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One diffusion acquisition and different white matter models: How does microstructure change in human early development based on WMTI and NODDI?

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Abstract

White matter microstructural changes during the first three years of healthy brain development are characterized using two different models developed for limited clinical diffusion data: White Matter Tract Integrity (WMTI) metrics from diffusional kurtosis imaging (DKI) and Neurite Orientation Dispersion and Density Imaging (NODDI). Both models reveal a non-linear increase in intra-axonal water fraction and in tortuosity of the extra-axonal space as a function of age, in the genu and splenium of corpus callosum and the posterior limb of the internal capsule. The changes are consistent with expected behavior related to myelination and asynchrony of fiber development. The intra- and extracellular axial diffusivities as estimated with WMTI do not change appreciably in normal brain development. The quantitative differences in parameter estimates between models are examined and explained in the light of each model's assumptions and consequent biases, as highlighted in simulations. Finally, we discuss the feasibility of a model with fewer assumptions.

Keywords

diffusion MRI; white matter; brain development; DKI; modeling; microstructure

1. Introduction

MRI has established itself as an excellent tool for the *in vivo* study of pathologies affecting the white matter (WM), such as multiple sclerosis (Young et al., 1981), or processes such as normal brain development (Holland et al., 1986). However, the typical resolution of an MR image is on the order of millimeters, while the characteristic length scales in neural tissues are on the order of microns. Diffusion MRI (dMRI) is therefore the method of choice to

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probe microstructure, because it is sensitive to the micron-scale displacement of water molecules, and is therefore strongly affected by the number, orientation and permeability of barriers (e.g. myelin) and the presence of various cell types and organelles (e.g. neurons, dendrites, axons, neurofilaments and microtubules) in living tissue (Beaulieu, 2002). In particular, dMRI can detect microstructural changes in the white matter related to myelination and demyelination, pruning, axonal loss, and has, for this reason, become particularly useful for assessing damage in white matter pathologies (Horsfield and Jones, 2002).

The human brain development in infancy and early childhood is another excellent example of microstructural changes that can be detected with dMRI. So far, these changes have been documented in detail using diffusion tensor imaging (DTI), currently the most widespread clinical dMRI method (Basser and Pierpaoli, 1996). Multiple DTI studies reported large non-linear increases in fractional anisotropy (FA), and decreases in diffusivities, respectively, during the first two years of life, consistent with the development and establishment of new axonal pathways and myelination of the fiber bundles; the expected asynchrony of maturation between different brain regions has also been observed using these metrics (Dubois et al., 2006; Hermoye et al., 2006; Mukherjee et al., 2002). Recently, the changes from birth up to 4.7 years were also documented with diffusional kurtosis imaging (DKI) (Paydar et al., 2014), a method which extends conventional DTI by estimating the kurtosis of the water diffusion displacement probability distribution (Jensen et al., 2005; Lu et al., 2006). This initial DKI study of development confirmed previous DTI reports, while highlighting that the patterns of change in mean kurtosis did not follow exactly those of FA, thus potentially complementing information from DTI metrics.

While diffusion MRI is very sensitive to microscopic changes, the metrics derived from the diffusion and kurtosis tensors lack structural specificity. Because the MR resolution does not permit the direct visualization of cellular-scale structures, an additional modeling step is therefore required in order to link the diffusion-weighted MR signals to physical quantities characterizing the tissue, such as intra/extra-cellular diffusivities, intra/extra-cellular volume fraction, typical axon diameter or cell size, neurite orientation dispersion (i.e. a measure of the neurites' orientation distribution relative to the principal fiber tract direction), etc. In the past few years, several models for white or gray matter addressing this issue have been proposed (Alexander et al., 2010; Assaf and Basser, 2005; Assaf et al., 2008; Fieremans et al., 2011; Fieremans et al., 2010; Jespersen et al., 2007; Stanisz et al., 1997; Zhang et al., 2012). Recently, two of these multi-compartment models — NODDI (Neurite Orientation Dispersion and Density Imaging) (Zhang et al., 2012), and a simplified version of CHARMED (Composite Hindered And Restricted Model of Diffusion) (Assaf and Basser, 2005), dubbed CHARMED-light — have been applied to diffusion data in newborns and have identified differences between main fibers in terms of intra-axonal water fraction and axon dispersion in agreement with expected classification and maturation (Kunz et al., 2014).

In this work, we analyze microstructural changes in major white matter tracts in infants aged 0 to 3 years old using two different biophysical models: White Matter Tract Integrity metrics (WMTI) from DKI (Fieremans et al., 2011) and NODDI. A more detailed description of the

parameters and assumptions of each model is provided in the Theory section. The acquisition time is particularly constraining when performing studies on newborns and infants. These two models are well suited as they typically only require diffusion data comprising 2 shells and 30–60 directions per shell, which can be acquired in five minutes or less on a clinical scanner, depending on other sequence parameters.

Our main objective is to highlight white matter structural changes in children aged 0 to 3 years, with improved specificity relative to DTI and DKI metrics. The existence of some *a priori* knowledge on the expected trend of model parameters with early age also enables a comparative assessment of the performance and limitations of the two models used. Next, simulations are employed to validate the discrepancies observed experimentally, as well as to evaluate the feasibility of a model that makes fewer assumptions.

2. Theory

Both WMTI and NODDI start from a common framework: the intra-axonal space (IAS) is modeled as a collection of cylinders with effective zero radius (the so-called “sticks” (Assaf and Basser, 2005; Behrens et al., 2003; Kroenke et al., 2004)), and the extra-axonal space (EAS) as a connected space where diffusion is anisotropic yet Gaussian. The “sticks” are impermeable, meaning exchange between the IAS and the EAS is neglected. The water MR signal has two contributions: water within the collective IAS and water in the EAS. The contribution of water inside the myelin is not included in either model since its MR signal decays too rapidly to be detected with the typical clinical dMRI parameters. From this perspective, it should be noted that the compartment fractions correspond to “measurable water” fractions and not to voxel volume fractions. This distinction is important since myelin takes up a non negligible volume of a white matter voxel (up to 40% in adult corpus callosum (Lamantia and Rakic, 1990)). NODDI further complements this description with a third compartment of Gaussian isotropic diffusion, capturing contribution from the cerebrospinal fluid (CSF), whereas WMTI neglects it. Figure 1 provides a schematic of the relevant parameters of this framework. Its full characterization is challenging, and therefore NODDI and WMTI each make further different simplifying assumptions in order to proceed, as discussed here in detail.

2.1 WMTI

WMTI is a model that relates DKI metrics directly to WM microstructure (Fieremans et al., 2011; Fieremans et al., 2010). While initially derived under the hypothesis of perfect axon alignment (Fieremans et al., 2010), it was later argued that, for clinically relevant diffusion times, both the EAS and the IAS can be modeled as Gaussian compartments, with effective parameters corresponding to the long time limit (“tortuosity limit”), whereby the non-Gaussian contribution from the IAS could be approximately neglected for a coplanar fiber dispersion of up to 30° (Fieremans et al., 2011). It should be noted that the angular spread of major white matter tracts such as corpus callosum is estimated at approximately 18° from histology and from diffusion spectroscopy of *N*-acetylaspartate (Ronen et al., 2013).

