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Towards tract-specific fractional anisotropy (TSFA) at crossing-fiber regions with clinical diffusion MRI

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Abstract

Purpose—White matter fractional anisotropy (FA), a measure implying microstructure, is significantly underestimated with single diffusion tensor model at crossing-fiber regions (CFR). We propose a tract-specific FA (TSFA), corrected for the effects of crossing-fiber geometry and free water at CFR, and adapted for tract analysis with diffusion MRI (dMRI) in clinical research.

Methods—At CFR voxels, the proposed technique estimates free water fraction (f_{iso}) as a linear function of mean apparent diffusion coefficient ($mADC$), fits the dual tensors and estimates TSFA. Digital phantoms were designed for testing the accuracy of f_{iso} and fitted dual-anisotropies at CFR. The technique was applied to clinical dMRI of normal subjects and hereditary spastic paraplegia (HSP) patients to test the effectiveness of TSFA.

Results—Phantom simulation showed unbiased estimates of dual-tensor anisotropies at CFR and high accuracy of f_{iso} as a linear function of $mADC$. TSFA at CFR was highly consistent to the single tensor FA at non-CFR within the same tract with normal human dMRI. Additional HSP imaging biomarkers with significant correlation to clinical motor function scores could be identified with TSFA.

Conclusion—Results suggest the potential of the proposed technique in estimating unbiased TSFA at CFR and conducting tract analysis in clinical research.

Keywords

TSFA; tract-specific fractional anisotropy; dual-tensor; free water elimination; Gaussian mixture model; tract analysis; diffusion MRI

Introduction

To accommodate complex “wiring” in the human brain with a volume of around 1.2 liters, a significant percentage of white matter (WM) fibers need to cross with each other. Diffusion magnetic resonance imaging (dMRI) in routine clinical research is usually acquired within a limited time of less than 5 minutes and with a relatively low b-value such as 1000 s/mm². The resultant voxel size is usually from 2×2×2 mm³ to 3×3×3 mm³ and crossing fibers exist in a large proportion of WM voxels. It is believed that almost half of the brain voxels contain crossing fibers (1). Fractional anisotropy (FA) (2) derived from the single tensor (ST) model and ranging from 0 to 1, has been widely used to infer the WM microstructural changes associated with many neurological or psychiatric disorders. However, ST FA is significantly underestimated (e.g. 3–5) at the crossing-fiber regions (CFR). In addition, tract-specific analyses including tract statistics (6–9), tract morphometry (10–11) and tract metric analysis (12–15) have become important due to great clinical significance of the tracts. With the extensive applications of FA in neurological and psychiatric studies such as phenotype characterization, drug testing and therapy monitoring, biased conclusions from the underestimated ST FA in tract analysis will have significant negative impacts on these studies. It is, therefore, critical to correct FA at the CFR for the effects of free water and crossing-fiber geometry and obtain the tract-specific FA (TSFA) for each crossed tract with routine clinical diffusion MRI (dMRI), namely single shell dMRI with 25–30 diffusion orientations.

There are roughly two approaches to get “a better estimate of FA” at the CFR. One is to propose an entirely new metric, such as GFA (generalized fractional anisotropy) (16–18) or GA (generalized anisotropy) (19). The other is to correct the underestimated FA since FA is still by far the most widely used metric inferring microstructure in clinical research. This paper represents our efforts along the direction in the second approach, especially as we are engaging FA measurement to analysis of WM tract where FA measurements at non-CFR voxels are reasonably valid disease biomarkers (e.g. 4, 7–15). Among all the signal models at CFR such as Gaussian mixture model (3, 20–33), diffusion kurtosis imaging (34) and higher order tensors (35–37), Gaussian mixture model has been used extensively and will be adopted in this study. We summarize the prior work (3, 20–30, 32–33, 39) in this area in Table 1 under the framework of Gaussian mixture model, including the parameters that each published method is able to estimate. Free water contamination can lead to severely underestimated FA in the WM voxels (38–40). However, as shown in Table 1, free water fraction (f_{iso}) in the Gaussian mixture model is usually neglected (20, 24, 26–27, 30). Furthermore, there has not been a method comprehensively estimating all major components of Gaussian mixture model, including two fractional anisotropies (FA1, FA2), two tensor component fractions (f_1, f_2) and f_{iso} , with a single shell dMRI. Earlier investigators have focused on estimating primary eigenvectors instead of FA or component fractions (f_1, f_2 and f_{iso}) of the multiple diffusion tensors with Gaussian mixture model (20–23). Jbadbdi et al (3) suggested that separating component fractions (f_1, f_2) at the CFR is important for statistical modeling while the two tensors were modeled as “sticks”, implying FA1 or FA2 equal to 1. More recently, Baumgartner et al (29) have provided almost complete estimates of all parameters, except that equal f_1 and f_2 was assumed. Without appropriate constraints, it has

been proven (28) that unbiased estimation of complete parameters in a Gaussian mixture model with a single shell dMRI is mathematically not possible. A two shell dMRI (28) has been demonstrated as a useful solution for comprehensive estimation of the parameters of Gaussian mixture model, but is difficult to be applied in routine clinical dMRI due to limitation of scan time.

