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Diffusion Tensor Imaging for Understanding Brain Development in Early Life

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Abstract

The human brain rapidly develops during the final weeks of gestation and in the first two years following birth. Diffusion tensor imaging (DTI) is a unique in vivo imaging technique that allows three-dimensional visualization of the white matter anatomy in the brain. It has been considered to be a valuable tool for studying brain development in early life. In this review, we first introduce the DTI technique. We then review DTI findings on white matter development at the fetal stage and in infancy as well as DTI applications for understanding neurocognitive development and brain abnormalities in preterm infants. Finally, we discuss limitations of DTI and potential valuable imaging techniques for studying white matter myelination.

Keywords

magnetic resonance imaging; diffusion tensor imaging; brain development; white matter; myelination; infancy

INTRODUCTION

Brain development is extremely rapid and dynamic during the fetal stage and in the first two years following birth. Brain development underpins cognitive and motor development in

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early childhood as well as the potential pathogenesis of neurodevelopmental disorders, such as autism, attention-deficit/hyperactivity disorder, and schizophrenia.

Magnetic resonance imaging (MRI) has significantly advanced our understanding of brain development and its correlates with cognitive development in early childhood. Using structural T_1-weighted and T_2-weighted MRI techniques, Knickmeyer et al. (2008) identified that total brain volume increased by 101% in the first year and by 15% in the second year. This robust growth of the human brain in the first two years of life was mainly driven by the gray matter growth, including the cortical and subcortical growth. The volume of the cortical hemispheres increased by 88% in the first year and by 15% in the second year. The volume of the subcortical region increased by 130% in the first year and by 14% in the second year (Knickmeyer et al. 2008). In contrast, the volume of hemispherical white matter increased by only 11% in the first year and by 19% in the second year (Knickmeyer et al. 2008).

Although white matter grows more slowly than does gray matter in terms of size, the early development of white matter, particularly white matter myelination, is a complex and long-lasting process. Myelination, the elaboration of myelin surrounding neuronal axons, starts late in embryonic development and continues through postnatal life. Due to the presence of myelin, electrical signals can move along nerve axons at high speed. The development of the myelin sheath enables rapid synchronized communication across the neural systems responsible for higher-order cognitive functioning.

In recent years, diffusion tensor imaging (DTI) has emerged as a method to noninvasively measure white matter microstructure in vivo throughout the life span, beyond structural size assessed using T_1- and T_2-weighted MRI. It has been widely used to investigate changes in white matter at different stages of brain development and their relationship to cognitive ability in early life. In this review, we first introduce diffusion MRI and DTI and summarize recent DTI findings on white matter development from the fetal stage to early childhood. We then review the applications of DTI to neurocognitive development in early-life and preterm research. Finally, we discuss the limitations of DTI and other potential imaging techniques for studying white matter development.

DIFFUSION MAGNETIC RESONANCE IMAGING AND DIFFUSION TENSOR IMAGING

MRI can be used to observe signals from various nuclei. However, MRI primarily measures the signal from protons of water molecules because more than 90% of protons in the body are located in water molecules. Interestingly, the water in the brain tissue diffuses in a restricted environment. The water diffusion reflects interactions with many obstacles, such as membranes and axonal fibers. Water molecule diffusion patterns can therefore reveal microscopic details about the brain tissue architecture, such as axonal orientation. Hence, water diffusion patterns have been considered useful for reflecting the underlying axonal organization of the brain.

Diffusion MRI is a technique that came into existence in the mid-1980s (Le Bihan & Breton 1985). It allows the in vivo and noninvasive imaging of the diffusion process of the water in the brain tissue. Diffusion MRI was designed to sensitize the MRI signal intensity to the amount of water diffusion. Pulsed magnetic field gradient, which introduces a linearly varied magnetic field in the three-dimensional space, is the technique used for this purpose. As precession of the proton is proportional to the magnet strength, the gradient pulse begins to precess at different rates, resulting in dispersion of the phase and signal loss across the spatial domain. Subsequently, another gradient pulse is applied in the same magnitude but with opposite direction to refocus or rephase the spins. However, the spins cannot be fully recovered during the refocusing process because water protons have moved during the time interval between the pulses. Hence, the signal measured by MRI is reduced. From the pulsed magnetic field gradient technique, the reduction in signal due to the application of the pulse gradient related to the amount of water diffusion can be derived at each location of the spatial domain. Alternatively, the signal loss is related to the water motion in this pulse gradient direction.

If ink is dropped into a cup of water, water freely diffuses, and the shape of diffusion becomes a sphere. This process, in which water diffuses in all directions by the same amount, is termed isotropic diffusion. In this case, only one measure—the diffusion constant—is needed to describe the diffusion. The diffusion constant is related to the diameter of the sphere. However, if the water motion is restricted in a tube, the diffusion process becomes more complicated, and the shape of water diffusion becomes ellipsoid. This type of diffusion, which often occurs in biological tissues, is termed anisotropic diffusion. The water tends to diffuse along a preferential axis or axes, such as axonal tracts in nervous tissues. Anisotropic diffusion cannot be characterized using a single diffusion constant but instead requires diffusion constants to be assessed at multiple diffusion directions.

Diffusion-weighted imaging (DWI) is a unique in vivo imaging technique that allows visualization of the water diffusion constant in different directions. DTI characterizes the ellipsoidal shape of the water diffusion profile in brain tissue using a symmetric positive definite tensor field derived from DWI. This tensor field measures the extent of diffusion in all directions in the three-dimensional space and hence maps the anisotropy of water diffusion in the brain, thus reflecting the organization and architecture of white matter fibers. Anisotropy is high because of the cylindrical geometry of the neuronal fibers in the white matter. In contrast, the diffusion anisotropy is very low in gray matter because the cellular geometry is more globular. Several metrics, such as fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD), derived from this tensor model are often used to reflect the microstructure of the brain anatomy. FA expresses the degree to which water diffusion is restricted in one direction relative to other directions. It ranges from zero to one, with zero being completely isotropic diffusion, and one being diffusion constrained in a single direction. The increase in FA with age in early life is explained by the ensheathment of oligodendrocytes around axons (Dubois et al. 2008, Hüppi & Dubois 2006). AD and RD reflect the rate of microscopic water motion parallel and perpendicular, respectively, to the direction of axonal fibers in a regional tissue; they are often used to evaluate water content (Provenzale et al. 2007). MD corresponds to the

directionally averaged magnitude of water diffusion. The decrease in AD, RD, and MD are related to the premyelination stages in early life (Dubois et al. 2008, Hüppi & Dubois 2006).