The WM model metrics are calculated based on the following relationships:

$$f_{\text{intra}} = \frac{K_{\text{max}}}{K_{\text{max}} + 3}, D_{e,n} = D_n \left[1 + \sqrt{\frac{K_n \cdot f_{\text{intra}}}{3(1-f_{\text{intra}})}} \right], D_{a,n} = D_n \left[1 - \sqrt{\frac{K_n(1-f_{\text{intra}})}{3 \cdot f_{\text{intra}}}} \right] \quad (1)$$

where K_{max} is the maximum kurtosis over *all* possible directions, and D_n , K_n , $D_{e,n}$, $D_{a,n}$ are, respectively, the overall diffusivity, kurtosis, extra-axonal diffusivity and intra-axonal diffusivity in a given diffusion direction $\mathbf{n}$. It should be noted that the signs in front of the square roots in Eq. (1) are based on the underlying assumption that $D_{a,n} < D_{e,n}$ (Fieremans et al., 2011). Equations in (1) are valid in any direction $\mathbf{n}$, so by choosing 6 or more independent directions, the compartmental diffusion tensors, $\hat{D}_a$ and $\hat{D}_e$, can be reconstructed. The apparent radial $D_{e,\perp}$ and axial $D_{e,\parallel}$ diffusivities of the connected extracellular compartment are then derived from the eigenvalues $D_{e,1}$, $D_{e,2}$, $D_{e,3}$ of $\hat{D}_e$ as $D_{e,\parallel} = D_{e,1}$ and $D_{e,\perp} = (D_{e,2} + D_{e,3})/2$. The intra-axonal space is not a connected compartment, thus apparent diffusivities are meaningless. Instead, the axial diffusivity along each axon is approximately estimated as the trace of the intra-axonal diffusion tensor: $D_a = \text{Tr}(\hat{D}_a)$.

WMTI therefore provides an estimate of intra-axonal water fraction f_{intra} , intra-axonal parallel diffusivity D_a , and extra-axonal axial and radial apparent diffusivities, $D_{e,\parallel}$ and $D_{e,\perp}$, respectively. Recent work has shown very good correlations between these metrics and histological measurements in cuprizone-induced demyelination (Falangola et al., 2014). Some estimation of the dispersion is also possible from the three eigenvalues of the IAS diffusion tensor (as $\langle \cos^2 \psi \rangle = D_{a,1}/\text{Tr}(\hat{D}_a)$), but WMTI is inherently expected to become invalid in the case of high fiber dispersion, as it neglects the kurtosis of the IAS. WMTI parameters and notations are collected in Table 1.

2.2 NODDI

NODDI was introduced in (Zhang et al., 2012). Briefly, the tissue is separated into three compartments: restricted intra-cellular, hindered extra-cellular and isotropic CSF, with the following conventions:

$$S/S_0 = (1-f_{\text{iso}}) \cdot (f_{\text{ic}} \cdot A_{\text{ic}} + (1-f_{\text{ic}}) \cdot A_{\text{ec}}) + f_{\text{iso}} \cdot A_{\text{iso}} \quad (2)$$

NODDI assumes neurites to be perfectly aligned locally, forming coherent domains (fiber tract segments or sub-bundles), and focuses on the orientation distribution of these domains in each voxel. It models these orientations by an axially-symmetric Watson distribution, characterized by a concentration parameter κ . Small values of κ correspond to large fiber dispersion (e.g. gray matter) and large values of κ to highly aligned axons (e.g. white matter tracts). NODDI is therefore designed to be applicable over the whole brain. The Watson distribution can be taken as a reasonable representation of fiber orientation dispersion in the white matter, in the light of electron microscopy tracking of individual axons in the mouse corpus callosum (Mikula et al., 2012). The main focus of NODDI is, in contrast to WMTI, the estimation of the parameter κ characterizing the dispersion of the fiber sub-bundles. On the flip side, both local intra- and extracellular diffusivities parallel to each sub-bundle are set equal to each other and fixed to a plausible value $D_a = D'_{e,\parallel} = D'_{\parallel}$ ($1.7 \mu\text{m}^2/\text{ms}$ in adults

and $2 \mu\text{m}^2/\text{ms}$ in newborns (Kunz et al., 2014; Zhang et al., 2012)). For disambiguation, extracellular diffusivities designated with a “prime” symbol refer to local diffusivities within a sub-bundle, and extracellular diffusivities without a “prime” symbol refer to apparent diffusivities over the entire voxel (see Figure 1). The local radial diffusivity of the EAS (i.e. perpendicular to the sub-bundle) is derived from a tortuosity model (Szafer et al., 1995):

$$D'_{e,\perp} = D'_{e,\parallel} \cdot (1 - f_{ic}). \quad (3)$$

Lastly, the diffusivity of the CSF is fixed to $3 \mu\text{m}^2/\text{ms}$. NODDI therefore provides an estimate of geometric parameters only: the intra-axonal water fraction f_{ic} , the isotropic water fraction f_{iso} , the concentration parameter of the Watson distribution κ , and the angles defining the mean orientation of the fiber distribution (θ , ϕ). Hence, the main limitation of NODDI is the absence of any direct diffusivity estimation, as well as a potential bias in other parameters due to fixing of the diffusivities. NODDI parameters and their conceptual comparison to WMTI ones are also described in Table 1.

2.3 Validity of model assumptions

The assumptions made in both WMTI and NODDI may be too oversimplifying, which could lead not only to reduced information about the microstructure, but also to a bias in the estimated parameters.

As WMTI neglects kurtosis in the IAS as well as higher order cumulants, the accuracy of the estimated parameters will progressively degrade with higher orientation dispersion. For instance, in the case of imperfect fiber alignment, the quantity $K_{\max}/(K_{\max} + 3)$ becomes a lower bound for f_{intra} . WMTI is therefore essentially suited for estimating microstructural parameters in highly aligned fiber bundles in the white matter (e.g. corpus callosum and cortico-spinal tract).

Since there is still no consensus yet as to whether the diffusivity of the IAS is higher than, lower than, or equal to that of the EAS (Benveniste et al., 1992; Duong et al., 1998; Jespersen et al., 2010), both WMTI's assumption on that matter ($D_a = D_{e,\parallel}$) and NODDI's ($D_a = D'_{e,\parallel}$) may be invalid.

In the particular case of NODDI, the fixing of axial diffusivities to an *a priori* value is an even stronger, and likely problematic assumption. Indeed, both in the IAS and the EAS, some biological variability is expected depending on the white matter region, stage of development and/or pathology. That variability would be interesting to capture, especially if it can be used as a biomarker — such as in stroke (Hui et al., 2012). Similarly, in the radial direction, Equation (3) imposes a one-to-one relationship between $D'_{e,\perp}$ and f_{ic} (since $D'_{e,\parallel}$ is fixed) which prevents a potential separation of trends between these two quantities, while this differentiation could distinguish between changes in axonal density and changes in myelin thickness (Novikov and Fieremans, 2012). There are also two other issues associated with the applicability of Equation (3). For one, in the tortuosity model used (effectively Archie's law), the ratio $D'_{e,\perp}/D'_{e,\parallel}$ is assumed equal to the volume fraction of extracellular space in the tissue. In the presence of myelin, this EAS fraction is expressed as

$\frac{g^2(1-f_{ic})}{f_{ic}+g^2(1-f_{ic})}$, where g is the g -ratio of the internal to external axonal diameter, rather than $(1-f_{ic})$, as assumed in (Zhang et al., 2012). Second, this tortuosity model (Equation (3)) has been shown to break down for tight packings, where the tortuosity strongly depends on the packing arrangement, not just on the overall volume fraction, and is therefore most likely not valid when looking at the main white matter tracts where axons are very dense (Fieremans et al., 2008; Novikov and Fieremans, 2012).

In this work, we attempt to explain quantitative differences observed experimentally between the two models in terms of the impact of the above-mentioned assumptions on parameter bias. We also provide an assessment of this bias through simulations.

