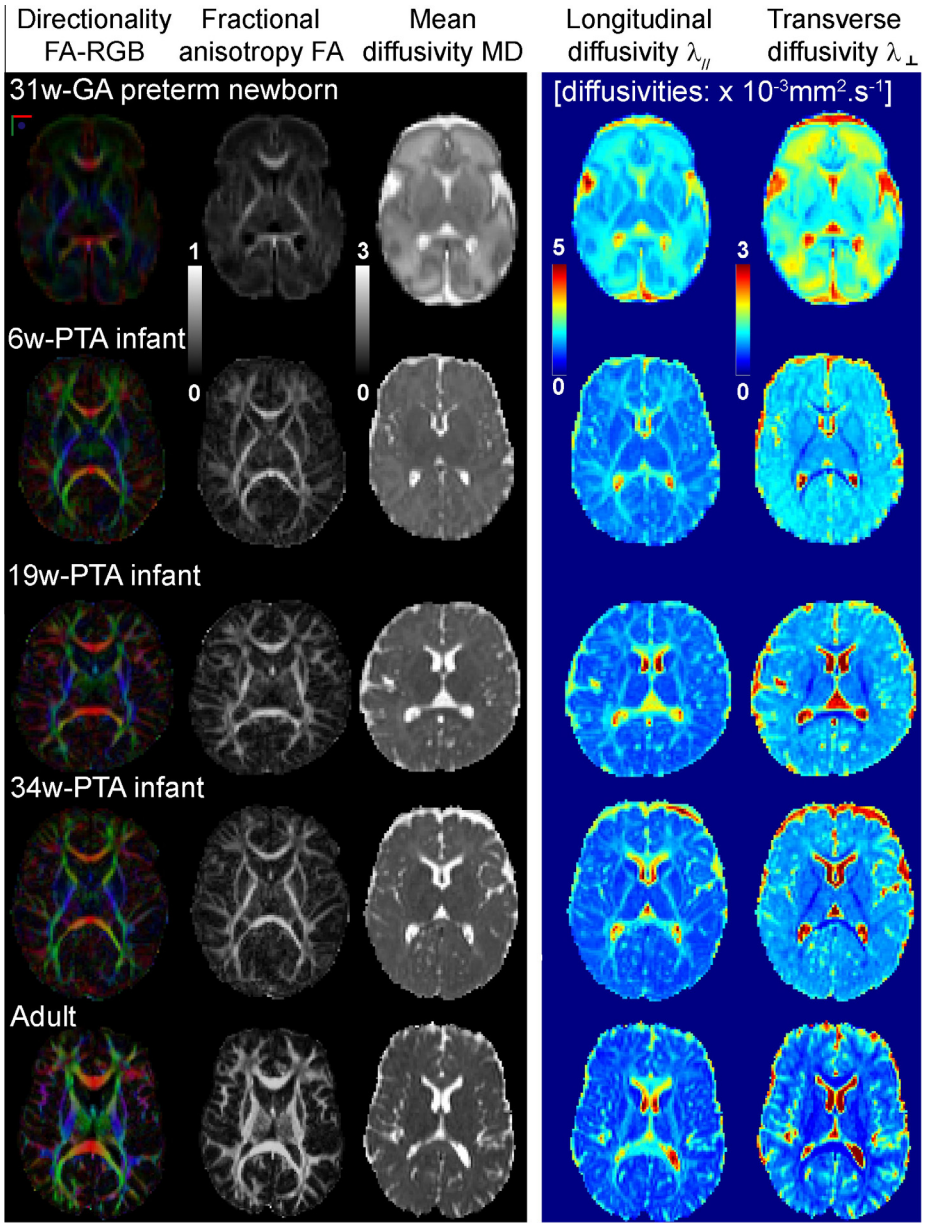

Fig. 2. DTI images of the developing brain. DTI maps are presented for the same subjects as in Fig. 1. Color-coded directionality maps (FA-RGB, where color informs on the direction of the tensor main eigenvector) nicely highlight early WM organization, and immature bundles already demonstrate high fractional anisotropy (FA). The different DTI parameters provide different contrasts between brain tissues. Within WM, FA increases with age, while mean (MD), longitudinal ($\lambda_{//}$) and transverse ($\lambda_{\perp}$) diffusivities (in 10^{-3} mm^2 s^{-1}) decrease.

2001). To take into account the spatial heterogeneity of the diffusion process, the diffusion information is generally encoded in different spatial directions, and the diffusion tensor (DT) formalism is used with the assumption that a single fiber orientation is present in each voxel of the image and that the diffusion process can be represented by an ellipsoid that encodes the tensor eigenvectors and eigenvalues. The diffusion tensor imaging (DTI) technique provides maps of quantitative and complementary parameters (Fig. 2): diffusion anisotropy (e.g. fractional anisotropy (FA)) (Beaulieu, 2002), mean diffusivity (MD = one third of the tensor trace), longitudinal diffusivity ($\lambda_{//}$ = diffusivity along the main tensor axis) and transverse diffusivity ($\lambda_{\perp}$ = diffusivity perpendicular to the main axis).

The trajectory of WM fibers can be further reconstructed virtually in 3 dimensions (3D) using tractography algorithms that follow the direction of the main DT eigenvector from a voxel to a neighboring voxel (Le Bihan and Johansen-Berg, 2012) (Fig. 3). The dissection of major WM bundles is then based either on the individual definition of regions crossed by the fibers, or through automatic classifications recently proposed for the adult brain, such as clustering (Guevara et al., 2011, 2012) and probabilistic methods (Yendiki et al., 2011). Recently, some alternatives to the tensor model have been proposed, such as Q-ball imaging, diffusion spectrum imaging (DSI) and high-angular resolution diffusion imaging (HARDI). These techniques enable to resolve multiple fiber orientations within a voxel, but

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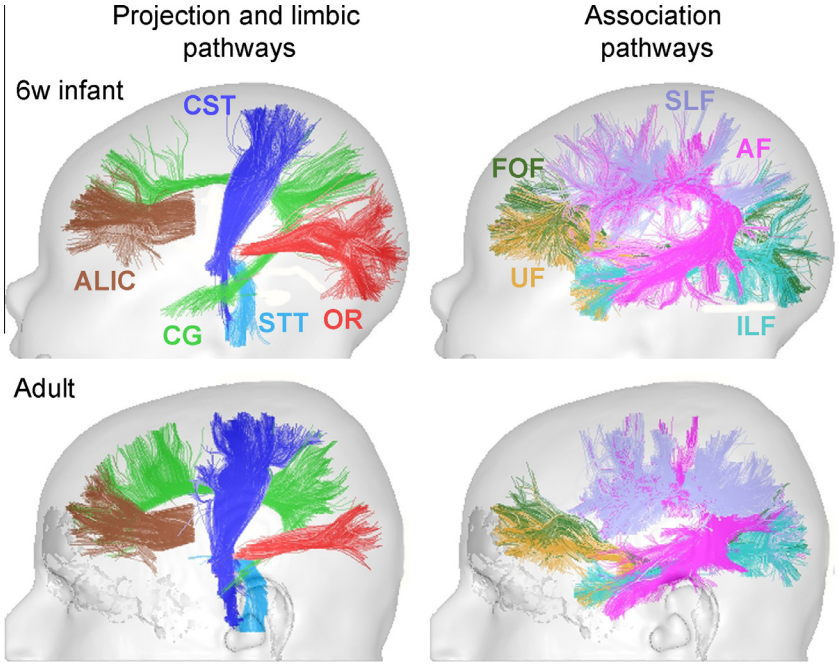

Fig. 3. Tractography of the developing WM bundles. Examples of major WM bundles, reconstructed with regularized tractography using Connectomist software (Duclap et al., 2012), are presented for the 6-week-old infant and the adult of Figs. 1 and 2: projection and limbic pathways (left column), and associative pathways (right column). Note the similar organization between the infant and adult brains. Abbreviations: AF, arcuate fasciculus; ALIC, anterior limb of the internal capsule; CG, cingulum; CST, cortico-spinal tract; FOF, fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; OR, optic radiations; SLF, superior longitudinal fasciculus; STT, spino-thalamic tract; UF, uncinate fasciculus.

they require long acquisition times hardly achievable *in vivo* in healthy unsedated infants.