Over the past several decades, many investigators have used DTI to examine white matter development during the fetal stage and infancy. Dubois et al. (2008) hypothesized three stages of white matter development that can be characterized using FA, AD, RD, and MD. These three stages sequentially involve fiber organization, membrane proliferation, and fiber myelination (as illustrated in **Figure 1**). At the first stage, axonal fibers appear to be more directionally organized. Dubois et al. (2008) hypothesized that progressive fiber organization may be reflected by an increase in anisotropy, which is due to an increase in AD and a decrease in RD. MD may remain unchanged. Water anisotropic diffusion exists in white matter in late intrauterine and premature infants (Kostovic & Jovanov-Milosevic 2006). The increased anisotropic diffusion process is linked to the developmental expansion of immature oligodendrocytes during the premyelination period (Drobyshevsky et al. 2005). Progressive fiber organization may be responsible for the anisotropy increase observed in unmyelinated white matter tracts of rats and rabbits (Drobyshevsky et al. 2005). In the human brain, high anisotropy is observed in poorly myelinated axons of premature newborns, such as the corpus callosum (Partridge et al. 2004). However, the change in the water diffusion profile due to the patterns of axonal fibers occurs at infancy and is not further observed between 5 and 17 weeks after birth (Dubois et al. 2006).

The second stage of white matter development is related to the proliferation of glial cell and oligodendrocyte lineage precursors and cytoskeleton. Dubois et al. (2008) hypothesized that this may be linked to a decrease in water content of the brain and an increase in membrane density, leading to a reduction in water diffusivity (AD, RD, MD) as illustrated in the middle section of **Figure 1**. However, white matter development during this stage is relatively isotropic and hence has little influence on anisotropy.

The third stage is the last phase of axonal myelination, which corresponds to the ensheathment of oligodendroglial processes around the axons (Wozniak & Lim 2006). The maturation of white matter at this stage can be reflected by an increase of FA (as illustrated in the right section of **Figure 1**). Moreover, this stage is accompanied by a decrease in both membrane permeability and extracellular distance between membranes in the orthogonal direction to the fibers (Beaulieu 2002), which leads to a decrease in RD and MD.

WHITE MATTER DEVELOPMENT IN EARLY LIFE

The human brain develops rapidly during the final weeks of gestation and in the first two years following birth. The maturation of the white matter is asynchronous; it occurs from the second trimester of pregnancy to the end of adolescence and peaks during the first year of life. Postmortem studies suggest that the global pattern of the myelination progression sequence follows a caudorostral gradient and progresses from the center to the periphery (Brody et al. 1987, Dubois et al. 2014, Gilles et al. 1983, Kinney et al. 1988). White matter myelination occurs earlier and more quickly (*a*) in proximal pathways than in distal ones; (*b*) in sensory pathways (somatosensory, vision, audition) than in motor ones; (*c*) in central regions than in polar ones; (*d*) in the occipital pole than in the posterior parietal white

matter and in the temporal and frontal poles; and (*e*) in projection fibers than in association fibers. Guillery (2005) suggested that this asynchrony in the maturation sequence may be relevant to the hierarchy of connections between cortical areas: 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) that develop later.

Fetal Brain Development

Postmortem high-resolution (100 to 500 μm) DTI studies identified multiple neural structures during the fetal period (Huang et al. 2006, Kolasinski et al. 2013). At 19 to 20 postconceptual weeks, the Sylvian fissure and temporal lobe are visible. The cerebellum is not well developed, and a large portion of the cerebral hemisphere is occupied by the ventricle. The basal ganglia and hippocampus can be clearly identified at this early stage. Among major projection fibers, the core regions of the internal capsule and the cerebral peduncle are well developed (see **Figure 2*a*,*b***). The proportion of the anterior and posterior limb of the internal capsule indicates that the anterior region is more developed. However, the corona radiatae are not clearly visible in the fetal brain. Among limbic fibers, the two most dominant tracts, the cingulum and fornix, are already present at 19 gestational weeks (see **Figure 2*a*,*b***). For the fetal brain at 20 gestational weeks, the formation of the corpus callosum is more advanced in the frontal lobe (the genu of the corpus callosum) rather than the occipital lobe (the splenium of the corpus callosum). Among association fibers, the uncinate fasciculus can be clearly identified in the fetal brain (see **Figure 2*c*,*d***). The other association fiber bundles, including the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, external capsule, and superior longitudinal fasciculus, show poor development at the end of the second trimester (see **Figure 2*c*,*d***). During the period from 24 to 32 weeks of gestation, the major event is the development of the corona radiata from the transformation of the tangential fetal fiber-architectonic stratification. All major segments of the cerebral white matter can be recognized: corpus callosum, corona radiata, centrum semiovale, and gyral white matter (which is not yet fully developed). Fibers continue to grow at the levels of the periventricular crossroads and of the ventricular part of the corpus callosum. By term birth, all major fiber systems are in place (see the center columns of panels *a–d* in **Figure 2**).

Beyond major white matter tracts, high-resolution (~100 μm) ex vivo DTI and tractography can also characterize the pathways reflecting the pattern of diffusion coherence associated with the dorsopallial ventricular/subventricular zone and subpallial ganglionic eminence in the human fetal brain (Kolasinski et al. 2013, Miller et al. 2011). Radial coherence reflects pathways running across the cerebral mantle, perpendicular to the cortical surface, whereas tangential coherence reflects pathways running parallel to the ventricular or cortical surface (Kolasinski et al. 2013, Takahashi et al. 2012). During postconceptual weeks 19 to 22, the pathways running within the dorsopallial ventricular/subventricular zone initially run tangential to the ventricular/subventricular border and then turn to a radial trajectory coursing toward the cortical plate (Kolasinski et al. 2013). In contrast, the pathways running within the ganglionic eminence show a dominant directionality tangential to the cortical surface. A clear tangentio-radial transition emerges from the ganglionic eminence and yields

the pathways coursing radially through the cerebral mantle to the cortical plate. These DTI findings are well supported by histological data (Parnavelas et al. 2002, Ulfig et al. 2000, Yokota et al. 2007).

Infant Brain Development

The first few years of life represent a critical period during which cerebral growth and maturation (synaptogenesis and myelination) are intense (Gilmore et al. 2007, Provenzale et al. 2007). The cranial perimeter increases at 0.5 cm per week. As illustrated in **Figure 3**, a basic pattern of the maturation process can be indicated as an FA increase and an MD decrease with age in a posterior-to-anterior and central-to-peripheral direction of maturation (Cascio et al. 2007; Dubois et al. 2006, 2008; Lobel et al. 2009; Paus et al. 2001; Provenzale et al. 2007).