After pointing out the potential limitations of each model, mainly related to their simplifying assumptions, the natural question that follows is whether, given the same acquired data, we can afford fewer model assumptions. For that purpose, we “release” the diffusivity values in the fitting procedure of NODDI, thus leading to a model dubbed “NODDIDA” (Neurite Orientation Dispersion and Density Imaging with Diffusivities Assessment), in which the signal is modeled as:

$$S=S_0[f_{intra} \cdot A_{ic}+(1-f_{intra}) \cdot A_{ec}] \quad (4)$$

Here, the tissue description is the same as in NODDI, except that the CSF compartment is neglected. Based on the taxonomy of models described in (Ferizi et al., 2013), NODDIDA is closest to the “Zeppelin.Watson” category, meaning the extracellular space is a Gaussian compartment with independent axial and radial diffusivities and the intracellular compartment follows a Watson distribution of sub-bundles. However, none of the models described in (Ferizi et al., 2013) allowed for independent axial diffusivities between the intra- and extracellular spaces. On the contrary, in NODDIDA, all three diffusivities (D_a , $D'_{e,\parallel}$, $D'_{e,\perp}$) are independent from each other. NODDIDA therefore fits six parameters: f_{intra} , D_a , $D'_{e,\parallel}$, $D'_{e,\perp}$, κ and S_0 ; the angles defining the main orientation of the fiber tract are determined beforehand from the diagonalization of the diffusion tensor. Table 1 explicitly relates this model to NODDI and WMTI. The practical applicability of NODDIDA is tested on synthetic MR data.

3. Materials and Methods

3.1 Data acquisition and processing

3.1.1 Subjects—An Institutional Review Board approved retrospective review was performed on brain MRIs in 55 pediatric subjects who underwent DKI imaging as part of a routine MRI exam under sedation at NYU School of Medicine from June 2009 to October 2010. The subjects ranged from 1 day to 2 years and 9 months in age, and all underwent brain MR imaging for non-neurological indications. Premature infants as well as subjects who had medical histories with possibly related intracranial/neurological manifestations (e.g. seizures or delayed myelination) were excluded from this study. All the included exams

were interpreted as normal by fellowship-trained board-certified neuroradiologists, and were reevaluated by a board-certified pediatric neuroradiologist for normalcy prior to inclusion.

3.1.2 MR acquisition—All subjects were scanned on a 1.5 T Avanto Siemens MR scanner (Siemens Medical Solutions, Erlangen, Germany) using a body coil for excitation and 8-channel head coil for reception. Whole brain diffusion weighted data were acquired using twice refocused spin-echo, single shot echo planar imaging along 30 diffusion gradient encoding directions and 3 b-values (0, 10000, 2000 s/mm²). The dataset is sufficient for WMTI, since kurtosis tensor estimation requires 3 b-values and at least 15 directions. While the optimal protocol recommended for NODDI consists in $b = 711$ s/mm², 30 directions and $b = 2855$ s/mm², 60 directions (Zhang et al., 2012), recent work has shown that the more standard protocol utilized here yields comparable performance (Wang et al., 2014). Other parameters included: TR/TE: 4500/96 ms, matrix size: 82×82; 28–34 slices (no gap); voxel size of $2.2\text{--}2.7 \times 2.2\text{--}2.7 \times 4\text{--}5$ mm³, 1 average, acquisition time: approximately 5 min. Datasets with an in-plane resolution of 2.2–2.3 mm were limited to six cases, all other 49 having an in-plane resolution of 2.6–2.7 mm. The ratio of datasets with a slice thickness of 4 or 5 mm was 50/50, and the slice thickness was not a function of age, but randomly distributed across the cohort. The SNR in the b=0 images was between 40 and 50 in 90% of cases.

3.1.3 Image pre-processing, DTI/DKI fitting and ROI selection—An in-house developed pipeline written in Matlab (MathWorks, Natick, MA, USA) was used for noise level estimation in each voxel (Veraart et al., 2013a), motion and eddy current correction (Ben-Amitay et al., 2012). The images were skull-stripped and a mask for CSF exclusion based on signal intensity in the b=0 image was created. Smoothing was applied on each slice using a Gaussian kernel (FWHM = 1.25 voxel size), but stopping at the border indicated by the CSF-excluding mask. This procedure minimizes the CSF contamination from smoothing close to the ventricles, while still reducing Gibbs ringing. Smoothing was applied to b=0 and b=1000 images only, so as not to alter the properties of the Rician noise distribution in the b=2000 images (Veraart et al., 2013b).

Diffusion and kurtosis tensors were estimated in each voxel using a constrained weighted linear least-squares algorithm (Veraart et al., 2013b) and maps of typical DTI/DKI metrics were calculated.

Three regions of interest (ROIs) consisting of highly aligned WM bundles (i.e. the genu and splenium of the corpus callosum (CC), as well as the posterior limb of the internal capsule (PLIC)) were drawn on the FA map for each subject. ROI drawing was performed by three investigators (A. P., H. S., J. N.). In order to ensure consistency of ROI drawing throughout the age range for a given structure, each of these investigators was assigned to draw a given anatomical structure for all the subjects. To further control for inter-observer variability, all ROIs were later carefully reviewed by a single board-certified pediatric neuroradiologist (S. M.).

3.1.4 Extraction of microstructure parameters from WMTI and NODDI—In each voxel of the three ROIs, the signal was fit using two different procedures, detailed below, to extract the parameters of interest from each model.

WMTI: The WMTI parameters were calculated from the diffusion and kurtosis tensors previously estimated, as indicated in Equation (1).

NODDI: The signal was fit using the NODDI toolbox (Zhang, 2013) and a two-step fitting procedure: first a grid search to find a reasonable starting point for the optimization, followed by a gradient descent to determine the maximum likelihood of the parameters (Zhang et al., 2012). The grid search consisted in all combinations of the following values: $f_{ic} = [0.2:0.1:0.8]$; $f_{iso} = [0.0; 0.1; 0.2; 0.4; 0.6]$; $\kappa = [2; 5; 10; 20; 30; 40; 50; 64]$. The axial diffusivities both in the IAS and EAS were fixed to a value of $2 \mu\text{m}^2/\text{ms}$, same as done on newborns in (Kunz et al., 2014).

The mean and standard error of the parameters of interest (f_{intra} , f_{iso} , $\langle \cos^2 \psi \rangle$, D_a , $D_{e,\parallel}$ and $D_{e,\perp}$) estimated from WMTI and NODDI were calculated over each ROI and each subject. For a given ROI, the mean value of a parameter P was correlated with subject age X . Three potential correlation relationships were tested: a non-linear relationship of the form $P = a \cdot e^{-bX} + c$, a linear relationship and a constant. To improve the reliability of the non-linear relationship estimation, results from three “older” subjects (ages 3.3, 3.6 and 4.6 years) who had undergone the same scanning protocol were included; indeed, since changes are still ongoing at age 3, later time points are necessary for asymptote estimation. The best relationship was selected based on the corrected Akaike information criterion (cAIC) (Hurvich and Tsai, 1989) between linear and non-linear, as well as significance of the non-linear and linear relationships compared to a constant one ($p < 0.05$). Tortuosity was calculated as $\alpha = D_{e,\parallel}/D_{e,\perp}$ for WMTI and $\alpha = D'_{e,\parallel}/D'_{e,\perp}$ for NODDI, and fit to the non-linear model specified above.

The two white matter models were compared in terms of parameter trend with age and correlations of absolute estimated values. Where applicable, differences in characteristics (e.g. tortuosity, orientation dispersion, etc) between the three white matter tracts were tested for significance using a paired t-test, based on NODDI and WMTI results separately. Only significant differences are reported in the Results. Although the reported p -values are not corrected for multiple ROI comparisons (effectively they should be multiplied by a factor 3 to account for the combinations of taking 2 ROIs out of 3), they would remain statistically significant after correction as well.