DTI correlates of WM maturation. DTI parameters are well suited to reveal information that is not apparent on T1w and T2w images during brain development (Fig. 2) (Neil et al., 2002; Huppi and Dubois, 2006). It is generally assumed that diffusivities decrease with maturation, while anisotropy increases in the developing WM (Neil et al., 1998; Huppi et al., 1998a) and decreases in the cortex during the preterm period (McKinstry et al., 2002; Ball et al., 2013). Transverse diffusivity decreases more in WM than in GM (Mukherjee et al., 2002), leading to a reversed contrast between newborns and adults on transverse diffusivity maps (Fig. 2). In WM bundles, changes are more intense for transverse than for longitudinal diffusivity (Mukherjee et al., 2002; Dubois et al., 2008b; Geng et al., 2012), with even no change in longitudinal diffusivity detected after 1 year of age (Gao et al., 2009). These parameter dynamics in WM bundles are consistent with the assumption of a cylindrically symmetric decrease in diffusion due to myelination process (Mukherjee et al., 2002).

Fifteen years ago, it had been suggested that the age-related decrease in mean diffusivity in both GM and WM would reflect the overall decrease in brain water content, while the increase in anisotropy in the WM would rather rely on its microstructure (e.g. packing and myelination) (Neil et al., 1998). Nowadays the current hypotheses on the relationships between these parameters and the maturational mechanisms are recognized as more complex in the WM (Fig. 4b).

Even in the absence of myelin, the tight organization of WM fibers inside a bundle lead to intrinsic anisotropy related to high longitudinal diffusivity contrasting with low transverse diffusivity (Beaulieu, 2002). Studies in rat pups have shown that the first evidence of anisotropy precedes initial myelin (Wimberger et al., 1995), and that this early anisotropy may be related to sodium-channel activity (Prayer et al., 2001).

During the first stage of myelination (“pre-myelination”), when glial cell bodies and membranes proliferate, both a decrease in brain water content and an increase in membrane density are observed, which imply decreases in mean, longitudinal and transverse diffusivities. Whereas this mechanism had initially been assumed spatially isotropic (Dubois et al., 2008b), recent evidence rather suggests that the initial extension of oligodendroglial processes is anisotropic in favor of the axonal direction (Zanin et al., 2011; Nossin-Manor et al., 2012). This anisotropy increase has been related to the maturation of the compound action potential and the development of immature oligodendrocytes in the rabbit developing WM (Drobyshevsky et al., 2005).

The following “true” myelination process (with the ensheathment of oligodendroglial processes around the axons) is further accompanied by a decrease in both membranes permeability and extracellular distance between membranes, implying an increase in anisotropy, a decrease in transverse diffusivity, but no change in longitudinal diffusivity. At crossing fibers places, the situation may appear puzzling when crossing

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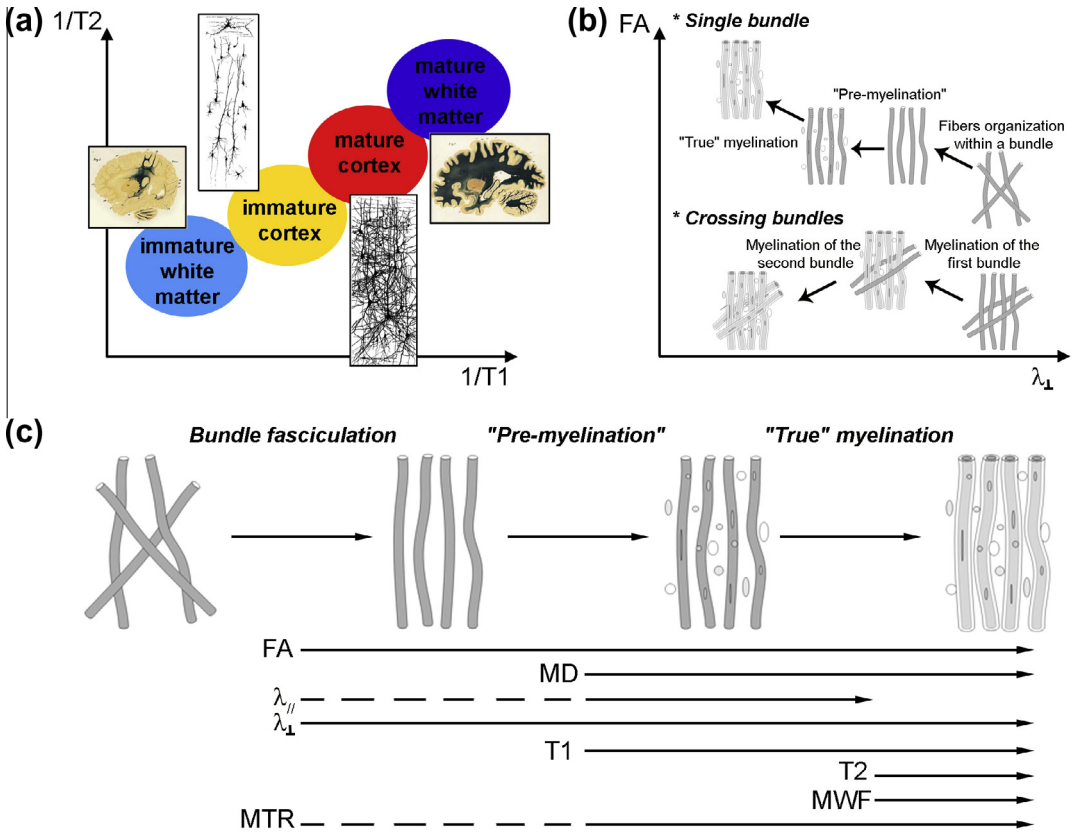

Fig. 4. Illustrations of maturation-related changes in MRI parameters. (a) The decreases in T1 and T2 relaxation times (increases in relaxation rates R1 = 1/T1 and R2 = 1/T2) are more intense in the developing WM than in the developing GM, which leads to contrast inversions on T1w and T2w images during the first post-natal year (Fig. 1). Post-mortem images of WM myelin staining were reproduced from (Flechsig, 1920). (b) During the myelination of WM fibers, two successive processes occur: ''pre-myelination'' with oligodendrocytes and membranes proliferation, and ''true'' myelination. Both lead to changes in DTI parameters: e.g. increase in fractional anisotropy (FA) and decrease in transverse diffusivity ($\lambda_\perp$) in the case of a single maturing bundle (upper row) (Dubois et al., 2008b). But changes are more complex in other configurations, for instance when crossing bundles are maturing at different times (lower row). (c) In summary, quantitative parameters are expected to change at different times depending on the major steps of WM maturation (bundles fasciculation, ''pre-myelination'', ''true'' myelination), suggesting strong parameters complementarity. In a single-bundle configuration, anisotropy (FA) increases, mean (MD) and transverse ($\lambda_\perp$) diffusivities decrease, while longitudinal diffusivity first increases (dashed line) then decreases (Dubois et al., 2008b). T1 and T2 relaxation times decrease, whereas myelin water fraction (MWF) and magnetization transfer ratio (MTR) increase (the dashed line corresponds to MTR observations in preterm corpus callosum (Nossin-Manor et al., 2012)).

bundles follow different maturational calendars: when the first bundle gets myelinated, anisotropy first increases, but it subsequently decreases when the second crossing bundle gets mature (the reverse argument has been detailed for neurodegenerative disorders (Douaud et al., 2011)); at the same time, diffusivities are decreasing (Fig. 4b).

Therefore anisotropy and longitudinal diffusivity are rather good markers of tissue macrostructure and organization, finely characterizing compactness, crossing fibers, etc. but the interpretation of their changes may remain difficult during WM maturation. On the contrary, transverse diffusivity consistently decreases with all maturational processes (Fig. 4c).

Recently, other geometrical diffusion measures (linear and planar diffusion anisotropies Cl and Cp) have been considered to model more accurately different WM microstructures in comparison with the classical cylindrical shape of a fiber bundle (Chen et al., 2011). During maturation, these parameters may be sensitive to changing compactness since after birth Cl growth velocities are highest in central WM while Cp growth velocities are highest in peripheral WM.

Finally, let us keep in mind that DTI parameters vary across bundles in the adult brain, in relation with their macroscopic geometry and compactness. Highlighting maturational effects in the developing brain thus requires either considering the developmental trajectories toward adulthood to evaluate the asymptotes of maturation, or normalizing infant measurements by the adult references (Dubois et al., 2008a).

Myelin-related imaging parameters

Other quantitative parameters relying on the myelin amount have been proposed to evaluate the maturation of WM.