From in vivo DTI, MD in the more superior locations is higher and decreases more quickly with age than that in the more inferior regions in the corticofugal pathway (i.e., the superior corona radiata > the posterior limb of internal capsule > the cerebral peduncle), and MD in the more anterior regions is higher and decreases more quickly with age than that in the more posterior regions in the corona radiata (the anterior portion > the superior portion > the posterior portion). The gray matter, the limbic fibers (including the fornix, the stria terminalis, and the cingulum), and some of the association fibers (such as the uncinate fasciculus, the external capsule, and the inferior fronto-occipital fasciculus) show relatively slow decreases in MD and slow increases in FA (Oishi et al. 2011). Within projection fibers, fibers that are located distant from the brain stem, including the corona radiata, posterior thalamic radiation (Aeby et al. 2009, Dubois et al. 2006, Gilmore et al. 2007, Hermoye et al. 2006, Hüppi & Dubois 2006), and the sagittal striatum, show a higher MD at 40 weeks of postconceptual age and a faster MD decrease than those that are located close to the brain stem, such as the posterior limb of the internal capsule, the retrolenticular part of the internal capsule, and the cerebral peduncle (Oishi et al. 2011). The white matter rich in crossing fibers, such as the corona radiata and the anterior limb of the internal capsule, shows a lower FA at 40 weeks of postconceptual age and a slower FA increase than those with fewer crossing fibers, including the posterior limb of the internal capsule, the retrolenticular part of the internal capsule, the cerebral peduncle, the posterior thalamic radiation, and the sagittal striatum (Oishi et al. 2011). Within association fibers, the superiorly located structures, including the superior longitudinal fasciculus and the superior fronto-occipital fasciculus, show a higher MD at 40 weeks of postconceptual age and a faster MD decrease than inferiorly located structures, such as the external capsule, the inferior fronto-occipital fasciculus, and the uncinate (Oishi et al. 2011).

From above, the patterns seen in MD are not observed in the FA analysis, especially for the structures rich in crossing fibers, such as the corona radiata (Dubois et al. 2014, Oishi et al. 2011). This is because the white matter myelination is known to begin earlier in the commissural and projection fibers than in the association fibers and earlier in the occipital and temporal lobes than in the frontal lobe (Brody et al. 1987). In general, myelination is observed at birth in pons and cerebellar peduncles and is followed by the posterior limb of the internal capsule, splenium of the corpus callosum and optic radiation at approximately

age 3 months. The genu of the corpus callosum and anterior limb of internal capsule follow at approximately age 6 months (Dubois et al. 2008, Staudt et al. 2000).

However, the origins of water diffusion anisotropy in DTI are still debated (Beaulieu 2002) because it exists in premyelinating states (Hüppi et al. 1998, Prayer et al. 2001) or in nonmyelinated nerves (Beaulieu & Allen 1994, Song et al. 2002). Hence, an increase in FA with age not only may rely on myelination but also may result in an increase in the fiber's density and in the bundle's volume. Owing to the expression of the myelin sheath and the increasing number of oligodendrocytes, the overall water content is thought to be reduced and the extracellular space is decreased. The FA increase may also relate to the unmyelinated oligodendrocyte ensheathment around axons as seen in a brain study on the rabbit, suggesting that developmental changes in anisotropy coincide with proliferation of immature oligodendrocytes before myelination (Drobyshevsky et al. 2005). Moreover, intra-axonal macromolecules and functional ionic channels are thought to complicate diffusion through axons, resulting in more anisotropic diffusion (Barkovich 2000, Wimberger et al. 1995).

Infant Brain Networks

Beyond the characterization of tissue property, DTI in conjunction with graphic network analysis has been recently used to investigate structural networks of the infant brain. **Figure 4** shows the flow for examining the structural network using DTI. Yap et al. (2011) showed that the whole-brain structural network exhibited the small-worldness property (small-world network) in the first two years of life. An examination of a large sample of normal neonates additionally supported that each cerebral hemisphere also exhibited the small-worldness properties at the neonatal period (Ratnarajah et al. 2013). These findings suggest that even in very early postnatal life the brain favors locally dense communication and minimizes the number of long-distance connections within and across two hemispheres. This topological organization of the brain at a global level was observed in the whole-brain structural network of adults (Gong et al. 2009) and functional networks of children and adults (Supekar et al. 2009). These findings support the idea that the human brain has efficient neural architecture for maximizing the power of information processing from birth.

Moreover, an increase in global efficiency for the information transfer was shown in the first two years of life (Yap et al. 2011). This is parallel to the rapid development of myelination and the role of myelination in the impulse propagation speed along the fiber. Furthermore, the infant brain is organized into a number of internally densely connected subnetworks with sparser connections relating them to work as an organic whole. Interestingly, the precuneus was identified as a provincial hub with the vast majority of links within its subnetwork.

Structural network analysis also revealed the first evidence of asymmetry of structural connectivity in the neonatal brain (Ratnarajah et al. 2013). In neonates, small-world characteristics were exhibited but did not differ between the two cerebral hemispheres, suggesting that neighboring brain regions are tightly connected to one another and that one region is only a few paths away from any other region within each hemisphere. Moreover, the neonatal brain showed greater structural efficiency in the left hemisphere than in the right, suggesting that the brain regions in the left hemisphere interconnect in better

integration and segregation as compared to the right hemisphere. Furthermore, in neonates, brain regions, including the precentral gyrus, precuneus, fusiform, entorhinal cortex, and insula, which are known to be involved at later ages in motor, language, and memory functions, play crucial roles in efficient communications in the left hemisphere, whereas brain regions such as the gyrus rectus, cingulate, hippocampus, and putamen, which are involved in emotional processes, play crucial roles in efficient communications in the right hemisphere. Together, these findings suggest that even at birth, the topology of each cerebral hemisphere is organized in an efficient and compact manner. Lateralization of such organization may support specific lateralized brain functions at birth.

DIFFUSION TENSOR IMAGING APPLICATIONS IN INFANT RESEARCH

White Matter Development in Relation to Cognition in Infants

DTI has been widely used to assess brain abnormalities and their functional correlations in clinical samples. Efficient signal transmission allows for efficient information processing. The cognitive development and performance depend in part on the organizational integrity of white matter connections within the brain. Hence, research efforts have increased on the use of DTI to non-invasively characterize brain development and its functional correlates in healthy samples in early life and represent a burgeoning field with great promise in developmental cognitive neuroscience.