3.2 Simulations

MR signal was computed based on the signal equation of the most “complete” model, i.e. a Watson distribution of “sticks”, with independent diffusivities (axonal D_a , and local extra-axonal $D'_{e,\parallel}$ and $D'_{e,\perp}$), and the existence of a CSF compartment (see Figure 1). Four sets of ground truths were generated, summarized in Table 2. At the level of diffusion and kurtosis tensors, all four combinations are equivalent, with very similar values for typical tensor metrics, chosen to correspond to measurements in the splenium and genu of infants aged 0 to 3 years (see Table 3 and Results section). However, at the level of model parameters, the

four combinations describe tissues with completely different properties. Set #1 is a case where WMTI assumptions are perfectly met: parallel fibers, $D_a = D_{e,\parallel}$ and no CSF compartment. Set #2 is a case where NODDI assumptions are perfectly met: $D_a = D'_{e,\parallel}$, relatively high dispersion and a CSF compartment. More general sets #3 and #4 likely represent biologically plausible cases, with some difference in diffusivities, a dispersion in agreement with histological data on corpus callosum (Ronen et al., 2013), and some CSF contamination (for Set #4).

The signal was simulated for the same MR protocol as used experimentally: $b = 1000$ s/mm², 30 directions; $b = 2000$ s/mm², 30 directions; one $b = 0$. Rician noise was added to the simulated signal, assuming a signal-to-noise ratio (SNR) of 50, consistent with the SNR estimate in the $b=0$ images of the pediatric data. Five hundred noise realizations were generated to obtain an estimate of parameter precision.

The two models at stake (WMTI and NODDI) were applied to obtain parameter estimates, as described in the ‘Data acquisition and processing’ sub-section. In the case of NODDI, for each set of ground truth, the axial diffusivity (common to IAS and EAS) was fixed to the weighted average $D_a \cdot f_{ic} + D'_{e,\parallel} \cdot (1 - f_{ic})$ of the true parameters.

The performance of the NODDIDA model was evaluated on Set #3, which was deemed more realistic than #1 and #2 and excluded, as a start, the potential confounding effects of CSF. The synthetic signal was fit to NODDIDA using a Levenberg-Marquardt algorithm with box constraints (Lourakis, 2004). The latter algorithm showed better performance on noiseless data than the default active-set algorithm in the NODDI toolbox. The starting point for the algorithm was the ground truth itself. NODDIDA estimates were produced for 2500 noise realizations.

4. Results

4.1 Development data

Changes in DTI and DKI metrics with age and development have been reported elsewhere on this pool of children (Paydar et al., 2014). Briefly, Figure 2 shows quantitative maps of DTI and DKI metrics in a 9 day old male and in a 323 day old male. Superimposed on the FA map are the three ROIs considered in this model analysis: genu of CC, splenium of CC and PLIC. Table 3 provides mean values of typical DTI/DKI metrics in each of these ROIs, across the 55 subjects. These values guided the choice of ground truths in the simulations (see Table 2).

4.1.1 Changes of model parameters in early development (Figs. 3–5)—Figures 3, 4 and 5 present results from NODDI and WMTI for the genu, splenium and PLIC, respectively, showing the following characteristics:

- Axonal water fraction: Both models reveal an increase in f_{intra} over the first three years of life, in all three ROIs considered. The best trend to describe this increase was found to be an exponential. The parameters characterizing this trend are collected in Table 4. Both WMTI and NODDI show a consistent asynchrony, with

f_{intra} increasing most rapidly in PLIC, followed by splenium and lastly genu. For a given ROI, the values of the time constant show good agreement between models as well. By age 3, the splenium is projected to have the highest intra-axonal water fraction, followed by genu and PLIC. This order was also consistent between models.

- CSF compartment fraction: Estimated by NODDI alone, the fraction did not change appreciably with age in the splenium (11% on average) and in the genu (5% on average). It was found to increase in PLIC from 0 to 3%. The overall values of f_{iso} are consistent with the localization of each ROI with respect to the ventricles. The increase of f_{iso} in PLIC is surprising, since this ROI is far from CSF and cannot be affected by larger ventricle size with age. Overall, the inter-subject and intra-subject variability of f_{iso} for a given ROI is fairly large.
- Orientation dispersion: Mean estimates of $\langle \cos^2 \psi \rangle$ over all 55 subjects are provided in Table 5. Both models rank splenium as the most aligned bundle, followed by genu and PLIC. Over the entire age range (0 to 3 years), $\langle \cos^2 \psi \rangle$ was indeed found to be significantly higher in splenium compared to both genu and PLIC ($p < 0.005$), and in genu compared to PLIC ($p < 0.001$), regardless of the model. Interestingly, NODDI does not display any trend in dispersion with age. WMTI shows an increase in alignment with age in all three ROIs, best described by the exponential model. The asymptote is reached within 6–12 months for PLIC and splenium, while the change is on-going at 3 years for genu.
- Parallel diffusivity in the IAS: NODDI provides no information since D_a is fixed to $2 \mu\text{m}^2/\text{ms}$. WMTI shows D_a to remain constant in splenium and genu and decrease slightly in PLIC.
- Axial diffusivity in the EAS: with NODDI, $D_{e,\parallel}$ is a function of $D'_{e,\parallel}$ ($\equiv 2 \mu\text{m}^2/\text{ms}$), $\langle \cos^2 \psi \rangle$ and f_{ic} (see Table 1) and thus appears to slightly decrease as f_{ic} increases. On the contrary, with WMTI, $D_{e,\parallel}$ is shown to increase with age in the splenium (+13%), while remaining constant in the genu and PLIC.
- Radial diffusivity in the EAS: $D_{e,\perp}$ is shown to decrease with age in all three ROIs, regardless of the model used. It should be noted that, in NODDI, $D_{e,\perp}$ and f_{intra} are related and the change in $D_{e,\perp}$ with age effectively mirrors that in f_{intra} (because $\langle \cos^2 \psi \rangle$ and f_{iso} are not found to change significantly). For WMTI, from age 0 to 3 years, the decrease in $D_{e,\perp}$ was most pronounced in the genu (−46%), followed by splenium (−40%) and PLIC (−15%).
- Tortuosity α : It was found to increase with age in all three ROIs and for both models. The trend with age was fit to an exponential model and the parameters characterizing this trend are collected in Table 4. By age 3, the splenium is projected to be the most tortuous tract, followed by genu and PLIC. This order was consistent between models. Quantitatively, for subjects aged 1 to 3, NODDI showed α to be significantly higher in splenium compared to both genu and PLIC ($p < 0.001$), while WMTI showed α to be significantly higher in both splenium and genu vs. PLIC ($p < 10^{-8}$). WMTI and NODDI show the same consistent asynchrony

as for f_{intra} : changes occur most rapidly in the PLIC, followed by splenium and genu. The time constants are perhaps not very reliable for the genu, since the asymptote is hardly reached at 3 years. For splenium and PLIC however, it is noteworthy that NODDI outputs — as expected — very similar rates of change for f_{intra} and α , while WMTI produces significantly different rates for these two parameters.

4.1.2 Model comparison (Figs. 3–6)—In spite of a relative agreement between the models in terms of parameter trends with age, the actual quantitative values output can vary quite significantly between the two. As observed in Figs. 3–5, WMTI produced highly distinct estimates of D_a and $D_{e,\parallel}$ (the latter approximately twice the former), while in NODDI, the combination of the assumption $D_a = D'_{e,\parallel}$ and a very subtle dispersion ($\langle \cos^2 \psi \rangle \approx 1$) led to $D_a \approx D_{e,\parallel}$. As a result, tortuosity estimates were higher with WMTI than with NODDI (+35% in the genu, +15% in the PLIC and +11% in the splenium).