Magnetization transfer ratio. The ''magnetization transfer ratio'' (MTR) informs about the ratio between free water and water with restricted motion, bound to

macromolecules such as proteins and lipids (McGowan, 1999). Thus it is thought to reflect the myelin amount and increase during WM maturation (Kucharczyk et al., 1994). Nevertheless, during the preterm period (26–34 w GA), MTR values have been found higher in the genu and splenium of the CC than in the PLIC and the periventricular white matter (PVWM) (Nossin-Manor et al., 2012). Since at this stage callosal fibers are highly organized, closely packed, but non-myelinated fibers, this technique appears to be sensitive not only to myelin-associated macromolecules, but also to the macromolecular density of axonal cytoskeleton components such as microtubules and neurofilaments (Nossin-Manor et al., 2012) (Fig. 4c).

Myelin water fraction. As for approaches based on ''multi-component relaxation'' (MCR) analyses, different pools of water molecules are modeled in each voxel (Spader et al., 2013). These pools can be distinguished from measured MR signals, on the basis of different relaxometry properties (T1 and/or T2) and of specific exchange relationships (Menon et al., 1991; Whittall et al., 1997; Beaulieu et al., 1998). Such decomposition is supposed to provide valuable information on the tissue microstructure. Whereas the exact number of pools to be modeled is still debated (Deoni et al., 2012b), a consistent pool of water related to myelin is always considered, and studies generally describe maps of ''myelin water fraction'' (MWF) (Fig. 1). This fraction drastically increases during WM maturation (Deoni et al., 2012a) (Fig. 4c). Contrarily to relaxation times, the definition of MWF is *a priori* independent from the magnetic field. But its computation is highly sensitive to both the acquisition protocol and the post-processing modeling, making direct comparisons across studies hardly achievable.

Practical considerations for imaging the developing brain

In vivo *imaging of the baby brain.* The pre- and post-term periods are radically different, not only in terms of brain organization (see next section) but also in terms of practical possibilities to obtain MR images. Because infants after term are generally healthy, ethical and practical issues are similar to older ages. On the contrary, the main difficulty in imaging the pre-term period is to obtain images of healthy (or at least not neurologically ill) brains. Imaging fetuses *in utero* is not commonly done without strong medical arguments. Similarly, preterm newborns are at high-risk of neurological lesions, and their physiological stage is very unstable making them difficult to move to MRI center without good reasons.

In all cases, imaging fetuses and infants is a challenge. Data are difficult to acquire first because of the techniques' sensitivity to motion. Without clinical indication, healthy babies cannot be sedated, then one cannot prevent a fetus to move within the womb, and quietness is difficult to obtain in infants during a long time. Thus, data acquisition should remain short, especially in preterms in whom it is difficult to maintain a stable thermal state inside the MR scanner. Acoustic noise should also remain reasonable, in order to avoid any acoustic trauma and discomfort, and to assure baby's sleep or quiet cooperation. Second, despite short acquisition time, image spatial resolution should be higher than in adults because cerebral structures are smaller. That is why the scarce images obtained at early ages (i.e. before 5 months of gestation) have been obtained in post-mortem fetuses with very long acquisition times.

Technical constraints of conventional imaging. The developing brain is changing every day, much more rapidly than the adult brain between 20 and 50 years of age, and T1w and T2w contrasts change with the brain tissues maturation. This contrast variability and the use of different MR sequences along the first post-natal year require dedicated post-processing tools for different developmental periods to segment unmyelinated and myelinated WM from other cerebral tissues (GM, cerebro-spinal fluid). However it may lead to misclassification of cerebral tissues (Matsuzawa et al., 2001; Choe et al., 2012), and the comparison across ages remains difficult.

Technical constraints of DTI. The signal-to-noise ratio (SNR) of DW images decreases with infants' age because both T2 relaxation times and diffusivities decline during the first post-natal months (Mukherjee et al., 2002). Actually the reliability of DTI estimation is influenced by SNR and by the number of diffusion directions. To a certain extent, acquiring more directions is equivalent to averaging (Dubois et al., 2006a). Adapting the number of diffusion directions according to the infants' age (with more numerous directions in older infants) is worth considering to make the data reproducible across subjects. Furthermore, DTI quantification is particularly sensitive to motion artifacts, and several strategies have been proposed to reduce or correct them during the acquisition (Dubois et al., 2006b) or in post-processing (Dubois et al., in revision).

IMAGING THE EARLY ORGANIZATION OF WM

Imaging the WM growth

Increase in WM volume. With all these difficulties in mind, we can try to appreciate the WM growth by estimating its volume from T1w and T2w images acquired before and after term (Fig. 5a). In normally developing fetuses *in utero*, the global volume of the intermediate zone and subplate (whose frontier remains difficult to delineate) increases from around 15 to 90 cm^3 between 21 w and 31 w GA, i.e. 15% per week (Scott et al., 2011). In premature neonates, the WM volume increases from around 50 cm^3 at 29 w GA to 170 cm^3 at 44 w GA, as reported in age-specific atlases (Kuklisova-Murgasova et al., 2011). Afterward, a longitudinal follow-up study in infants has demonstrated that WM volume increases from around 164 cm^3 at term

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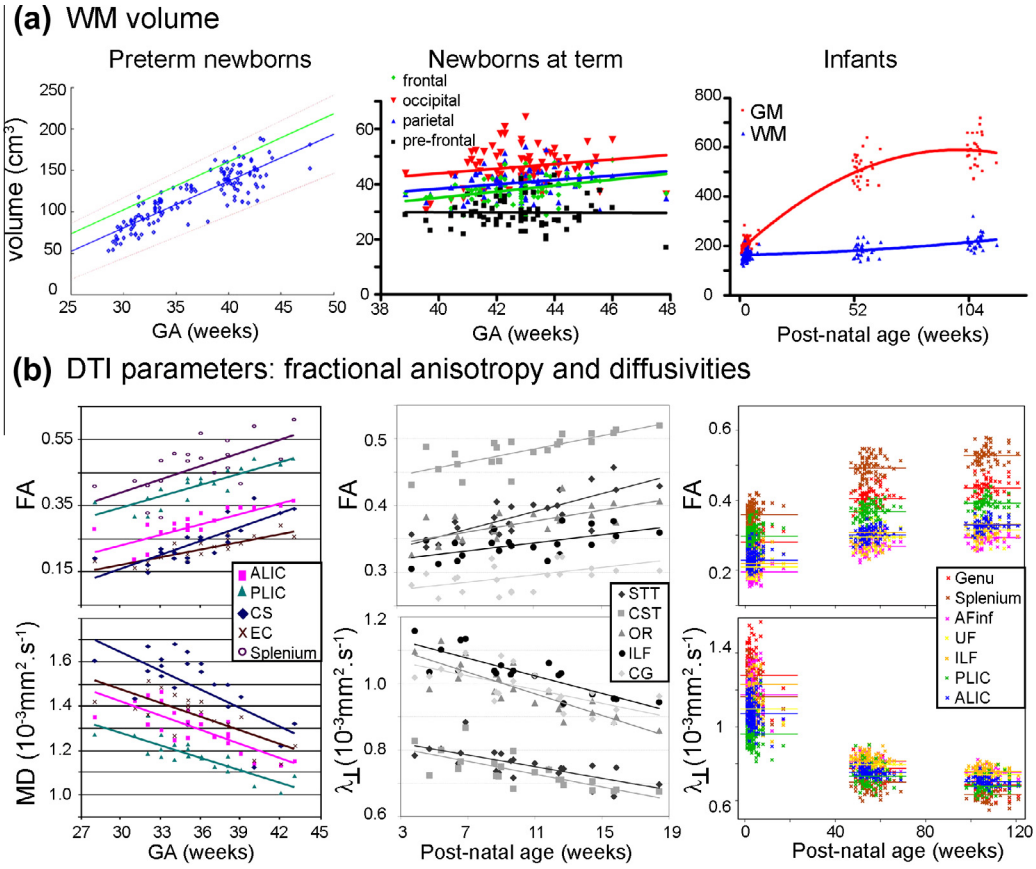

Fig. 5. Age-related changes in WM volume and DTI parameters. Age-related changes in WM volume (a) and in DTI parameters (b) are highlighted in different populations: preterm newborns (left column), at term-born newborns or infants (middle column) and during the first two post-natal years (right column). Note that WM volume increases more slowly than GM volume. Fractional anisotropy (FA) increases in major WM bundles, while mean (MD) and transverse ($\lambda_\perp$) diffusivities decrease. DTI parameters strongly differ among WM bundles. Figures were adapted with permission from different studies: WM volumes in preterm newborns imaged at 3 T (Kuklisova-Murgasova et al., 2011), in newborns at term imaged at 3 T (Gilmore et al., 2007), in infants at 0, 1 year and 2 years of age imaged at 3 T (Knickmeyer et al., 2008); DTI parameters in preterm newborns imaged at 1.5 T (Partridge et al., 2004), in infants imaged at 1.5 T (Dubois et al., 2008b), in infants at 0, 1 year and 2 year of age imaged at 3 T (Geng et al., 2012). Abbreviations: AFinf, inferior branch of the arcuate fasciculus; ALIC, anterior limb of the internal capsule; CG, cingulum; CS, centrum semiovale; CST, cortico-spinal tract; EC, external capsule; ILF, inferior longitudinal fasciculus; OR, optic radiations; PLIC, posterior limb of the internal capsule; STT, spino-thalamic tract; UF, uncinate fasciculus.

birth to 183 cm^3 at 1 year of age (i.e. increase by 11% per year), to 218 cm^3 at 2 years of age (i.e. increase by 19% per year).