The white matter myelination progression sequence has been suggested to parallel language acquisition (Pujol et al. 2006, Su et al. 2008). In a cross-sectional study, Pujol et al. (2006) detailed quantitative assessment of the time course of myelination in the bilateral lateral perisylvian region between birth and age 39 months. Anterior and posterior regions of the bilateral lateral perisylvian cortex were assessed along with a nonlanguage, sensorimotor control region. The difference between the rates of myelination for language regions and for the control region was identified. The 50th percentile of myelination was achieved by 6 months of age for the control region but not until 18 months of age for both the anterior and the posterior language regions. The 90th percentile of myelination was achieved by age 8 months for the nonlanguage control region and age 35 months for the language regions. Vocabulary acquisition is accelerated after 18 months of age, once a rapid myelination phase is attained in the language regions.

In addition to language function, working memory emerges in infancy and plays a pivotal role in subsequent adaptive cognitive development. However, the neural networks important for the development of working memory during infancy are relatively unknown. Recently, Short et al. (2013) showed the first evidence that in 12-month-old infants visuospatial working memory performance correlated with DTI microstructural characteristics of white matter tracts connecting brain regions known to be involved in working memory, including the genu of the corpus callosum, anterior and superior thalamic radiations, anterior cingulum, and arcuate fasciculus. This relationship was independent of individual variations in age and developmental level (Short et al. 2013). Better working memory scores were associated with higher FA and lower RD values in these selected white matter tracts. Brain regions connected by these specific tracts are well known to support working memory in older children and adults (Courtney et al. 1997, Jonides et al. 1993, Klingberg 2006, Kwon

et al. 2002, Nagy et al. 2004). Therefore, the ability to characterize subtle individual differences in infant brain development assessed using DTI associated with complex cognitive functions holds promise for improving our understanding of normative development in neurocognitive periods of developmental plasticity.

The correlates of infant memory were recently investigated with DTI of the microstructural characteristics of white matter in 6-month-old infants. Microstructure variation in posterior aspects of the ventral visual pathway was associated with the speed at which the infant is able to process and encode information about the stimulus (Colombo & Mitchell 2009). A shorter look duration is thought to reflect faster acquisition of information about the habituated stimulus, whereas a longer look duration may be the most valid and reliable aspect of habituation with regard to both individual and developmental differences (Colombo et al. 1990). Moreover, FA values in the memory circuitry, including fornix, hippocampus, parahippocampus, and inferior temporal gyrus, predicted the performance of novelty preference in infants at 6 months of age. These findings are consistent with previous hypotheses that individual differences in performance on habituation and novel preference could reflect overall brain development and myelination as well as variation specific to the visual system, hippocampus, and supporting memory circuitry (Colombo et al. 1987).

Preterm Research

Prematurity is associated with a higher risk for neurodevelopmental impairments (Eikenes et al. 2011, Moore et al. 2013, Perenyi et al. 2013, Serenius et al. 2013) that appear to be related to early brain abnormalities. The most important brain abnormalities of prematurity are cerebral white matter injury (Volpe 2003) and periventricular leukomalacia (Woodward et al. 2006), which result in disrupted white matter maturation and chronic myelination disturbances (Volpe 2008). These brain alterations are better measured with DTI, whereby increased FA and decreased MD characterize white matter maturation (Berman et al. 2005). Indeed, brain abnormalities found with DTI appear to be normal with traditional MRI, such as T_1- or T_2-weighted MRI (Counsell et al. 2008). Hence, DTI has been widely used to describe and quantify the white matter maturation and myelination processes in preterm or at-term newborns (Hüppi et al. 1998, Miao et al. 2014, Padilla et al. 2014). DTI enhances our understanding of the encephalopathy of prematurity, which is heavily affected by preoligodendrocyte and axonal injury and aberrant white matter development.

Converging evidence suggests that preterm infants at term-equivalent age exhibit abnormalities in FA in the corpus callosum (Anjari et al. 2007, Hasegawa et al. 2011, Padilla et al. 2014, Thompson et al. 2011). Very preterm infants (≥23 and ≤33 weeks' gestational age) without apparent white matter lesions exhibit affected development of the posterior corpus callosum, depending on the degree of prematurity (Hasegawa et al. 2011, Thompson et al. 2011). Additionally, Anjari et al. (2007) and Thompson et al. (2011) reported lower FA values in the genu of the corpus callosum in preterm infants at term-equivalent age in comparison with term infants. We recently found that FA in the genu of the corpus callosum increases as a function of gestational age even in term infants (≥37 weeks' gestational age) (Leutscher-Broekman et al. 2014). However, the mechanism for such prematurity influences is unclear and may include the timing of exposure to the extrauterine environment. During

the second half of pregnancy, the organization and maturation of axonal pathways are highly vulnerable processes. Early exposure to the extrauterine environment could cause the maturation disruption of the corpus callosum, as late pregnancy is a critical period for the axonal growth of the corpus callosum, particularly at the genu and splenium.

The influences of prematurity on the corpus callosum perhaps can persist into late life, a hypothesis that is supported by evidence from studies on preterm children, adolescents, and adults (Eikenes et al. 2011, Feldman et al. 2012, Mullen et al. 2011, Nagy et al. 2003, Skranes et al. 2007, Vangberg et al. 2006, Yung et al. 2007). Possible explanations for the reduced anisotropy are increased membrane permeability, reduced axon density, and decreased fiber organization. These findings suggest that cerebral abnormalities seen in preterm infants may be irreversible.

The corpus callosum integrates sensory, motor, cognitive, and emotional functions from both hemispheres (Constable et al. 2008). In preterm infants, FA in both the genu and splenium of the corpus callosum was associated with the cognitive level assessed using developmental quotient (Wang et al. 2013). High MD values and short fiber lengths of the callosal splenium of preterm infants at term-equivalent age were associated with psychomotor delay at age 2 years (De Bruine et al. 2013). A positive association between FA in the corpus callosum and total IQ has been seen in children (Yung et al. 2007), adolescents (Narberhaus et al. 2007), and young adults born prematurely (Eikenes et al. 2011). These findings are consistent with evidence that the corpus callosum size is significantly correlated with gestational age, Wechsler Performance IQ, and memory performance in preterm children (Caldu et al. 2006). Abnormal corpus callosum volume has been associated with learning and behavioral difficulties, speech and language delays, and cognitive impairment as well as motor function and cerebral palsy in previous neuroimaging studies (Counsell et al. 2008, Mathew et al. 2013, Northam et al. 2012, Rademaker et al. 2004, Saksena et al. 2008). Higher MD in the splenium of the corpus callosum at birth was associated with poor outcome at 18 months as classified by the Mental Developmental Index of the Bayley Scales of Infant and Toddler Development (Takenouchi et al. 2010).

