Estimation of the Axonal Density Using DKI: a Validation Study

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Introduction

Diffusional kurtosis imaging (DKI) has been proposed as a clinically feasible extension of DTI to probe the restricted water diffusion in biological tissues [1,2]. Recently, an idealized diffusion model of white matter (WM) suitable for DKI analysis has been introduced [3], which allows for quantifying the axonal water fraction (AWF). The AWF, a measure of axonal density, has been incorporated earlier in advanced diffusion models [4-6], including the biexponential model [7,8]. In this study, we elaborate further on the estimation of the AWF using DKI and validate its measurement by comparing to the slow diffusion volume fraction obtained from biexponential fitting in three healthy young adults.

Methods

Theory: To model the water diffusion in the WM, we assume that WM is composed of myelinated axons that are all aligned approximately parallel to each other. The remainder of the WM is referred to as the extra-axonal space (EAS) and treated as an effective medium. The AWF is defined as the volume fraction of water in the axons relative to the total visible water volume. Water exchange between the two compartments is neglected. Using the DKI-information allows estimation of the AWF on a voxel-by voxel basis according to:

$$f = \frac{K_i}{K_i + 3}, \quad \text{where } K_i \text{ is the maximum kurtosis over all diffusion directions.} \qquad (1)$$

Alternatively, the AWF can be found from a biexponential fit, which is used in this study as a validation of the DKI WM model. We emphasize that according to our model, the fast- and slow diffusion components do not correspond to the extra- and intracellular space [7], but rather to the intra-and extra-axonal space [8].

Imaging: On a 3 T wide-bore Siemens Verio system, data sets were acquired from three healthy volunteers (27 y/o female, 28 y/o female and 28 y/o male). For the DKI-analysis, diffusion-weighted images (DWIs) were acquired along 30 gradient directions for b = 0, 1000, 2000 s/mm^2 with a twice-refocused spin-echo echo-planar sequence with TR = 8700 ms, TE = 96 ms, matrix = 82 × 82, FOV = 222 × 222 mm², 40 slices, slice thickness = 2.7 mm, NEX = 11 for b = 0, NEX = 2 for b = 1000, 2000 s/mm^2, band width = 1355 Hz/pixel within a total time of 20 min. For the biexponential analysis, additional DWIs were acquired along the axial direction for 16 b-values (b = 0 – 7000 s/mm^2 in increments of 500 s/mm^2) using a standard Stejskal-Tanner diffusion preparation. Imaging parameters were: TR = 12500 ms, TE = 132 ms, matrix = 104 × 104, FOV = 280 × 280 mm², 40 slices, slice thickness = 2.7 mm, NEX = 8 for all b-values, band width = 1502 Hz/pixel. The total acquisition time was 36 min.

Processing: The multidirectional DWIs were used to calculate DTI and DKI parametric maps using in house Matlab code [9]. The AWF in each voxel was derived using Eq. (1), whereby K_i is taken as the maximum of calculated kurtosis-values along 10,000 randomly chosen directions based on the kurtosis tensor. Twenty-one ROIs were identified for the biexponential analysis on the color-coded FA-map by selecting fibers that are oriented in a plane perpendicular to the axial diffusion direction. For each ROI, the signal of the DWIs acquired along the axial direction was averaged and fitted by a biexponential function. The fitting procedure was performed in Matlab using the trust region algorithm with the robust option set to bisquare. The fraction f corresponding to the slow diffusion coefficient is then used for comparison to the AWF of our DKI WM model.

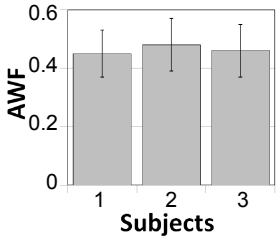

Figure 1: Mean values of the AWF in 3 healthy young adults. The error bars represent the standard variation for selected WM regions with aligned fibers.

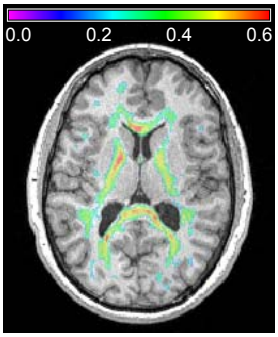

Figure 2: Parametric axial image of the AWF as overlay on the MPRAGE image.

Results

Average values and standard deviations of the AWF for the three subjects are plotted in Fig. 1. WM voxels were selected that contained fibers with a homogeneous orientation where the coefficients of linearity c_L, planarity c_P and sphericity c_S [10] fulfill $c_L \geq 0.4$, $c_L \leq 0.2$, $c_S \leq 0.35$. An example of an AWF-map is shown in Fig. 2. The biexponential model fits the diffusion-weighted data very well ($R^2 \geq 0.997$) with a fitted slow diffusion coefficient of 0.06 ± 0.02 μm^2/ms. For each ROI, the DKI-derived AWF is plotted in Fig. 3 against the biexponential slow diffusion volume fraction, yielding a slope of 0.93 ± 0.2 and a correlation of $R^2 = 0.70$.

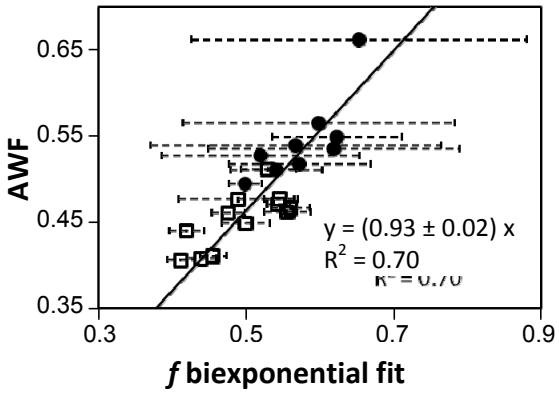

Figure 3: *In vivo* validation of the DKI WM model for ROIs in the genu, splenium and midbody of the corpus callosum (●), and the forceps major and inferior fronto-occipital fasciculus (□). The error bars represent the 95% confidence bounds on the fitted volume fraction.

Discussion

We have presented a model for estimating the AWF, a measure for axonal density, by exploiting the additional information DKI provides beyond DTI. The AWF-values are consistent between subjects (Fig. 1). The AWF-map (Fig. 2) and ROI analysis (Fig. 3) show that the axonal density is highest for ROIs in the corpus callosum. We have validated the DKI WM model against the biexponential model. The fitted slow diffusion coefficient in the direction transverse to the fiber direction is very small, supporting the validity of our model assumption of a highly restricted axonal compartment. Figure 3 shows a good agreement between the AWF and the volume fraction f obtained from a biexponential fit with high b-value data.

Whereas other advanced diffusion models typically require high b-values [4-8], our DKI WM model is based on b-values only up to 2000 s/mm^2. Hence, assessing the axonal density by DKI analysis is clinically feasible and could potentially provide important information on neurodegenerative disorders.

[1] Jensen et al, *Magn Reson Med* **65**:1432,2005; [2] Jensen et al, *NMR Biomed* **23**:698,2010; [3] Fieremans et al ISMRM 2009 p. 1569; [4] Assaf and Basser, *NeuroImage* **27**:48,2005; [5] Jespersen et al, *NeuroImage* **49**:205,2010; [6] Alexander et al, *NeuroImage* **52**:1374,2010; [7] Clark et al, *Magn Reson Med* **44**:852,2000; [8] Maier et al, *Magn Reson Med* **51**:321,2004; [9] Tabesh et al, *Magn Reson Med*, 2010: doi: 10.1002/mrm.22655; [10] Westin et al, *Med Image Anal* **6**:93,2002;