Thus at these ages WM growth is relatively slow in comparison with the rapid GM growth (by 149% in the first year and 14% in the second year), leading to a decrease in the percentage of WM when normalized for the total brain volume (Gilmore et al., 2007; Knickmeyer et al., 2008). Subsequently the WM volume increases at a higher rate than GM volume throughout childhood (Matsuzawa et al., 2001), and the ratio between WM and GM volumes dramatically increases during childhood and adolescence (Groeschel et al., 2010).

Imaging a mix of several processes. While WM tissue is imaged as a whole on T1w and T2w images, its volume increase actually reflects several processes that occur successively or concomitantly during development, but whose contributions are hard to separate. WM composition is changing dramatically, especially during the mid-gestation period which is marked by neuronal migration: pyramidal neurons follow radial patterns along glial fibers, from the central periventricular region to the cortical periphery, while interneurons follow tangential patterns from the ganglionic eminence. Axonal connections are also growing from central gray nuclei and from cortical regions. Besides, the vascularity is developing according to a radial organization. These coherent structural patterns are mixing, making the dissection of growing fascicles difficult. Concurrently, glial cells proliferate: oligodendrocytes play a crucial role to myelinate axonal fibers during the late pre-term and post-term periods, while the contribution of developing astrocytes and microglia is still poorly understood, notably in terms of metabolism. Overall, several mechanisms contribute to the global increase in WM volume, and more subtle MRI techniques are thus required to detail the axonal organization in the growing WM.

Before term: imaging the growth of fiber connections

Post-mortem investigations with conventional MRI. Correlation studies between histology and

conventional MRI with high spatial resolution in post-mortem fetuses (Judas et al., 2005; Rados et al., 2006) have shown that three fiber systems are recognizable as early as 12 w GA: the CC, the fornix and the hemispheric stalk, which represents a massive connection between the telencephalon and the diencephalon and contains all the projection fibers of the developing internal capsule, including the thalamo-cortical fibers. During the mid-fetal period (17–24 w GA), a substantial elaboration of major cerebral fiber systems is observed in the ''intermediate zone'' (the fetal ''WM''). In the fronto-polar and occipito-polar regions, the fiber architectonics of the fetal cerebrum displays a tangential axon strata. Below the CC, the fornix is well developed. The CC, the internal and ECs are growing. In the central WM, the ''periventricular crossroads'' are the intersections between these major fiber systems: callosal fibers (transverse direction), associative fibers (sagittal direction), thalamo-cortical/cortico-fugal fibers (radial direction).

Between 24 and 32 w GA, the major events are the development of the corona radiata, from the transformation of the tangential fetal fiber-architectonic stratification. All major segments of the cerebral WM can be recognized: CC, corona radiata, centrum semiovale (CS), gyral WM (which is not yet fully developed because the subplate zone remains interposed between the corona radiata and the cortex). Fibers continue to grow at the levels of the periventricular crossroads and of the ventricular part of the CC, which leads to a blurring on post-mortem images. By term birth, all major fiber systems are to be in place.

Post-mortem investigations with diffusion imaging. DTI imaging is an exquisite technique to detail the developing organization of WM and precise the developmental calendar observed on conventional images. Imaging fetuses post-mortem at 19–20 w GA confirmed that limbic fibers (CG, fornix) develop first (entire trajectories visible at 19 w GA) and association fibers last (Huang et al., 2006). The CC, the UF and inferior longitudinal fasciculus (ILF) become apparent between 13 and 22 w GA (Huang et al., 2009). At 20 w GA, the CC formation is more advanced in the frontal lobe (genu and forceps minor) than in other regions (splenium and forceps major, body). The core regions of projection fibers are well-developed early on, but not the peripheral regions (i.e. the corona radiata), and the ALIC develops before the posterior limb.

The more elaborated technique of HARDI tractography applied to post-mortem fetuses between 19 w to 42 w GA (Takahashi et al., 2012) has clarified the calendar of tract development. A few immature long-range association pathways are visible early on in the WM (e.g. the uncinate and fronto-occipital fascicles), and short-range cortico-cortical tracts emerge prior to gyrification in regions where sulci will later develop. An early dominant radial organization of WM that gradually diminishes by term age is observed. This feature disappears first in dorsal parieto-occipital regions, second in ventral fronto-temporal regions; earlier at the depths of sulci than in the crests of gyri. At 19 w GA, the ganglionic eminence presents a dominant tangential organization which gradually disappears by term. These radial and tangential patterns are related to neuronal migration as confirmed by the combination of HARDI technique with the structural analysis of conventional images in post-mortem fetuses between 21 w and 24 w GA (Kolasinski et al., 2013). The radial pattern originates in dorsopallial ventricular/subventricular zone, while the tangentio-radial patterns originate in subpallial ganglionic eminence. These patterns regress in a caudo-rostral and lateral–ventral to medial–dorsal direction across this short developmental period. The post-mortem application of immunomarkers to radial glial fibers, axons, and blood vessels has enabled to decipher the histological origins of the HARDI-defined coherence (Xu et al., 2012), suggesting that the radial coherence in the fetal WM likely reflects a mixture of radial glial fibers (at mid-gestation), penetrating blood vessels (that are consistently radial), and radial axons (among radial, tangential and oblique axons).

In vivo investigations. Data acquired *in vivo* in preterms and fetuses have confirmed post-mortem studies. Using diffusion imaging, the early laminar organization of the cerebrum (cortical plate, subplate zone, intermediate zone, subventricular and periventricular zones, germinal matrix) has been delineated in 25–27 w GA preterm newborns (Maas et al., 2004). Imaging studies of *in utero* fetuses have described that the pyramidal tract and the splenium and genu of the CC are depicted early on and may be reconstructed in 3D using tractography algorithms between 18 and 37 w GA (Bui et al., 2006; Kasprian et al., 2008; Pontabry et al., 2013), as well as the Probst bundles in cases of CC agenesis (Kasprian et al., 2013). In preterms, association tracts and subcortical projection tracts are also identified (Partridge et al., 2004; Dudink et al., 2007).

After term: imaging the WM bundles and developing connectivity

Imaging the WM bundles. After term birth, almost all prominent WM tracts are identified despite low anisotropy values (Hermoye et al., 2006). This early organization has been further mapped in 3D in infants between 1 and 4 months of age, using a dedicated protocol for acquisition and post-processing (Dubois et al., 2006a, 2008b). Most commissural bundles (genu, body and splenium of the CC), projection bundles (CST, spino-thalamic tract (STT), OR, ALIC), limbic bundles (fornix and CG) and associative bundles (EC, uncinate, arcuate, superior and inferior longitudinal fascicles) can be detected and tracked (Fig. 3). In a longitudinal study using a dedicated DTI atlas, a similar organization of the major bundles has been shown between newborns and toddlers of 1 and 2 years of age (Geng et al., 2012).

However, some associative bundles that mature later on (see section 'Imaging the maturation of white matter'), such as the superior longitudinal fasciculus, demonstrate large changes in fiber orientations during the first

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post-natal months (Zhang et al., 2007). High-field imaging at 3 T may enable the precise exploration of subtle connections within specific developing networks (e.g. the language network (Dubois et al., in preparation)). Actually one should keep in mind that DTI methodology does not enable to decipher between exact fiber directions in the place of crossing fibers, particularly when crossing bundles are maturing at different rates and over different time periods. This leads to erroneous interpretation on the presence/absence of a bundle in the developing brain. Accordingly, the dorsal pathway of the developing language network (the AF) may not seem to fully connect temporal and frontal regions in newborns (Perani et al., 2011; Brauer et al., 2013), but this might be artifactually related to its low maturation in comparison with the crossing CST (Dubois et al., in preparation).