In addition to findings related to the corpus callosum, several studies also consistently identified abnormalities in the internal capsule in prematurity. Preterm infants at term age showed reduced anisotropy in the internal capsule compared to infants born at term (Dudink et al. 2007, Hüppi et al. 2001, Pogribna et al. 2013, Rose et al. 2009). It was recently shown that even in the normal range of gestation (37 to ~41 weeks), FA in the anterior limb of the internal capsule changes as a function of gestational age (Broekman et al. 2014). Anisotropy in the posterior limb of the internal capsule was found to be reduced in a group of 11-year-olds with a history of preterm birth (Nagy et al. 2003), suggesting persistence of prematurity-related white matter abnormalities into late life.

The internal capsule is visible in the second trimester of pregnancy using tractography in ex vivo DTI (Huang et al. 2006, 2009). Despite the fact that its fibers are not fully mature, the internal capsule still connects with extensions to the thalamus and basal ganglia (Knaap & Valk 1990). These tracts are involved in several neural circuits supporting basic brain functions at birth. For example, the internal capsule is a major cortico-subcortical white

matter bundle that contains fibers running from the thalamus to the basal ganglia as well as connecting the thalamus to the frontal lobe, which is responsible for regulation of sensorimotor functions. Low FA values and decreased fiber lengths of the posterior limb of the internal capsule at term-equivalent age are associated with psychomotor delay and cerebral palsy at the age of 2 years (De Bruine et al. 2013). Previous studies found the internal capsule to be vulnerable to brain damage (e.g., cerebral palsy) in the perinatal and early postnatal period (Hoon et al. 2009, Shinohara et al. 1976, Yoshida et al. 2010). Reduced MD in the posterior limb of the internal capsule at birth is associated with poor neuromotor outcome at follow-up (average of 12.9 months) (Hunt et al. 2004). The reduced anisotropy in the internal capsule signifies poorer connectivity and is associated with reduced motor skills in adolescents with a history of preterm birth (Vangberg et al. 2006).

Other white matter regions have been highlighted in preterm studies; however, findings are less consistent. Nevertheless, early differences in brain maturation have great clinical implications. The integrity of axons is important in mediating neurological functions. Deficits of the complex interneuronal connections can presage cognitive impairments. Increased diffusivity in the brain stem and cerebellum is associated with intraventricular hemorrhage (IVH) in prematurely born infants, which demonstrates that IVH is associated with cerebellar hypoplasia (Tam et al. 2011). Cerebellar integrity appears to be critical for learning to predict visual sensory consequences of motor commands (Izawa et al. 2012). Reduced FA and higher RD within the entire cerebellothalamo-cerebral pathway predict lower working memory, which is a novel contribution to the understanding of cerebral-cerebellar communication (Law et al. 2011).

TECHNICAL CONCERNS REGARDING IMAGING ACQUISITION

Advanced Diffusion-Weighted Magnetic Resonance Imaging

As discussed above, DTI is valuable for studying brain white matter development in children in early life. However, a major shortcoming of DTI is that it can reveal only one dominant fiber orientation at each location, yet between one-third and two-thirds of the voxels in the human brain white matter are thought to contain multiple fiber bundles crossing each other (Behrens et al. 2007). High-angular-resolution diffusion imaging (HARDI) (Tuch et al. 2002) addresses this well-known limitation of DTI. HARDI measures diffusion along *n* uniformly distributed directions on the sphere and can characterize more complex fiber geometries, where the acquired number of diffusion gradient directions is greater than that for DTI. Several reconstruction techniques can be used to characterize diffusion based on the HARDI signals. One method is based on higher-order tensors (Barmpoutis et al. 2009, Ghosh et al. 2008) and leverages prior work on DTI. Another method is Q-ball imaging, which uses the Funk-Radon transform to reconstruct an orientation distribution function (ODF). The model-free ODF is the angular profile of the diffusion probability density function of water molecules and has been approximated using different sets of basis functions such as spherical harmonics (Descoteaux et al. 2007, Frank 2002, Hess et al. 2006, Ozarslan & Mareci 2003). Such methods are relatively fast to implement because the ODF is computed analytically. By quantitatively comparing fiber orientations retrieved from ODFs against histological measurements, Leergaard et al. (2010)

showed that accurate fiber estimates can be obtained from HARDI data, further validating the use of HARDI in brain studies.

In contrast to DTI and HARDI, multishell diffusion-weighted imaging (mDWI) acquires data through the q-space at multiple b-values in order to more accurately reconstruct the ensemble average propagator (EAP). The EAP estimation using mDWI better characterizes more complex neural fiber geometries and non-Gaussian diffusion behavior when compared to single b-value techniques (Wu & Alexander 2007). Recently, new q-space imaging techniques, diffusion spectrum imaging (DSI) (Kuo et al. 2008, Tuch et al. 2001, Wedeen et al. 2005) and hybrid diffusion imaging (HYDI) (Wu & Alexander 2007), have been developed for estimating the EAP. HYDI is an mDWI technique that samples the diffusion signal along concentric spherical shells in the q-space. DSI and HYDI employ the fast Fourier transform to reconstruct the EAP. It has been demonstrated that DSI has the ability to resolve crossing fibers at the scale of a single MRI voxel and to identify long association tracts in the brain, including the superior longitudinal fasciculus subcomponents I, II, and III; the fronto-occipital fasciculus; the middle longitudinal fasciculus; the uncinate fasciculus; the extreme capsule; the arcuate fasciculus; the inferior longitudinal fasciculus; and the cingulum bundle (Schmahmann et al. 2007). These association tracts shown in DSI are largely consistent with those seen using autoradiographic histological tract tracing (Schmahmann et al. 2007). Wedeen et al. (2008) further demonstrated that DSI tractography accurately shows the known anatomic fiber crossings in the optic chiasm, centrum semiovale, and brain stem; fiber intersections in the cerebellar folia and the caudate nucleus; and radial fiber architecture in the cerebral cortex. However, none of these examples of fiber crossing and complex structure was identified using DTI analysis of the same data sets. These findings indicate that DSI is able to image crossing fibers in the brain (Wedeen et al. 2008); hence, DSI has the potential to cast new light on the organization of the human brain in the normal state.

Nevertheless, HARDI and mDWI have not been widely used in studying normal brain development in early life and neurodevelopmental disorders. This is mainly because of their required acquisition times, which may not be compatible with unsedated pediatric populations.

