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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 the 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.

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 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

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.

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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 (WMTI) metrics 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 5 min 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.

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. Fig. 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.

WMTI

WMTI is a model that relates DKI metrics directly to WM microstructure (Fieremans et al., 2011; Fieremans et al., 2010). While initially

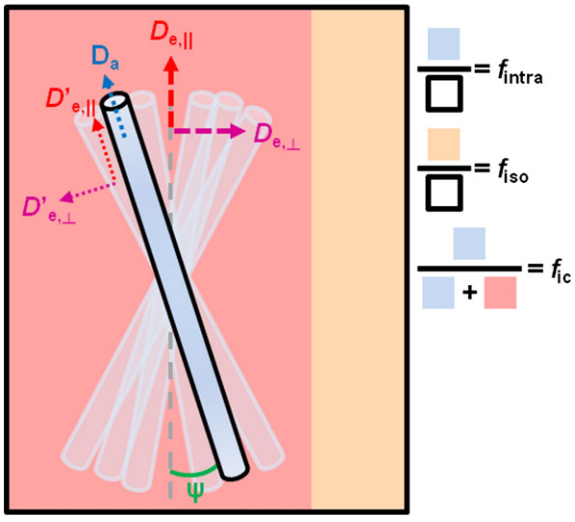

Fig. 1. Schematic of the general white matter fiber model. The meaning of each compartment fraction is color-coded; the entire voxel is designated by a black square contour. Fiber sub-bundles have a given orientation distribution about the main bundle axis (vertical axis in the figure). The local diffusivities within each sub-bundle are denoted as D_a, $D'_{e,||}$ and $D'_{e,\perp}$. Apparent diffusivities $D_{e,||}$ and $D_{e,\perp}$ 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.

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 the 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:

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

where $K_{\max}$ is the maximum kurtosis over *all* possible directions, and $D_{\mathbf{n}}$, $K_{\mathbf{n}}$, $D_{e,\mathbf{n}}$, and $D_{a,\mathbf{n}}$ 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 $D_{a,\mathbf{n}} \leq D_{e,\mathbf{n}}$ (Fieremans et al., 2011). The equations for $D_{a,\mathbf{n}}$ and $D_{e,\mathbf{n}}$ 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 $D_{e,||}$ diffusivities of the connected extracellular compartment are then derived from the eigenvalues $D_{e,1} \geq D_{e,2} \geq D_{e,3}$ of $\hat{D}_e$ as $D_{e,||} = D_{e,1}$ and $D_{e,} = (D_{e,2} + D_{e,3})/2$. 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, $D_{e,||}$ and $D_{e,\perp}$, respectively. Recent work has shown very good correlations between these metrics and histological measurements in cuprizone-induced demyelination