Developing WM connectivity. Recently, the wiring pattern of cerebral connections and the maturational calendar have been reinterpreted in the framework of small-world topology (Hagmann et al., 2010). The principal characteristics observed in adults have been found in infants demonstrating that the infant brain is neither fully connected, nor only locally connected (Fan et al., 2011; Yap et al., 2011; Pandit et al., 2013). This result might appear trivial, given the anatomical results reviewed above showing that the short and main long-distance connections are already observed before term, but this approach has the advantage to have no *a priori* and to place the brain within a mathematical formalism. Longitudinal studies performed from birth to two years of age and based on regional GM volumes (Fan et al., 2011) and on the number of fibers passing through pairs of regions (Yap et al., 2011) have been interpreted as showing an increase in integration and a decrease in functional segregation.

Behavioral and functional studies certainly support such hypotheses, but structural studies are confronted with several unsolved drawbacks. For example, the difficulties in GM/WM segmentation vary with age due to changes in T1w and T2w contrasts; weakly myelinated fibers may appear shorter because of lower anisotropy that impacts tractography reconstructions; smaller head size creates partial volume effects that might blur connectivity results in younger infants. Finally, network efficiency is sometimes indirectly inferred from diffusion metrics (Hagmann et al., 2010), and not directly from the transfer times of the neural information, whereas the information propagation at the same latency in the infant and adults brains may not require a similar tract myelination because of the different brain sizes (Salami et al., 2003). Fortunately, combining these structural measures with electrophysiological and/or resting-state fMRI has indeed shown a strengthening of the correlations between structural and functional connectivities (Hagmann et al., 2010).

IMAGING THE MATURATION OF WM

When the bundles are in place, a slow process of maturation begins, following a different calendar in different bundles.

Different periods of WM maturation

Before term: localized myelination. Before 36 w GA, unmyelinated WM is the most prominent brain tissue according to T1w and T2w images, and an abrupt increase in myelinated WM is detected between 35 and 41 w GA (Huppi et al., 1998b). However, there is earlier evidence of myelination in specific WM regions (Counsell et al., 2002) such as the inferior and superior cerebellar peduncles before 28 w GA, the PLIC, the CST around the central sulcus and the corona radiata from 36 w GA on.

DTI studies of *in utero* fetuses (Righini et al., 2003; Bui et al., 2006; Kasprian et al., 2008; Jiang et al., 2009) and ex utero preterm newborns as young as 26 w GA (Huppi et al., 1998a,b; Neil et al., 1998; Miller et al., 2002; Dudink et al., 2007; Aeby et al., 2009, 2012) have found the general pattern of age-related decrease in mean diffusivity and increase in anisotropy in different WM regions (pyramidal tract, CC, frontal and occipital regions). In longitudinal imaging between 28 and 43 w GA (Partridge et al., 2004), early differences have been further identified between several projection and association pathways, with low mean diffusivity and high FA in cerebral peduncles, internal capsule and commissural tracts of the CC, suggesting an early maturation of these tracts (Fig. 5b) and confirming the analyses done on T1w/T2w images.

After term: major changes related to myelination. After term, WM myelination is intense in the developing brain, and quantitative MRI parameters have underlined successive maturational periods: acute changes during the first post-natal months, less rapid modifications during toddlerhood, and slower changes thereafter until young adulthood. It is particularly obvious for DTI parameters (Fig. 5b): decrease in MD and increase in FA are rapid during the first post-natal year and slower during the second year (Mukherjee et al., 2001; Forbes et al., 2002; Hermoye et al., 2006; Geng et al., 2012; Sadeghi et al., 2013). Age-related decreases in diffusivities have been modeled through exponential decays from birth to childhood (Mukherjee et al., 2001), or by a sigmoid function (Gompertz growth function, based on intuitive variables related to delay, speed, and expected asymptotic value) longitudinally from birth to 2 years of age (Sadeghi et al., 2013).

In the same way, T1 and T2 decreases are particularly rapid over the two first years (Engelbrecht et al., 1998; Haselgrove et al., 2000), yielding to exponential decays with age (Fig. 6a) (Leppert et al., 2009). Conversely, the MTR increases exponentially (Engelbrecht et al., 1998; van Buchem et al., 2001) (Fig. 6b). Between 3 and 60 months, the increase in MWF is best modeled by a modified Gompertz function which is characterized by four distinct parameters: the developmental lag, the transitionary period and two growth rates (Fig. 6c) (Dean et al., 2014).

To summarize, for all MRI and DTI parameters, the dynamic of changes is intense between birth and 2 years of age, which does not match the relatively slow

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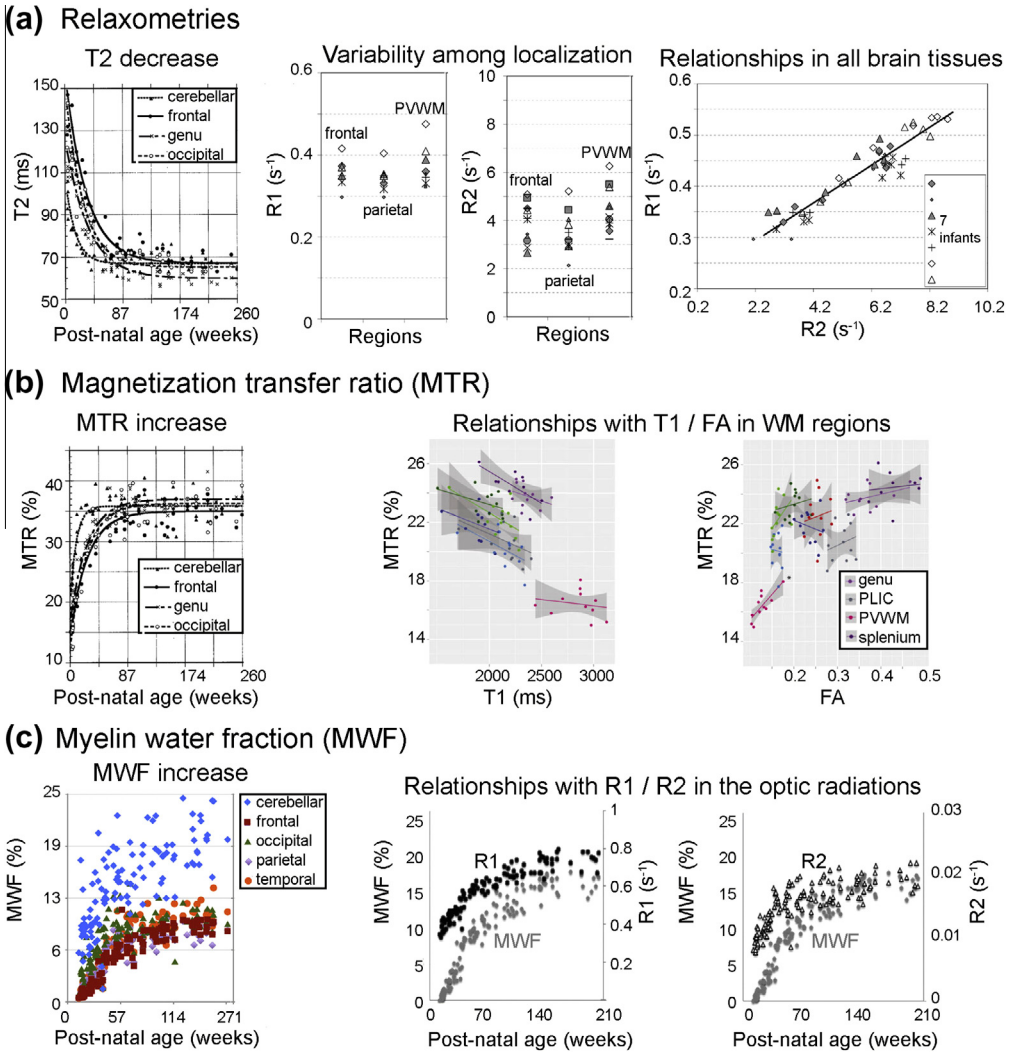

Fig. 6. Age-related changes in quantitative parameters related to myelin. Relaxation times T1 and T2 (a), magnetization transfer ratio (MTR) (b) and myelin water fraction (MWF) (c) are shown during infancy and toddlerhood. T1 and T2 decrease exponentially with age while relaxation rates (Ri = 1/Ti), MTR and MWF increase (left column). Note parameters variability across WM regions, which demonstrate different temporal maturation courses (left and middle columns). Some correlations between the parameters have been shown (right and middle columns), but these correlations mainly rely on co-variations with the infants age. Figures were adapted with permission from different studies: age-related changes in T2 and MTR at 1.5 T in infants (Engelbrecht et al., 1998), variability in relaxation rates at 3 T in newborns at term (Williams et al., 2005), correlations between MTR, T1 and FA at 1.5 T in preterm newborns (Nossin-Manor et al., 2012), MWF increase at 3 T in infants (Deoni et al., 2012a). Abbreviations: PLIC, posterior limb of the internal capsule; PVWM, peri-ventricular white matter.

increase in WM volume during this developmental period. Furthermore these non-linear patterns of changes reveal considerable regional variations across and along WM bundles because of myelination asynchrony.