Recently, the human connectome project proposed an approach to reduce scan time by capitalizing on the simultaneous excitation of multiple brain slices and sharing diffusion preparation among all slices excited (Van Essen et al. 2012). This imaging approach is accomplished with multiple receivers and multiband excitations developed for functional MRI (Larkman et al. 2001, Moeller et al. 2010). Acquiring many slices during a single echo-planar echo train and a single contrast preparation period permits subsecond whole-brain coverage at 2- or 3-mm isotropic resolution and hence substantially reduces acquisition times for DW MRI. These advances will benefit diffusion data directly through higher data acquisition rates without serious losses in signal-to-noise ratio, and indirectly by reducing the total number of diffusion gradient pulses per whole-brain scan, which allows more time for gradient coil cooling when very high b-values are used. Accelerated imaging will enable the collection of many hundreds or even thousands of diffusion-encoded data points per voxel.

Beyond Diffusion-Weighted Magnetic Resonance Imaging

The MRI metrics derived from DTI, such as FA, AD, and RD, are informative but nonspecific. They reflect broad changes of tissue microstructure in the brain, which hence makes interpretation of the brain development in early life challenging. In the first 24 months after birth, the brain undergoes considerable changes, including synaptogenesis and myelination. However, water diffusion anisotropy exists prior to myelination (Hüppi et al. 1998, Prayer et al. 2001) or in non-myelinated nerves (Beaulieu & Allen 1994, Song et al. 2002). An increase in FA with age may rely on myelination or may result from an increase in the density of fibers and the volume of bundles. The overall water content can be reduced and the extracellular space can be decreased because of the expression of myelin sheath and the increasing number of oligodendrocytes. Moreover, intra-axonal macromolecules and functional ionic channels are thought to complicate diffusion through axons, resulting in more anisotropic diffusion (Barkovich 2000, Wimberger et al. 1995). Large FA and RD values are noted in nonmyelinated nerves from an ex vivo study (Beaulieu 2002) and in the frontal lobe regions of one-week-old infants (Dubois et al. 2008), where myelin is not yet present in the postmortem brain tissue (Provenzale et al. 2007). Thus, these DTI measures more likely characterize the local fiber architectural milieu (fiber coherence, density, size, and myelination); therefore, caution should be taken when ascribing observed changes to any specific microstructural alterations.

Recently, several MRI techniques, including magnetization transfer (MT) imaging (Vavasour et al. 2011, Wolff & Balaban 1989), T_1 and T_2 relaxometry (Bartzokis et al. 2010, Glasser & Van Essen 2011, Van Essen et al. 2012), and multicomponent relaxometry (Deoni et al. 2008, 2012; Kroeker & Henkelman 1986; Menon et al. 1991; Whittall et al. 1997), have been developed to provide a more specific measure of myelin content. MT is an MRI technique that examines the interaction between mobile protons in water and motionally restricted nonaqueous protons, and it has been proposed as a marker for myelin in the brain tissue. MT utilizes the exchange of magnetization between mobile and motionally restricted protons through chemical processes and diffusion to obtain information about the nonaqueous proton pool. The magnetization transfer ratio (MTR) reflects the interaction between the motionally restricted and mobile proton pools: A decrease in the immobile proton pool, an increase in the mobile pool, or both processes occurring simultaneously may cause a decrease in MTR. The MTR is significantly correlated with myelin examined in the postmortem tissue (Schmierer et al. 2004). Myelin contributes to the motionally restricted proton pool, and a loss of myelin consequently leads to a reduction of MTR. Hence, changes in the MTR in the brain tissue have been often attributed to changes in myelin content (Armstrong et al. 2004, Chen et al. 2005, Giacomini et al. 2009).

Converging evidence has suggested that the longitudinal (T_1) and transverse (T_2) relaxation times are sensitive to the arrival of myelin precursor proteins and the establishment of the myelin sheath. The relaxation times are also sensitive to changes in bulk water content and compartmentalization related to axonal fiber density and size, iron content, membrane permeability, and cholesterol content (MacKay et al. 2009). Sigalovsky et al. (2006) found an increased R_1 signal (the inverse of T_1) in the posterior medial Heschl's gyrus, which reflects the high myelin content of primary auditory cortex. Yoshiura et al. (2000) reported

that Heschl's gyrus has a lower intensity in the T_2-weighted image than does the superior or middle temporal gyri. These findings suggest that the myelin content of a cortical area covaries with the intensity of the T_1- and T_2-weighted (T_1w and T_2w) images, but in opposite directions. Glasser & Van Essen (2011) computed the ratio of T_1w/T_2w image intensities, termed myelin map, to eliminate the MR-related image intensity bias and enhance the contrast-to-noise ratio for myelin. The spatial gradient of the myelin map provides sharp transitions in myelin content across the cortical surface, which has excellent agreement with the gradients of published probabilistic cytoarchitectonically defined cortical areas.

A multicomponent relaxometry technique is multicomponent analysis of T_1 and T_2 relaxation, which quantifies the myelin-bound water signal, termed the myelin water fraction (MWF). The MWF has been suggested as a surrogate measure of myelin content and is strongly correlated with histological assessment (Laule et al. 2006). Moreover, MWF has been shown to have greater myelin specificity than diffusion anisotropy has (Madler et al. 2008). Deoni et al. (2011, 2012) have demonstrated the application of multicomponent relaxometry to the study of infant brain development. **Figure 5** shows the MWF, T_1, and T_2 maps from the age of 3 months to 60 months. **Figure 6** illustrates the MWF values in major white matter tracts and lobes. Both figures show asynchrony of white matter maturation in early life. The pattern of white matter maturation shown in MWF has demonstrated strong correlations with postmortem myelin-staining techniques (Laule et al. 2006, 2008) but not necessarily to DTI metrics of white matter, such as FA, AD, and RD (Kolind et al. 2008, Madler et al. 2008).

An emerging multicomponent relaxometry technique, multicomponent-driven equilibrium single-pulse observation of T_1 and T_2 (mcDESPOT), offers potential advantages over conventional multicomponent relaxometry approaches, namely decreased acquisition times, increased volumetric coverage (i.e., whole brain), and improved spatial resolution. The mcDESPOT myelin water fraction measures, denoted as myelin volume fraction (VF_M), have shown consistency with MWF values but are larger than MWF. The mcDESPOT technique replicated the pattern of myelination histologically observed by Flechsig (1920) as well as the in vivo findings (Deoni et al. 2011, 2012). This work has shown a nonlinear developmental trajectory of VF_M from infancy to childhood, which follows an approximate log-growth pattern. Recently, O'Muircheartaigh et al. (2014) employed the mcDESPOT technique and investigated associations of white matter myelination with early cognition with infants and toddlers. The white matter myelination underlying frontal and temporal cortices showed significant relationships to expressive and receptive language abilities. These relationships had a significant interaction with age, with VF_M becoming more strongly associated with language skills with age. These data provide evidence that a changing coupling exists between developing myelin and cognitive development.