Figure 6 shows correlation plots for f_{intra} , $\langle \cos^2 \psi \rangle$ and $D_{e,\perp}$ as estimated by WMTI and NODDI. The main following trends were observed:

- The correlation between f_{intra} values is very high but a systematic trend is noticeable: $f_{\text{intra}}(\text{NODDI}) > f_{\text{intra}}(\text{WMTI})$.
- The correlation between models for $\langle \cos^2 \psi \rangle$ is poorer than for f_{intra} . WMTI outputs higher dispersion than NODDI (except in the PLIC).
- The quantitative agreement over $D_{e,\perp}$ is overall very good.

4.2 Simulations

Simulation results are plotted in Figure 7. In Set #1 (fully parallel fibers and an axial diffusivity higher in the EAS than in the IAS, Fig. 1a), WMTI performs very well in the noiseless case and the impact of finite SNR is mainly in the underestimation of $\langle \cos^2 \psi \rangle$ by 8%. WMTI is found to maintain good performance in the presence of some dispersion (Sets #3 and #4) and some CSF (Set #4) as long as $D_a < D_{e,\parallel}$. All estimated parameters are within 10% of the ground truth for SNR=50. The performance of WMTI breaks down when the ground truth corresponds to the assumptions of NODDI: equal local axial diffusivities in the IAS and EAS and high dispersion (Set #2). In this case, D_a is largely underestimated (−57%) and $D_{e,\parallel}$ overestimated (+30%), likely because of the underlying assumption $D_a < D_{e,\parallel}$. This bias is accompanied by an underestimation of the dispersion (error on $\langle \cos^2 \psi \rangle$ of +30%) and of f_{intra} (−30%). In all four sets, the estimates of WMTI are very precise, thanks to the robustness of the weighted linear least squares fitting procedure of the diffusion and kurtosis tensors.

In parallel, NODDI performs very well for a ground truth that matches its underlying assumptions (Set #2), with a bias on all parameter estimates within 8% for SNR=50, while breaking down in Sets #1, #3 and #4, where the artificial use of an equal axial diffusivity between IAS and EAS (although favorably chosen as the weighted average of the true values of D_a and $D'_{e,\parallel}$ for each set) causes substantial error in other model parameters: dispersion is overemphasized ($\langle \cos^2 \psi \rangle$ underestimated by 14–19%), while f_{intra} is

overestimated by 34–53%, and the CSF compartment by 5–6 points. Like WMTI, NODDI provides a very robust fit that produces very precise estimates. It is noteworthy that the CSF fraction is the least precise one, outputting values up to 0.12 for a real fraction of 0, and between 0.05 and 0.20 for a real fraction of 0.08–0.12.

To a large extent, the behavior of the two models highlighted in simulations matches the experimental observations from the development data. Both in simulations and experiment:

- The best agreement between models is found for $D_{e,\perp}$. Importantly, simulations show that $D_{e,\perp}$ is also the parameter that is most reliably estimated both in terms of accuracy and precision. This result is quite encouraging as $D_{e,\perp}$ is thought to be specifically sensitive to myelination.
- NODDI systematically gives a higher estimate of f_{intra} than WMTI.
- WMTI produces highly distinct estimates of D_a and $D_{e,\parallel}$, while NODDI's are very similar (because of the initial assumption $D_a = D'_{e,\parallel}$ for each sub-bundle, and the fairly moderate dispersion).
- The parameter with poorest precision in NODDI is f_{iso} .

One parameter for which the behavior somewhat differs between experiments and simulations is $\langle \cos^2 \psi \rangle$. In simulations, WMTI is shown to output more aligned configurations than NODDI. Experimentally, WMTI outputs less aligned configurations than NODDI in genu and splenium. One possible explanation could be the use of a perfect axial symmetry (via the Watson distribution) as a ground truth in the simulations, while asymmetry in the real data could significantly modify the eigenvalues of $\hat{D}_a$ and thus $\langle \cos^2 \psi \rangle$.

The estimates for Set #3 using NODDIDA are collected in Table 6. Because NODDIDA fits for all the parameters of the model instead of fixing a subset of them, the fit robustness is deteriorated compared to NODDI. Thus, three of the five model parameters — f_{intra} , D_a , and κ — have very poor precision. Figure 8 provides a further glimpse into the behavior of NODDIDA. The scatter plots reveal that the estimates of these three parameters are also largely correlated. We will come back to these observations in the Discussion section.

5. Discussion

The main objective of this work was to study the changes in WM microstructure during the first 3 years of life, using two different biophysical models based on clinically acquired diffusion data. The discussion will focus on three aspects. First, we assess the changes occurring in three highly coherent white matter tracts (genu, splenium and PLIC) during the first three years of life as obtained from each of the two models and compare to expected trends from previous literature; we also discuss potential limitations of the current study. Second, we discuss differences between the two models in the light of experimental quantitative discrepancies and of simulation results. Finally, we touch on the possibility of releasing model assumptions in clinical data.

5.1 Early changes in major white matter tracts

Our fit results based on experimental data show that the trends of evolution from age 0 to 3 years are overall unaffected by the choice of model (NODDI or WMTI). Importantly, the ranking of the three ROIs in terms of increase in both f_{intra} (intra-axonal water fraction) and tortuosity of the extra-cellular space is consistent between models: the changes are fastest in PLIC, followed by splenium and finally genu. Similarly, both models found the splenium to be the most aligned and tortuous bundle, followed by genu and PLIC. The latter quantitative differences were statistically significant. The trends are consistent with the developmental neuroscience tenet that white matter maturation (i.e., myelination and pruning) proceeds in an inferior-to-superior and posterior-to-anterior manner reflecting associated functions: primary sensory regions develop before areas mediating higher order executive processes (Colby et al., 2011; Kemper, 1994; Yakovlev and Lecours, 1967).

In both models, the intra-axonal water fraction and the tortuosity increase dramatically from age 0 to 3 years, and the rates of increase show the PLIC to be the fastest one changing and the first one to plateau, followed by the splenium, and finally by the genu. These results are consistent with a rapid increase in FA and MK measured in the early years of life (Paydar et al., 2014). The changes in intra-axonal water fraction and tortuosity likely result from active myelination, via the reduction of the extra-axonal space, and not from an increase in number of axons. Indeed, there is evidence that in humans the number of axons in the CC is already at its maximum in the newborn, and that this number is effectively reduced after birth by pruning, a process by which redundant or aberrant circuits are removed (Kostović and Jovanov-Milošević, 2006). On the other hand, myelination is a later process in WM development, which peaks in the first post-natal year and continues to the end of adolescence. Importantly, fiber myelination is asynchronous and, for our three ROIs, happens in the following order: the PLIC is among the first fibers to myelinate, showing mature myelin already at birth, followed by the CC splenium (mature myelin between first and third post-natal months) and by the genu (mature myelin from the 6th month) (Dubois et al., 2013). Given that the PLIC and splenium relay motor and somatosensory fibers to the occipital, parietal and temporal lobes and that the genu interhemispherically connects the cognitive prefrontal and orbitofrontal regions, the order of development indicated by the rates of change of intra-axonal water fraction and tortuosity in the three ROIs matches the expected chronology of myelination (Colby et al., 2011; Kemper, 1994; Yakovlev and Lecours, 1967).

As mentioned previously, for splenium and PLIC, WMTI estimated different rates for axonal water fraction and tortuosity, suggesting myelination does not impact these two parameters in a parallel fashion. WMTI could thus disentangle between changes in axonal density and in myelination. Previous Monte Carlo simulation work indeed suggested that, in the event of either demyelination or axonal loss, the relation between tortuosity and f_{intra} is highly nonlinear and depends on the details of axonal packing within a bundle (Fieremans et al., 2012; Novikov and Fieremans, 2012). This feature has recently been used to highlight the vulnerability of late-myelinating versus early-myelinating tracts in Alzheimer's Disease (Benitez et al., 2013; Fieremans et al., 2013).