Spatio-temporal sequence of WM maturation

Maturation asynchrony across WM bundles. The interest of DTI studies rests in the quantification of differences across WM bundles, detailing a progression of maturation from a central-to-peripheral and a posterior-to-anterior direction (Oishi et al., 2011). For instance, the increase in anisotropy appears greater in non-compact ones (corona radiata and peripheral WM) than in compact WM structures (CC, internal capsule, cerebral peduncle) across the first three post-natal years (McGraw et al., 2002). Diffusivities and anisotropy show different evolutive patterns across brain regions of the preterm brain (Nossin-Manor et al., 2012) and of the infant brain during the first two post-natal years (Geng et al., 2012), with highest FA in the CC and lowest mean diffusivity in the PLIC.

By taking advantage of the different sensitivities of diffusivity and anisotropy to maturational processes, a model based on the parameter changes during the ''pre-myelination'' and the ''true'' myelination periods was build to describe the bundles maturational stages in infants between 4 and 18 weeks of post-natal age in comparison with an adult group (Dubois et al., 2008b). This model enabled to detect early spatio-temporal differences in the maturation progression of a set of

bundles, from the more to the less mature bundles: (1) the CST, (2) the STT and the fornix, (3) the OR, the arcuate and inferior longitudinal fascicles, (4) the ALIC and the CG. In a similar way, three distinct phases of maturation, with specific dynamics for each bundle type, have been modeled and identified in the fetal WM between 23 and 38 w GA: (i) the axonal organization, (ii) the myelination gliosis, and (iii) the myelination, which appears early in the CST, followed by the OR and the CC (Zanin et al., 2011).

Regional asynchrony in WM maturation is also observed by MTR, showing a relatively mature stage at 12.9 and 15.6 m in the occipital and frontal WM respectively, and at 17.7 and 18.7 m in the splenium and genu of CC (Xydis et al., 2006). The spatio-temporal pattern of myelination progression is also nicely demonstrated through MWF (Deoni et al., 2011, 2012a). It rises earlier in a frontal–parietal region (projection fibers) than in an frontal region (association fibers) during childhood, following the standard caudal-to-rostral trend (Lancaster et al., 2003). In infants between 3 and 11 months of age, MWF increases in the cerebellum, pons, and internal capsule; it further increases caudo-cranially from the splenium of the CC and OR (at 3–4 months); to the occipital and parietal lobes (at 4–6 months); and then to the genu of the CC and frontal and temporal lobes (at 6–8 months) (Deoni et al., 2011). The spatio-temporal pattern provided over a larger age range (3–60 months) is coherent with histological studies of myelination (Deoni et al., 2012a).

Maturation progression within a WM bundle. The spatial resolution of DTI also allows to studying maturation along a WM tract: maturation does not evolve at the same time and speed in different spatial locations within a bundle (Partridge et al., 2005; Colby et al., 2012). During the first two post-natal years, changes near cortical regions generally appear smaller than in brain central regions (Geng et al., 2012). In preterm newborns between 28 and 43 w GA, the motor tract and the somatosensory radiations of the CST begin to myelinate during the late preterm period first at the level of the internal capsule (Berman et al., 2005). Maturation further seems to proceed earlier in the motor pathway than in the sensory one at the vertex where motor fibers initiate from the cortex. From term-equivalent age (Berman et al., 2005; Geng et al., 2012), the anisotropy profile presents a local dip at the level of the corona radiata, which suggests the beginning and ongoing maturation of crossing pathways (fibers of the CC and superior longitudinal fasciculus).

The myelination progression in the visual pathways of infants between 6 and 17 weeks of post-natal age has also been studied, showing two asynchronous fronts of maturation in the OR: an early wave in the anterior region, initiating from the lateral geniculate nucleus, and a later catching-up wave in the posterior region, initiating from the occipital cortex (Dubois et al., 2008c). According to the assumption that myelination proceeds from the neuron body to the periphery (McCart and Henry, 1994), this pattern may result from the respective myelination of the geniculo-cortical (projection) fibers and cortico-geniculate (feedback) fibers, with a delayed maturation of the cortical retrocontrol to the thalamus relative to bottom-up fibers.

Sophisticated approaches to map WM maturation asynchrony

Recently, original approaches that combine MRI parameters have been proposed to measure even more precisely the maturation across WM regions.

Correlations between MRI parameters. The different parameters (T1, T2, DTI, MTR, MWF) capture different properties of WM maturation (Fig. 4c). Some studies have described specific correlations between them, but most have missed to take into account their major age-related dependencies.

In neonates, a strong correlation has been detected between relaxation rates R1 (1/T1) and R2 (1/T2) among different WM regions (Williams et al., 2005) (Fig. 6a). In the kitten WM, DTI mean diffusivity seems to correlate more with R2 than with R1 (Baratti et al., 1999), whereas maps of mean diffusivity demonstrate a pattern of regional variations similar to T1 maps in preterm newborns between 26 and 45 w GA (Nossin-Manor et al., 2012).

According to the inverse correlation between MTR increase and T2 decrease in WM after term birth, it has been assumed that both changes rely on fast proton relaxation within macromolecules in myelinated tissue (Engelbrecht et al., 1998). An inverse correlation between MTR and T1 is observed in preterm newborns near term (Nossin-Manor et al., 2012) (Fig. 6b). MTR is also positively correlated with FA in WM during the preterm period, suggesting a coupling between the increase in concentration of pre-myelination-associated macromolecules and the increase in axonal alignment and axonal density (Nossin-Manor et al., 2012) (Fig. 6b). The comparison of MWF measurements with age-related dynamics of T1 (R1) and T2 (R2) relaxation times (rates) has shown that all parameters are sensitive to WM maturation in infants, but in different ways suggesting that they provide complementary information on maturation processes (Lancaster et al., 2003; Deoni et al., 2012a) (Fig. 6c).

Since T1, T2, DTI, MTR and MWF maps show regional variations following different evolutions with age, these parameters are to be sensitive to multiple and complementary mechanisms of WM development. It is only by combining and comparing these parameters that one can hope to outline comprehensive patterns of the tissue macro- and microstructures. For instance, in preterm infants the CC displays high values of MTR, T1, FA and longitudinal diffusivity and low transverse diffusivity values, because callosal fibers are highly organized, closely packed, with high axonal density of microstructural components (e.g. microtubules, neurofilaments), leading to high directionality, coherence and restriction, but the fibers are not myelinated and the water content is high (Nossin-Manor et al., 2012). On the other hand, the PLIC shows in the preterm period

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(pre-myelinating stage) low values of MTR, FA and diffusivities and high T1 values, resulting from a lower fiber packing density than in the CC, a lower macromolecular density, along with lower directionality and coherence but higher restriction; at term, the increase in MTR values, along with lower transverse diffusivity, are markers of the myelination process (Nossin-Manor et al., 2012). Thus a clever use of these different parameters, informed by a better understanding of the mechanisms they are sensitive to, do provide more precise *in vivo* maps of the WM maturation.

Multi-parametric imaging. Dealing with multi-parametric data will open new perspectives in the study of WM development. Combining the time trajectories of anisotropy, longitudinal and transverse diffusivities may definitely provide accurate landmarks on maturation asynchrony across bundles (Sadeghi et al., 2013). Modeling the information from structural (T1w, T2w, PD images) and DTI data (longitudinal and transverse diffusivities) with modified Legendre polynomials has also provided an absolute measure of maturation (rate of change) and a relative measure (time shift) (Prastawa et al., 2010). Maps of growth rates demonstrate slow regions (e.g. internal capsule) and rapidly growing regions (e.g. deep WM in anterior and posterior regions, temporal lobe). Maps of time shifts based on structural data demonstrate gradual changes in regions that undergo myelination, while surprisingly those based on DTI data mostly highlight differences between central and peripheral regions (Prastawa et al., 2010).