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Glossary

T_1	the longitudinal relaxation time that is required to regain longitudinal magnetization following a radio frequency pulse
T_2	the transverse relaxation time that measures how long the resonating protons remain coherent or precess in phase following a 90° radio frequency pulse
Myelination	the process in which glial cells produce an insulating myelin that wraps around nerve axons
Diffusion tensor imaging (DTI)	an imaging technique that is thought to reflect fiber density, axonal diameter, and myelination in white matter
Diffusion-weighted imaging (DWI)	technique that provides image contrast that is dependent on the molecular motion of water
Projection fibers	fibers that connect the cortex with lower sensory or motor centers, such as the thalamus, brain stem, and spinal cord
Small-world network	a highly efficient and clustered graph with nodes that are not neighbors of each other but can reach from one to another by a small number of steps
Global efficiency	a measure of the overall capacity for parallel information transfer and integrated processing

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SUMMARY POINTS

1. Diffusion tensor imaging characterizes the ellipsoidal shape of the water diffusion profile in the brain tissue using a symmetric positive-definite tensor field derived from diffusion-weighted images.
2. Fractional anisotropy and water diffusivity can be derived from diffusion tensor imaging and used to characterize different stages of white matter development in early life.
3. A basic pattern of the maturation process of white matter can be indicated as a fractional anisotropy (FA) increase and a mean diffusivity (MD) decrease with age in a posterior-to-anterior and central-to-peripheral direction of maturation.
4. The white matter myelination is known to begin earlier in the commissural and projection fibers than in the association fibers, and earlier in the occipital and temporal lobes than in the frontal lobe.
5. The brain in early life exhibits small-world characteristics, but they do not differ between the two cerebral hemispheres, which suggests that neighboring brain regions tightly connect to each other and that within each hemisphere, one region is only a few paths away from any other region.
6. The neonatal brain shows greater structural efficiency in the left hemisphere than in the right, which suggests that the brain regions in the left hemisphere interconnect in better integration and segregation compared with the right hemisphere.
7. Preterm infants at term-equivalent age exhibited abnormalities in FA in multiple brain regions, but most consistently in the corpus callosum. This prematurity influence on the corpus callosum may persist into late life.
8. The DTI measures likely characterize the local fiber architectural milieu (fiber coherence, density, size, and myelination), and therefore caution should be taken when ascribing observed alterations to any specific microstructural changes.

FUTURE ISSUES

1. What is the pattern of cortical myelination development in early life?
2. What is the relationship between cortical folding development and white matter myelination?
3. To what extent can we understand the cognitive development of infants from the point of view of white matter myelination as well as structural connectivity?
4. How will we remedy the lack of longitudinal DTI studies that investigate the long-term impact of premature birth on white matter development and its relationship with cognition?
5. What future imaging technique will be used for characterizing brain myelination?

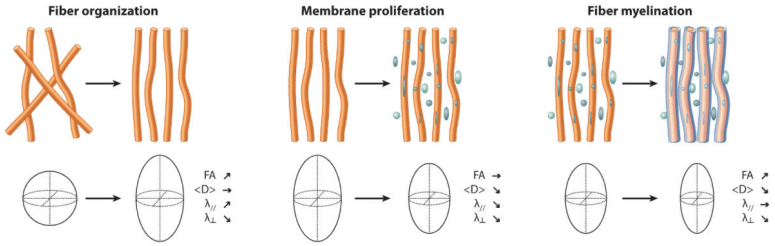

Figure 1.

The hypothesized relationship between maturational processes and diffusion indices in white matter. Abbreviations: FA, fractional anisotropy; >D<, mean diffusivity; $\lambda_{//}$, axial diffusivity; $\lambda_{\perp}$, radial diffusivity. Adapted with permission from Dubois et al. (2008).

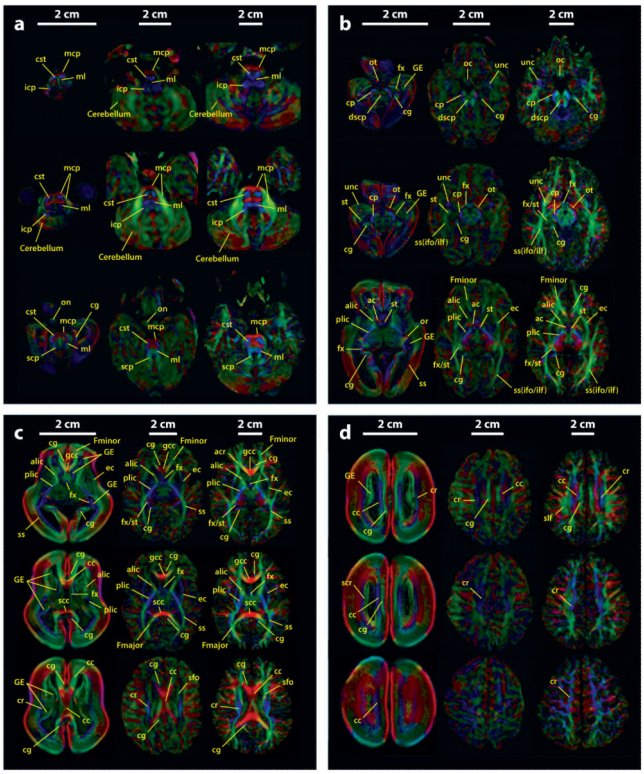

Figure 2.

Panels *a* and *b*, respectively, show axial images of 19-gestational-week fetal (*left*), 0-year (*center*), and 5-year (*right*) brains at the levels of the brain stem and midbrain. Panels *c* and *d*, respectively, show axial images of 20-gestational-week fetal (*left*), 0-year (*center*), and 5-year (*right*) brains at the levels of the corpus callosum and the superior corona radiata. Abbreviations: ac, anterior commissure; acr, anterior corona radiate; alic, anterior limb of internal capsule; cc, corpus callosum; cg, cingulum; cr, corona radiata; cst, cortical spinal tract; dscp, decussation of superior cerebellar peduncle; ec, external capsule; Fmajor, forceps major; Fminor, forceps minor; fx, fornix; gcc, genu of corpus callosum; GE, ganglionic eminence; icp, inferior cerebellar peduncle; ifo, inferior fronto-occipital peduncle; ilf, inferior longitudinal fasciculus; mcp, middle cerebellar peduncle; ml, medial lemniscus; oc, optical chiasm; on, optical nerve; or, optical radiation; ot, optical tract; plic, posterior limb of internal capsule; scc, splenium of corpus callosum; scp, superior cerebellar peduncle; scr, superior region of corona radiata; sfo, superior fronto-occipital fasciculus; ss, sagittal stratum; st, stria terminalis; unc, uncinate fasciculus. Adapted with permission from Huang et al. (2006).