The increase in tortuosity is largely due to a decrease in $D_{e,\perp}$. In the case of WMTI, the relative decrease in $D_{e,\perp}$ between age 0 and 3 years was most pronounced in the genu, followed by splenium and PLIC. This is consistent with PLIC having engaged its myelination already pre-birth, whereas genu and splenium start it at birth while rapidly reaching high levels (they are among the most myelinated tracts). Interestingly, while myelination tends to increase f_{intra} and decrease $D_{e,\perp}$, pruning would have the opposite effect. While both processes are thought to occur in the time period studied here, it is clear that the impact of myelination dominates the overall trend.

Contrary to NODDI, WMTI allows to estimate the intra- and extra-axonal diffusivities. By definition, D_a and $D_{e,\parallel}$ should not be sensitive to myelination, but rather be specific markers for the intracellular and extracellular diffusion, respectively. Our results show very little change in these parameters with age, as would be expected in normal development. The fact that these compartment diffusivities do not change appreciably, whereas the overall axial diffusivity (weighted by f_{intra}) systematically decreases in early development (Dubois et al., 2013), suggest that WMTI may effectively disentangle between the IAS and EAS. Due to their consistency in control subjects, D_a and $D_{e,\parallel}$ as estimated from WMTI have the potential to become sensitive biomarkers of pathology for the intra- and extra-axonal spaces, as has previously been shown in stroke (Hui et al., 2012). The decrease in overall axial diffusivity on the other hand raises the question of the actual value of IAS and EAS axial diffusivity fixed in the NODDI model; in this work the choice was made of keeping it consistent throughout subjects and brain regions ($D_a = D'_{e,\parallel} = 2 \mu\text{m}^2/\text{ms}$) but one could also argue that this value should be set lower in the 2–3 year old range. This underlines once more how arbitrary the choice of diffusivity in NODDI is, trying to account for age, regional variability or pathology.

Regarding fiber dispersion, both models show the splenium to be the most aligned and tortuous tract, followed by genu and PLIC. This is consistent with previous DTI inferences from FA measurements. The angular spread of the splenium estimated from NODDI is in excellent agreement with estimates from diffusion spectroscopy of *N*-acetylaspartate (18.6°) and histology (18.1°) in the human corpus callosum (Ronen et al., 2013). The measured dispersion validates a posteriori the use of WMTI in splenium and genu; PLIC is perhaps at the border of WMTI validity. While NODDI showed all three tracts to maintain comparable dispersion throughout early life, WMTI displayed slightly increased alignment with age in all three ROIs. This increased fiber coherence could be the result of pruning, especially when paired with an increase in $D_{e,\parallel}$ in the case of splenium. While an increased $D_{e,\parallel}$ could also result from larger ventricles with age, hence more partial volume from CSF, particular care was taken to minimize CSF contamination in the processing, and no increase in f_{iso} with age was picked up by NODDI in the splenium.

5.2 Limitations of the current model-based development study

One potential limitation of the current analysis is its retrospective nature. However, the diffusion protocol employed ($b=1000$ and 2000 s/mm^2 , 30 directions each) is close to optimal both for WMTI and NODDI models. Longitudinal information on the neurologic development of the subjects would have also been useful, but in practice it is extremely

difficult to obtain. The variation in spatial resolution between datasets caused some variability in SNR. However, the Rician bias was accounted for in the NODDI fitting procedure, and was found to be insignificant in the DKI fitting procedure (by comparing the current weighted linear least-squares algorithm with a conditional least-squares algorithm (Veraart et al., 2013a)). Moreover, because the difference in spatial resolution between the datasets was uncorrelated with the subject age, it is highly unlikely that these differences affected the trend of parameters with age highlighted in this study.

Another potential confounding factor is the overall increase in head size and in white matter tracts during the age period studied. However, if it is accepted that the number of axons does not vary dramatically after birth in the structures considered here (and if anything, it decreases through pruning), then the change in overall tract volume is likely attributable to myelination.

While hand-drawn ROIs are no longer the norm, with most studies turning to group-averaged atlas-based approaches, in the particular case of the developing brain the former was preferred due to the rapidly changing size and contrast of white matter structures in this age range. Furthermore, while ROI drawing by three independent investigators may have introduced some degree of inter-observer variability, the potential investigator-related bias was constant through the age range for a given ROI; additionally, no definite discrepancy was identified in their drawing techniques upon final overall inspection by a single pediatric neuroradiologist.

In order to guarantee the applicability of the both WMTI and NODDI to the data, this study was limited to three highly coherent white matter tracts: the genu, the splenium and the PLIC. It would be of great interest and value to assess microstructural changes with age in other white matter tracts throughout the brain.

5.3 Sources of discrepancy between WMTI and NODDI

The overall agreement of trends with age between models, as well as with literature reports on early white matter fiber development, suggests that the simple picture of representing WM geometry as a collection of narrow impermeable tubes embedded in the extra-axonal space captures the most essential part of the dMRI signal. However, the quantitative mismatch between the estimated parameters raises a flag concerning the different supplemental assumptions underlying NODDI and WMTI, which may translate into different biases in the parameters estimated by each model. One of the most remarkable features is the disagreement in axial diffusivities as fixed by NODDI and fit by WMTI, for all three ROIs. Interestingly also, the different time course of change in f_{intra} vs. tortuosity highlighted by WMTI (but absent from NODDI by design) could suggest that myelination does not impact these two quantities in a parallel fashion, which also questions the use of the low-density (mean field) tortuosity approximation in NODDI for such tight axonal packings.

The differences in behavior between WMTI and NODDI were further tested in simulations and the features that stood out were overall in excellent agreement with those observed in the development data: disagreement in axial diffusivities between models, higher estimate of f_{intra} by NODDI, best agreement between models for $D_{e,\perp}$.

The advantage of simulations is that characteristic behaviors of the models can be inferred. For instance, if the ground truth corresponds to highly aligned fibers and unequal intra- and extra-axonal diffusivities, the experimentally measured non-zero kurtosis in the parallel direction ($AK \sim 0.4$) would have to be explained in NODDI by artificially introducing higher orientation dispersion and/or the presence of a CSF compartment, since the intra- and extra-axonal diffusivities are set equal by design. Our simulations indeed show that, in such cases (Sets #1, #3 and #4), NODDI produces non-negligible overestimation of fiber dispersion. The reliability of f_{iso} also appears questionable, since a non-zero estimate can reflect either an existing CSF compartment or a bias from fixing the axial diffusivity values: this translated into larger uncertainty for this parameter compared to the others, both in experiments and simulations. WMTI, on the other hand, considers only two compartments and therefore explains the experimentally measured non-zero axial kurtosis by different diffusivities in each compartment. Also, the approximation of the IAS by a Gaussian anisotropic compartment is expected to break down in case of high fiber dispersion, where the simulations show an overestimation of the degree of fiber alignment, as well as bias in the diffusivity estimates. Experimentally, these two very different behaviors of NODDI and WMTI are best illustrated in the PLIC, which has the poorest overall agreement in parameters, and where it is yet unclear whether the orientation dispersion is exaggerated by NODDI to account for non-zero axial kurtosis under the hypothesis of equal axial diffusivities and very small CSF compartment, or the PLIC lies at the border of WMTI applicability and thus WMTI parameters are biased.

Overall, the main source of difference between the two models, as well as of potential bias and uncertainty seems to be related to axial diffusivities. This problem is not unexpected, being related to a general issue of estimating parameters of multiexponential models when the diffusion weighting is relatively weak technically, within the convergence radius of the corresponding cumulant expansion (Kiselev and Il'yasov, 2007). Naturally, such estimates are much more reliable in the transverse direction, where one of the diffusivities is fixed (e.g. to zero in the perfectly aligned limit), leading to a more robust fit of $D_{e,\perp}$.