DTI parameters may also be combined with quantitative relaxation times T1 and T2. Because of the complex relations between these parameters in developing bundles (Kulikova et al., 2013a), an original measure of maturation has been defined in infants between 3 and 21 weeks of post-natal age to summarize the changes in all parameters while taking into account their possible correlations. This measure, based on the computation of the Mahalanobis distance in comparison with a group of adults, confirms the evidence of WM maturation asynchrony over a short developmental period and outperforms univariate approaches (Kulikova et al., 2013b). It further provides a quantitative evaluation in weeks of the developmental delays between WM bundles. The maturation order provided by this multi-parametric approach during the first post-natal year is congruent with the, from the most to the least mature bundle: the STT; the OR; 6 weeks later: the middle portion of the CST and the fornix; 12 weeks later: the inferior portion of the CST; 7 weeks later: the genu and splenium of the CC and the superior portion of the CST; 6 weeks later: the inferior CG; 3 weeks later: the CC body and the superior CG; 3 weeks later: the inferior longitudinal, fronto-occipital and uncinate fascicles; 2 weeks later: the EC; 3 weeks later: the ALIC; 4 weeks later: the superior longitudinal and arcuate fascicles literature (Kulikova et al., in preparation).

FUNCTIONAL CORRELATES OF MRI BIOMARKERS OF WM MATURATION

In healthy infants, WM maturation correlates with psychomotor acquisitions (Prayer and Prayer, 2003) but the exact relationships between cerebral structure and function remain difficult to grasp. Brain anatomical analyses might help to understand the biological bases of cognitive development, by revealing the early structural specificities that may underlie human complex functions such as language, and by mapping correlations between structural indices and functional efficiency. WM studies are also crucial to understand early functional impairments such as the ones triggered by preterm birth.

Early WM asymmetries in highly lateralized functional networks

Finding which hemisphere is the left one on an axial image of an adult human brain is usually relatively easy thanks to the Yakovlev torque creating right frontal and left occipital petalias, and a steeper and shorter right sylvian fissure (Toga and Thompson, 2003). Some of the structural asymmetries observed in the peri-sylvian regions (Heschl gyrus, *planum temporale*, superior temporal sulcus (STS)) have been described during the early brain development of fetuses and preterm newborns (Chi et al., 1977; Feess-Higgins and Laroche, 1987; Dubois et al., 2008a, 2010a). Other asymmetries evolve later on during development: for instance the posterior extension of the sylvian fissure progresses until adolescence and adulthood (Sowell et al., 2002). At the functional level, the left-hemisphere specialization for language processing is observed early on in infants (Dehaene-Lambertz et al., 2002, 2006) and already at 6 months of gestation (Mahmoudzadeh et al., 2013), and the lateralization of the somato-sensory response is also detected at birth (Erberich et al., 2006). The origins and relationships between these early anatomical and functional asymmetries are still debated.

Using DTI in healthy infants, three WM regions have been shown asymmetric early on (Dubois et al., 2009): (1) the temporal part of the AF is larger on the left; (2) its left parietal part shows a better microscopic organization than the right; (3) the CST is more mature in the left hemisphere between the cerebral peduncles and the PLIC. These two bundles have also been shown asymmetric in preterm infants at term-equivalent age (Liu et al., 2010) and in adults (Buchel et al., 2004; Parker et al., 2005). Since these WM pathways are related to language and motor networks, such early structural asymmetries might be biomarkers of the genetic constraints driving development of lateralized functions in the human brain, although no strict correlation has been found between asymmetries of the motor pathways and later handedness.

Myelin content is also asymmetrical in multiple WM regions, with no significant change over time during infancy (O'Muircheartaigh et al., 2013): toward the left hemisphere in the temporal/occipital lobe on the trajectory of the arcuate and inferior longitudinal

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fascicles, in the medial frontal and posterior parietal lobes; toward the right hemisphere in the dorsal external/extreme capsule and in central WM. Furthermore, language ability correlates with MWF rightward asymmetry in the external/extreme capsule and with MWF leftward asymmetry in frontal WM, and such relationships seem to stabilize around 4 years of age (O'Muircheartaigh et al., 2013).

Correlations between DTI parameters and functional measurements

The key question that encourages further *in vivo* MRI studies of the developing brain is to which extent advanced structural imaging provides biomarkers of the sensori-motor and cognitive development of infants. In the developing language network, the time course of WM myelination parallels language acquisition, with lexical explosion after 18 months of age (Pujol et al., 2006; Su et al., 2008). Similar relationships have been highlighted in 12-month-old infants, where visuospatial working memory performance correlated with DTI microstructural characteristics of WM tracts connecting brain regions known to be involved in working memory (genu of the CC, anterior and superior thalamic radiations, anterior CG, AF), beyond individual variations in age and developmental level (Short et al., 2013).

Structure–function correlations can also be highlighted by comparing MRI parameters with neurophysiological measures. In the visual system during the first post-natal months, several maturation processes (e.g. fiber myelination, retina and cortex development) lead to a dramatic decrease of the latency of the first response wave to a visual stimulus (P1) as measured by event-related potentials, from about 260 ms at birth to about 120 ms at 4 months of age (McCulloch et al., 1999). This decrease is related to an increase in the conduction speed of the neural impulse, which is correlated to the OR microstructure and maturation (FA and transverse diffusivity) beyond the effect of age (Dubois et al., 2008c). This correlation study of EEG and DTI measurements (obtained in the same infants) outlines the functional significance of structural markers during WM maturation. The ability to characterize individual anatomical and functional differences across infants is very promising for the understanding of normal development with special focus on experience-dependent mechanisms and critical periods of plasticity. It is also crucial for the definition of biomarkers that will characterize and detect early perturbations of developmental trajectories.

Functional correlates of MRI biomarkers in preterm newborns

Based on the results obtained in healthy infants, early biomarkers of neurological deficits are searched for, especially in the case of premature birth. The early organization and maturation of axonal pathways is a highly vulnerable process during the second half of pregnancy (Kostovic and Jovanov-Milosevic, 2006). In infants born prematurely, brain growth is disturbed by the change from *in utero* to ex utero environment, and the difficulties to maintain a stable homeostasis. But whereas the neurodevelopmental disabilities of children born prematurely are now rather well described, the underlying alterations of brain development (that lead to disabilities) remain poorly understood (Ment et al., 2009).

Early impairments in WM development. MRI studies might provide early biomarkers of functional outcome and of specific disturbances of cognitive development. While several reviews have detailed WM abnormalities related to prematurity (periventricular leucomalacia, punctate lesions, diffuse excessive high signal intensity (DEHSI)) and their long-term effects on the child brain (for example (Ment et al., 2009; Rutherford et al., 2010), we here summarize only major findings observed in preterm infants without gross brain lesions and imaged below 2 years of age.

The impact of prematurity on WM development has been mainly evaluated by comparing preterms at term-equivalent age with full-term infants. Preterm infants present with less GM/WM differentiation and myelination in comparison with full-term newborns (Huppi et al., 1996; Mewes et al., 2006). The macrostructure of the CC is impaired, with reduced volume correlating with lower GA at birth (Thompson et al., 2012). Using voxel-based analyses (Rose et al., 2008) or tract-based spatial statistics (TBSS) (Anjari et al., 2007), FA reductions were found in several WM regions (CS, frontal WM, CC, internal and ECs), but higher FA associated with lower T2 values were also observed in cortico-spinal projections, suggesting a decreased number of crossing inter-hemispheric fibers associated with a decreased water concentration (Rose et al., 2008).

Beside WM, thalamic development is also dramatically disrupted by prematurity, with reduced volume related to abnormalities in ''allied'' WM structures (CSTs and CC) at term-equivalent age (Ball et al., 2012b). The thalamo-cortical loop seems highly vulnerable, with diminished connections between the thalamus and frontal cortices, supplementary motor areas, occipital lobe and temporal gyri in preterm infants (Ball et al., 2012a). Prematurity is also related to widespread reductions in the connection strength of WM tracts involving all cortical lobes and several subcortical structures during the second post-natal year (Pandit et al., 2013).