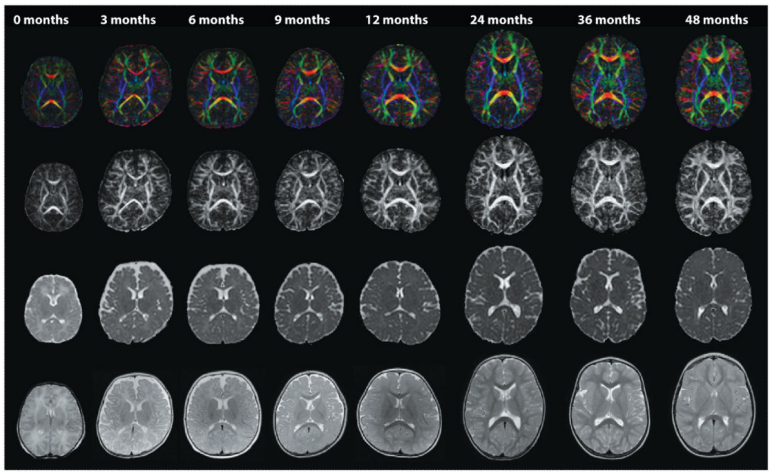

Figure 3.

Axial images of children at age of 0, 3, 6, 9, 12, 24, 36, and 48 months. Rows show (*top to bottom*) color maps, fractional anisotropy, mean diffusivity, and T_2-weighted images. Figure adapted with permission from Hermoye et al. (2006).

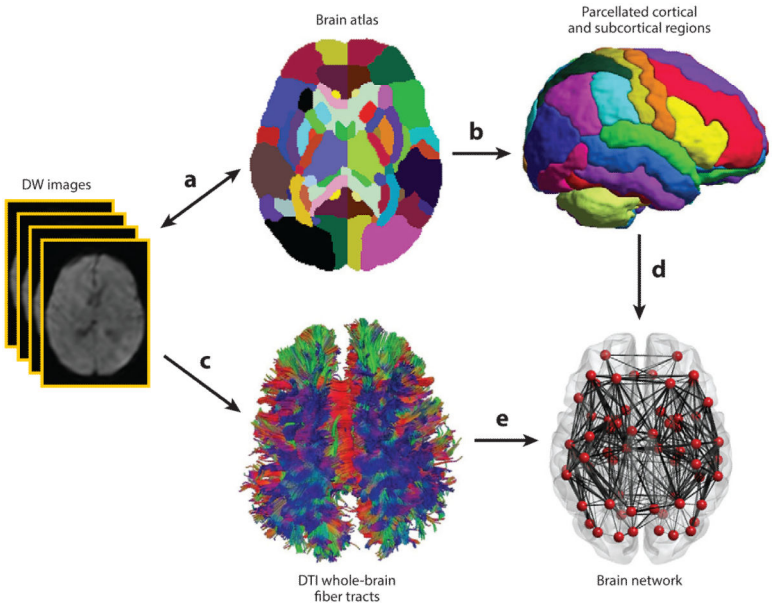

Figure 4.

The major processes involved in structural network analysis using diffusion tensor imaging (DTI). (*a*) Diffusion-weighted (DW) images of each subject are aligned to those of the brain atlas. (*b*) The parcellation of cortical and subcortical regions using the brain atlas. (*c*) The whole-brain tractography using DTI deterministic tractography. (*d*) Nodes (*red spheres*) representing cortical and subcortical regions. (e) Weighted edges (*black lines*) obtained using the tract information. Figure adapted with permission from Ratnarajah et al. (2013).

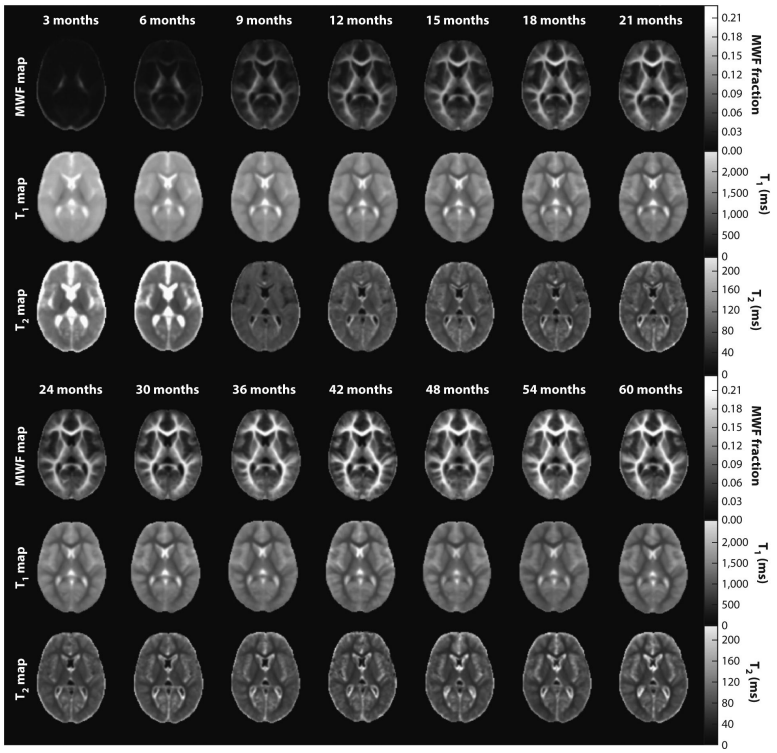

Figure 5.

The mean myelin water fraction (MWF), T_1, and T_2 maps from seven age groups are respectively shown from the top to bottom rows. Note that T_2 was only calculated in voxels with a corresponding T_1 less than 3,500 ms for ages 9 months and above. Figure adapted with permission from Deoni et al. (2012).

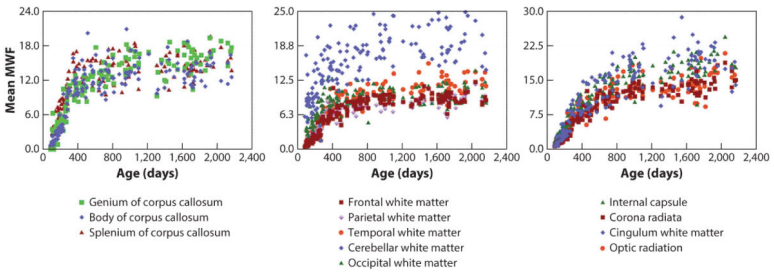

Figure 6.

Scatter plots of the mean myelin water fraction (MWF) at ages 0 days to 2,400 days. Figure adapted with permission from Deoni et al. (2012).