5.4 Relaxing model assumptions

A model such as NODDIDA, with all parameters released, seems very appealing by avoiding any artificial assumptions aside from postulating the axially symmetric Watson distribution and neglecting the CSF compartment. However, with the current limited diffusion acquisition, simulations (Fig. 8) demonstrated that all the relevant parameters of this model cannot be reliably untangled using nonlinear fitting, and the reduction in model assumptions comes at the cost of degraded precision and artifactual parameter correlations. This behavior could be explained by the existence of a particularly shallow direction in parameter space, precluding the fitting algorithm from finding the true global minimum in the presence of even limited noise. In this context, a proper fit would therefore require some regularization, which has not been designed yet.

One can thus question how much information can be unambiguously extracted from a diffusion acquisition of 2 shells with moderate b-values and with 30 directions per shell. In these clinically feasible acquisitions, it currently seems impossible to disentangle between

effects of dispersion and of difference in axial diffusivities between the IAS and EAS. Table 2 already gave a good indication of this apparent degeneracy in the parameter estimation, since very similar DKI metrics (and in particular AK) could be generated from very different combinations of dispersion and diffusivities. The acquisition of a more advanced dataset (particularly higher-b shells, beyond the convergence radius of the cumulant expansion) could potentially improve the fit robustness of NODDIDA and give access to all of the model parameters at once. This of course will come at the expense of acquisition time, reducing clinical applicability, but such approaches have been shown as promising in more dedicated studies (Jespersen et al., 2010; Jespersen et al., 2007).

6. Conclusion

White matter models such as WMTI or NODDI come with the promise of more specific biomarkers for developmental and pathological changes, compared to empirical metrics based on DTI or DKI. They have the potential to disentangle between the IAS and EAS and therefore specifically assess (de)myelination, axonal damage/loss, change in orientation dispersion, etc, and thus improve our understanding and follow-up of development, ageing and pathology. In the current work, we report changes in the intra-axonal water fraction, fiber alignment and compartment diffusivities during the first three years of normal brain development, as estimated using WMTI and NODDI. Most trends are qualitatively independent of the white matter model used and in full agreement with expected on-going myelination (large non-linear increase in f_{intra} and tortuosity with age), fiber classification (splenium is the most aligned and tortuous fiber, followed by genu and PLIC), and asynchrony of development (PLIC engaged its myelination pre-birth and the evolution of its parameters levels off most rapidly, followed by splenium and genu). The quantitative estimates, however, are model-dependent, exhibiting biases and limitations related to the models' assumptions: with limited diffusion data, accuracy is sacrificed in favor of precision. The “ultimate WM model” — with an optimum reached between precision and constraints — is yet to be developed. For that, one would need to reach a deeper physical intuition as to which biophysical parameters affect the dMRI signal most, and thereby can be robustly quantified.

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Abbreviations

AD	Axial Diffusivity
AK	Axial Kurtosis
CC	Corpus Callosum

CSF	Cerebrospinal Fluid
dMRI	Diffusion MRI
DKI	Diffusional Kurtosis Imaging
DTI	Diffusion Tensor Imaging
EAS	Extra-Axonal Space
FA	Fractional Anisotropy
FWHM	Full Width at Half-Maximum
IAS	Intra-Axonal Space
MD	Mean Diffusivity
MK	Mean Kurtosis
NODDI	Neurite Orientation Dispersion and Density Imaging
NODDIDA	Neurite Orientation Dispersion and Density Imaging with Diffusivities Assessment
PLIC	Posterior Limb of the Internal Capsule
RD	Radial Diffusivity
RK	Radial Kurtosis
ROI	Region Of Interest
WM	White Matter
WMTI	White Matter Tract Integrity Metrics

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Figure 1.

Schematic of the general white matter fiber model. The meaning of each compartment fraction is color-coded; the entire voxel is designated by a black square contour. Fiber sub-bundles have a given orientation distribution about the main bundle axis (vertical axis in the Figure). The local diffusivities within each sub-bundle are denoted as D_a , $D'_{e,||}$ and $D'_{e,⊥}$. Apparent diffusivities $D_{e,||}$ and $D_{e,⊥}$ for the EAS in the whole voxel are a function of local ones, f_{ic} and of the orientation distribution of the sub-bundles. For clarity of presentation, the myelin sheaths are not represented in the schematic.

Figure 2.

Parametric maps of main DTI/DKI metrics in an axial brain slice from a 9 day old male (top) and a 323 day old male (bottom). The color scalebar is from 0 to 3 $\mu\text{m}^2/\text{ms}$ for diffusivities, 0 to 1 for FA, and 0 to 3 for kurtoses. Overlaid on the FA map are the three ROIs considered for model analysis: genu (red), splenium (green) and PLIC (blue).

Figure 3.

White matter parameter evolution with age in the genu of the CC. Both models highlight a continued increase in intra-axonal water fraction and tortuosity which do not plateau in the first 3 years of life, a trend consistent with on-going myelination. WMTI displays a trend of increase in fiber alignment, which could be a manifestation of continued pruning in the first year of life, while NODDI does not. While the axial diffusivities are set very similar in the NODDI model, they are fit to distinct values by WMTI, with $D_a < D_{e,\parallel}$. Errorbars represent standard error on the parameter across the ROI. The errorbars for the tortuosity were omitted in favor of legibility. The dashed lines are the best fit found for the parameter change with age (between a choice of constant, linear or exponential).

Figure 4.

White matter parameter evolution with age in the splenium of the CC. Trends are very similar to those observed in the genu (see Fig. 3), with a more rapid increase in intra-axonal water fraction in the first year of life, consistent with earlier myelination in the splenium vs. the genu. WMTI displays a trend of increase in fiber alignment and in axial diffusivity of the EAS, which could be an indicator of pruning. Errorbars represent standard error on the parameter across the ROI. The dashed lines are the best fit found for the parameter change with age (between a choice of constant, linear or exponential).

Figure 5.

White matter parameter evolution with age in the PLIC. Compared to genu and splenium, the increase in intra-axonal water fraction is greatest in the first year of life, after which it almost plateaus, consistent with PLIC myelination starting before birth. The increase in tortuosity is also less pronounced than in genu and splenium. Errorbars represent standard error on the parameter across the ROI. The dashed lines are the best fit found for the parameter change with age (between a choice of constant, linear or exponential).

Figure 6.

Correlation plots for the values of f_{intra} , $\langle \cos^2 \psi \rangle$ and $D_{e,\perp}$ estimated by NODDI and WMTI. The points are color-coded according to age: the darkest blue represents the youngest subject and the darkest red the oldest. The coefficient of correlation ρ is indicated in the legend for each ROI.

Figure 7.

Estimated parameters on four synthetic datasets (a: Set #1, b: Set #2, c: Set #3, d: Set #4, see Table 2) using NODDI and WMTI. Represented are parameter estimates from noiseless data (magenta) and from data with SNR=50 (blue; the errorbars represent standard deviation of estimation over 500 noise realizations).

Figure 8.

Simulations highlighting the coupling of NODDIDA model parameters for the current diffusion acquisition protocol (see Methods). The signal was simulated based on the NODDIDA model and a ground truth [$f_{\text{intra}} = 0.32$; $\langle \cos^2 \psi \rangle = 0.90$; $D_a = 1.15/D'_{e,\parallel} = 2.85/D'_{e,\perp} = 1.1 \mu\text{m}^2/\text{ms}$]. Rician noise corresponding to SNR=50 was added. Fitted parameters from 2500 noise realizations are plotted (red dot: ground truth).

Table 1

Conceptual comparison between WMTI, NODDI and NODDIDA parameters. The parameters in the leftmost column are biophysical quantities that can be derived from all three models presented, and can therefore be readily compared between models.