Correlations with behavioral measures. Local reductions in WM volumes at term-equivalent age in the sensorimotor and mid-temporal regions are strongly correlated with measures of cognitive and motor development between 18 and 20 months of corrected age (Peterson et al., 2003). In the absence of apparent WM lesions, higher mean diffusivity values at the level of the CS at term-equivalent age have been associated with poorer developmental quotient on the Griffiths Mental Development Scales at 2 years of corrected age (Krishnan et al., 2007). Similarly, a TBSS analysis has shown that developmental quotient at 2 years corrected age is related to FA in subparts of the CC at

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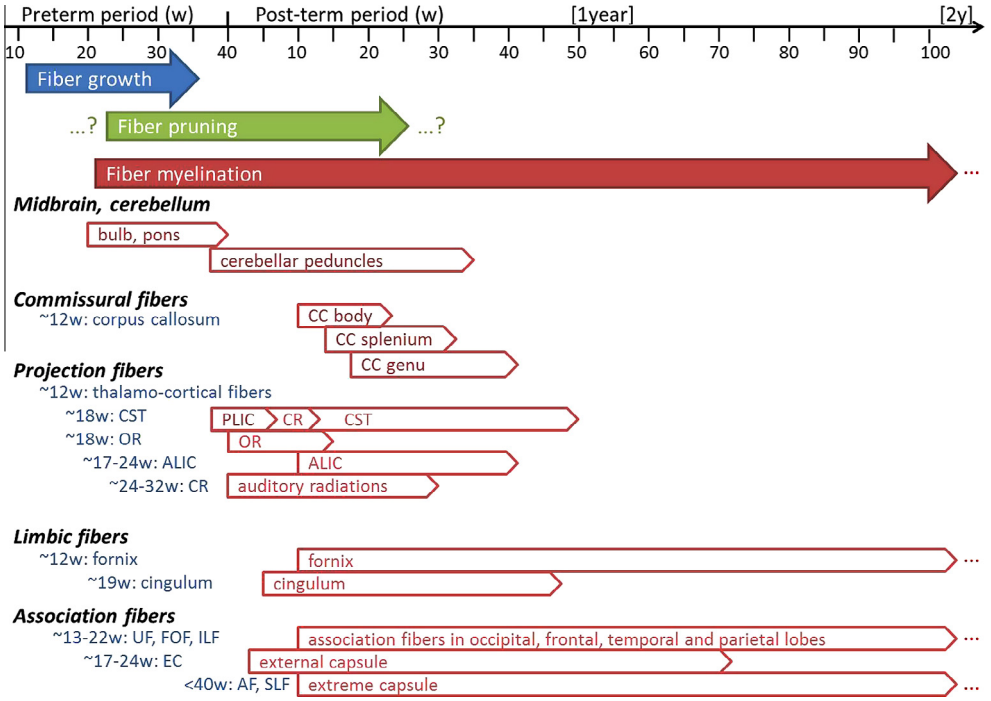

Fig. 7. General time-line of WM development. The time-courses of developmental mechanisms are tentatively summarized across WM bundles, according to post-mortem investigations and MRI studies. These mechanisms include the growth, pruning and myelination of axonal fibers, during the pre-term and post-term periods (fetal and post-natal ages in weeks). For each mechanism, approximate time periods are indicated. To our knowledge, information on the beginning and ending of axonal pruning are missing in the human brain. Purple-bordered arrows refer to the myelination process. Abbreviations: AF, arcuate fasciculus; ALIC, anterior limb of the internal capsule; CC, corpus callosum; CG, cingulum; CR, corona radiate; CST, cortico-spinal tract; EC, external capsule; FOF, fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; PLIC, posterior limb of the internal capsule; OR, optic radiations; SLF, superior longitudinal fasciculus; STT, spino-thalamic tract; UF, uncinate fasciculus. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

term-equivalent age; performance sub-scores to FA in the CC and right CG; and eye-hand coordination sub-scores to FA in the CG, fornix, anterior commissure, CC and right uncinate fasciculus (UF) (Counsell et al., 2008).

Focus on the developing visual system. Three studies have focused on the early development of the visual system in preterm infants, because this function matures early on and is frequently impaired by premature birth. Between 29 and 41 w GA, the microstructural development (FA) of the OR has been correlated with the newborn visual maturity (scores from a visual fixation tracking assessment) independently of GA (Berman et al., 2009). This has been confirmed at term-equivalent age, with a specific correlation between the visual assessment score and the FA in the OR, independently from GA at birth, GA at scan or presence of lesions on conventional MRI (Bassi et al., 2008). A recent study has further evidenced an effect of the period of premature extra-uterine life in addition to the degree of prematurity: indeed, visual function around term-equivalent age seems related to FA in the OR at that age, but also to FA evolution pattern, as characterized by the rate of increase between two successive scans (the first between 30 and 36 w GA, the second at term-equivalent age between 39 and 46 w GA) (Groppo et al., 2012). The alteration of WM pathways microstructural maturation during the late preterm period thus impacts the visual function at birth.

CONCLUSION

Characterizing the dynamics of human brain development and the structural bases of functional maturation requires *in vivo* studies of the healthy newborn and infant. These studies are challenging and require dedicated methodologies for image acquisition and post-processing. But it is worth the effort since new quantitative markers of maturation have been recently validated, also providing a better understanding of the deleterious effects of early disturbances such as prematurity.

Mechanisms of WM development are complex and intermingled. In terms of early WM organization, the growth and wiring of axonal fibers occur mostly during the preterm period, whereas the pruning of aberrant or useless connections rather starts during the first post-natal weeks along with external stimulations. Afterward, fibers get myelinated and progressively functionally mature, which may result from neuronal activity and also reinforce it. WM maturation further impacts on the functional efficiency of brain networks, which correlates with the infant acquisitions. All these mechanisms occur at different times and speeds according to cerebral

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regions and involved functions, with maturation proceeding until adulthood in some associative frontal and temporal regions. A tentative summary of the timeline of WM development during the preterm period and the first post-natal months can be provided from post-mortem investigations and *in vivo* MRI studies (Fig. 7). Although relatively coherent, some variations in the time courses are observed because the techniques are differently sensitive to mechanisms of WM organization and maturation. Let us keep in mind that MRI techniques remain indirect and macroscopic approaches to explore the developing microstructure. They can hardly investigate some mechanisms (e.g. fiber pruning), but their main advantage is to be non-invasive techniques that can be applied *in vivo* in healthy fetuses and infants. For instance, they are the only conceivable approach to investigate how brain maturation is influenced early on by environmental factors and nutrition (e.g. boosting of WM myelination by breastfeeding (Deoni et al., 2013)).

Other emerging MRI techniques, such as magnetic susceptibility mapping and phase imaging, are promising to help characterize the microstructural properties of the developing WM (Zhong et al., 2011; Lodygensky et al., 2012; Chen et al., 2013). Of course, WM changes are not completed by 2 years of age, but are protracted in some brain regions until the end of adolescence; however it is beyond the scope of the current article to review all existing studies based on structural MRI (Paus et al., 1999, 2001; Paus, 2005, 2010; Giedd and Rapoport, 2010) and DTI (Barnea-Goraly et al., 2005; Eluvathingal et al., 2007; Lebel et al., 2008; Faria et al., 2010; Lebel and Beaulieu, 2011). Finally, the interactions between the developing WM connectivity and the development of cortical regions will probably take a place of honor soon, since an increasing number of studies have recently provided early quantitative markers of cortical maturation (Leroy et al., 2011a), that may also correlate with the development of infant cognitive abilities (Aeby et al., 2013; Travis et al., 2013).

To sum, correlation approaches based on complementary imaging approaches (including anatomical and functional imaging and behavioral assessments) enable to explore the developing brain at several levels, from brain structure development to the infant motor and cognitive acquisitions. Beyond normal development, these studies are crucial to understand the mechanisms of pathologies that result from early cerebral anomalies (e.g. genetic diseases, epilepsies, mental retardation, learning disorders), to assess the influence of early disturbances related to fetal conditions (e.g. intra-uterine growth restriction, teratogen exposures) or perinatal events (e.g. premature birth, neonatal stroke), and to follow the efficiency and robustness of medical interventions.

Acknowledgments—The author research is supported by the Fyssen Foundation, the McDonnell Foundation, the "Ecole des Neurosciences de Paris", the "Fondation Motrice", the "Fondation de France", the French National Agency for Research (ANR), the CIBM imaging center from Geneva and Lausanne, the Swiss National Science Foundation, the Leenards Foundation and the European consortium NEOBRAIN.

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Please cite this article in press as: Dubois J et al. The early development of brain white matter: A review of imaging studies in fetuses, newborns and infants. Neuroscience (2014), http://dx.doi.org/10.1016/j.neuroscience.2013.12.044

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(Accepted 16 December 2013)
(Available online xxxx)