Parameter	Significance	WMTI	NODDI**	NODDIDA
f_{intra}	Intra-axonal water fraction	$\frac{K_{\text{max}}}{K_{\text{max}}+3}$	$f_{\text{ic}} \cdot (1 - f_{\text{iso}})$	f_{ic}
f_{iso}	CSF fraction	-	f_{iso}	-
$\langle \cos^2 \psi \rangle \equiv \tau_1$	Fiber dispersion*	$\frac{D_{a,1}}{\text{Tr}(\hat{D}_a)}$	$-\frac{1}{2\kappa} + \frac{1}{\sqrt{\pi}e^{-\kappa}\text{erfi}(\sqrt{\kappa})\sqrt{\kappa}}$	
D_a	Parallel diffusivity along each axon	$\text{Tr}(\hat{D}_a)$	D_a	D_a
$D_{e,\parallel}$	Apparent axial diffusivity of the EAS	$D_{e,1}$	$D'_{e,\parallel} - D'_{e,\parallel} \cdot f_{\text{ic}} \cdot (1 - \tau_1)$	$D'_{e,\parallel} \cdot \tau_1 + D'_{e,\perp} \cdot (1 - \tau_1)$
$D_{e,\perp}$	Apparent radial diffusivity of the EAS	$\frac{(D_{e,2} + D_{e,3})}{2}$	$D'_{e,\parallel} - D'_{e,\parallel} \cdot f_{\text{ic}} \cdot \frac{(1 + \tau_1)}{2}$	$\frac{D'_{e,\parallel}(1 - \tau_1) + D'_{e,\perp}(1 + \tau_1)}{2}$
a	Tortuosity***	$D_{e,\parallel}/D_{e,\perp}$	$D'_{e,\parallel}/D'_{e,\perp}$	

* $\langle \cos^2 \psi \rangle$ varies from 1/3 for isotropically-dispersed orientations to 1 for strictly parallel orientations

** In NODDI, the quantities D_a and $D'_{e,\parallel}$ are set equal and fixed to an *a priori* value. The other parameters are the result of a fitting procedure. The simplified relationships between local and apparent extracellular diffusivities in NODDI fall from Equation 3.

*** In the case of WMTI, the definition of tortuosity is exact for perfectly aligned fibers ($D'_{e,\parallel} = D_{e,\parallel}$) and an approximation otherwise.

Sets of parameters used as ground truth in the simulations. The theoretical effective parameters are calculated based on the input ones using relations from Table 1.

Table 2

	Set #1	Set #2	Set #3	Set #4
	0.3	0.55	0.32	0.35
f_{ic}				
D_a ($\mu\text{m}^2/\text{ms}$)	1.0	2.5	1.15	1.2
$D'_{e,\parallel}$ ($\mu\text{m}^2/\text{ms}$)	2.8	2.5	2.85	2.7
$D'_{e,\perp}$ ($\mu\text{m}^2/\text{ms}$)	1.1	2.5*(1-0.55)=1.13	1.1	1.1
κ	∞	4.5	10.6	10.6
f_{iso}	0	0.12	0	0.08
D_{iso} ($\mu\text{m}^2/\text{ms}$)	3.0	3.0	3.0	3.0
f_{intra}	0.3	0.48	0.32	0.32
D_a ($\mu\text{m}^2/\text{ms}$)	1.0	2.5	1.15	1.2
$D_{e,\parallel}$ ($\mu\text{m}^2/\text{ms}$)	2.8	2.14	2.67	2.54
$D_{e,\perp}$ ($\mu\text{m}^2/\text{ms}$)	1.1	1.31	1.19	1.18
$\langle \cos^2 \psi \rangle$	1	0.74	0.90	0.90
AK	0.4	0.4	0.4	0.4
AD ($\mu\text{m}^2/\text{ms}$)	2.2	2.2	2.1	2.1
MD ($\mu\text{m}^2/\text{ms}$)	1.3	1.3	1.3	1.3
RD ($\mu\text{m}^2/\text{ms}$)	0.8	0.9	0.8	0.9
MK	0.9	0.9	0.9	0.9
RK	1.4	1.4	1.3	1.4
FA	0.58	0.51	0.54	0.49

Table 3

Mean DTI and DKI metrics measured across all 55 subjects (age 0 to 3 years) in the three regions of interest retained. Diffusivities are expressed in $\mu\text{m}^2/\text{ms}$.

	MD	AD	RD	FA	MK	AK	RK
Genu	1.3 ± 0.3	2.2 ± 0.3	0.9 ± 0.3	0.5 ± 0.1	0.7 ± 0.2	0.4 ± 0.1	1.3 ± 0.8
Splenium	1.3 ± 0.2	2.2 ± 0.3	0.8 ± 0.3	0.6 ± 0.1	0.9 ± 0.3	0.4 ± 0.1	1.7 ± 0.9
PLIC	1.0 ± 0.1	1.5 ± 0.1	0.8 ± 0.1	0.4 ± 0.1	0.7 ± 0.2	0.4 ± 0.1	1.2 ± 0.4

Table 4

Characteristics of the non-linear increase (expressed as $a \cdot e^{-bX} + c$) in f_{intra} and tortuosity α , during the first 3 years of life, as estimated using NODDI and WMTI: time constant (in years), intercept (value at age 0) and estimate at age 3 years. The mean values are provided with 95% confidence bounds, assuming normal distributions.

		NODDI			WMTI		
		Time constant (years)	Intercept (t=0)	Estimate at 3 years	Time constant (years)	Intercept (t=0)	Estimate at 3 years
f_{intra}	Genu	1.3 ± 0.3	0.19 ± 0.10	0.62 ± 0.08	1.3 ± 0.4	0.23 ± 0.10	0.52 ± 0.09
	Splenium	0.8 ± 0.2	0.21 ± 0.09	0.64 ± 0.06	0.7 ± 0.2	0.24 ± 0.06	0.57 ± 0.04
	PLIC	0.4 ± 0.1	0.33 ± 0.02	0.55 ± 0.01	0.3 ± 0.1	0.23 ± 0.02	0.39 ± 0.01
α	Genu	1.9 ± 0.6	1.2 ± 0.7	2.9 ± 0.7	1.6 ± 0.7	1.8 ± 1.1	3.4 ± 1.1
	Splenium	0.8 ± 0.3	1.1 ± 0.7	3.6 ± 0.5	1.5 ± 0.6	1.8 ± 1.0	3.6 ± 1.1
	PLIC	0.5 ± 0.2	1.4 ± 0.1	2.4 ± 0.1	0.9 ± 0.4	1.6 ± 0.2	1.9 ± 0.2

Table 5

Mean fiber dispersion (expressed as $\langle \cos^2 \psi \rangle$) over all 55 subjects. For convenience, an equivalent angle of dispersion $\tilde{\psi}_{eq}$ is provided.

	NODDI		WMTI	
	$\langle \cos^2 \psi \rangle$	$\tilde{\psi}_{eq} (^{\circ})$	$\langle \cos^2 \psi \rangle$	$\tilde{\psi}_{eq} (^{\circ})$
Genu	0.86	22	0.79	28
Splenium	0.89	19	0.83	24
PLIC	0.66	36	0.76	30

Table 6

Performance of the NODDIDA fitting procedure on ground truth Set #3.

	Ground truth	NODDIDA estimate	Bias	Precision
f_{intra}	0.32	0.35 ± 0.07	+ 9%	$\pm 20\%$
$D_a(\mu\text{m}^2/\text{ms})$	1.15	1.39 ± 0.58	+ 21%	$\pm 42\%$
$D'_{e,\parallel}(\mu\text{m}^2/\text{ms})$	2.85	2.88 ± 0.31	+ 1%	$\pm 11\%$
$D'_{e,\perp}(\mu\text{m}^2/\text{ms})$	1.1	1.08 ± 0.14	-2 %	$\pm 13\%$
κ	10.6	16 ± 12	+ 51%	$\pm 75\%$