With a single shell dMRI and under the framework of dual-tensor Gaussian mixture model, we present in this paper a technique for unbiased estimates of FA1, FA2, $f1$, $f2$ and f_{iso} , among which FA1 and FA2 in CFR voxels will be separated and assigned to two tracts as TSFA after correcting for the effects of free water and crossing-fiber geometry. f_{iso} in the CFR voxels was estimated from the calibration linear line based on mean apparent diffusion coefficient ($mADC$). Compared to previous methods based on Gaussian mixture model in Table 1, this technique is capable of estimating full repertoire of parameters, simultaneously, in an unbiased manner with a single shell dMRI. Digital phantoms were designed for testing the accuracy of f_{iso} and the accuracy of fitted dual-anisotropies at CFR. The estimation of dual-tensor anisotropy has been optimized under the framework of clinical dMRI with single low b-value and acquired within 5 minutes. In the non-CFR voxels, FA was estimated with free water elimination technique (39). The proposed technique for estimating TSFA was further tested with the dMRI data obtained from 3T Philips and 3T GE scanners with 30 and 25 diffusion gradient directions, respectively. Clinical dMRI of hereditary spastic paraplegia (HSP) patients was also used to test the effectiveness of TSFA in clinical research.

Methods

Overview of the technique

The proposed technique includes two major features: estimation of TSFA after correcting for the effects of crossing-fiber geometry and free water at CFR and tract-specific analysis with TSFA. Fig. 1 schematically illustrates this method. The FA for the crossed tracts is significantly underestimated at CFR with the ST FA (Fig. 1a). After identification of the voxels of CFR in Fig. 1a and free water correction, dual-tensor fitting was conducted as shown in Fig. 1b. The crossed tracts were then separated in Fig. 1c and one of the two TSFA was assigned to each tract based on the alignment of the primary eigenvector of the tensors in the crossing-fiber voxel to the primary eigenvectors of the tensor in the surrounding non-CFR voxels. In Fig. 1c, the TSFA profiles of the two crossed tracts were obtained, and they were usually more uniform than the ST FA profile of the same tract.

We developed and tested a technique for TSFA estimation with three steps below. In the first step, we demonstrated the detailed procedures of estimating TSFA at CFR with dual-tensor fitting after free water elimination and applying TSFA for tract analysis. Next, we tested estimation of f_{iso} as a linear function of $mADC$ and estimation of dual-tensor anisotropies (FA1, FA2) and component fractions ($f1$, $f2$) at CFR with digital phantoms. In the last step, we compared TSFA at CFR voxels to FA at the non-CFR voxels with dMRI of normal human subjects and applied the technique to the clinical HSP case.

Step #1-1: Dual-tensor fitting with free water correction

We identified CFR first with the planar index $C_p = 2(\lambda_2 - \lambda_3)/(\lambda_1 + \lambda_2 + \lambda_3)$ (41), calculated from the eigenvalues (λ_1 , λ_2 and λ_3) of the single tensor. All the voxels where $C_p > 0.2$ were marked as CFR voxels (24, 26).

Gaussian mixture signal model with free water component—A Gaussian mixture signal model including f_{iso} (3, 23, 25, 29, 32) was used for the CFR voxels as follows,

$$S = S_0(f_{ios}e^{-bD_{ios}} + f_1e^{-b\overline{G_i^T D_1 G_i}} + (1-f_1-f_{ios})e^{-b\overline{G_i^T D_2 G_i}}) \quad [1]$$

where f_1 and f_{iso} are the volume fractions of the first fiber bundle and free water respectively, b is the applied b-value, S_0 is the signal with no diffusion weighting, D_{ios} is the diffusion coefficient of the free water component in the voxel, $\overline{G_i}$ is the i th gradient vector with i as the index of the i th gradient vector, $\overline{D_1}$ and $\overline{D_2}$ are the two tensors representing the first and second fiber bundles.

Estimation of f_{iso} at CFR with linear function—dMRI with at least two shells, besides b_0 , are required to estimate f_{iso} in the CFR voxels (28). As this technique is designed for single shell dMRI, we hypothesized that f_{iso} in the CFR voxel could be estimated *a priori* as a linear function of $mADC$: $f_{iso} = c_1 * mADC + c_2$, where c_1 and c_2 are two fixed scalar coefficients. Measurement points from whole brain CFR voxels of 5 normal subjects were used for fitting coefficients c_1 and c_2 . Specifically, at each CFR voxel, f_{iso} was obtained from nonlinear fitting of Gaussian mixture model in [1] using two shell ($b = 1000$ s/mm² and $b = 2500$ s/mm²) dMRI data and $mADC$ was measured with low b (1000 s/mm²) dMRI data (acquisition procedure described in details below). A digital phantom described in details below was designed to test the accuracy of estimating f_{iso} at CFR with this linear function which could serve as a calibration line for f_{iso} estimation.

Estimation of $\overline{D_1}$ and $\overline{D_2}$ at CFR after free water elimination— $\overline{D_1}$ and $\overline{D_2}$ in [1] were fitted at the CFR voxels after f_{iso} was estimated with the linear function described above. The details of the constraints and algorithm used to fit $\overline{D_1}$ and $\overline{D_2}$ are elaborated in the Appendix.

Calculation of FA1, FA2 and weighted FA—Anisotropy at non-CFR voxels was the ST FA. ST FA and FA_i ($i = 1, 2$) (42) of each tensor after dual-tensor fitting at CFR, was calculated using the equation

$$FA_i = \sqrt{(\lambda_{1i} - \lambda_{2i})^2 + (\lambda_{1i} - \lambda_{3i})^2 + (\lambda_{2i} - \lambda_{3i})^2} / \sqrt{2(\lambda_{1i}^2 + \lambda_{2i}^2 + \lambda_{3i}^2)} \quad [2]$$

Weighted FA at CFR was calculated by the following equation, $(f_1 * FA_1 + (1 - f_{iso} - f_1) * FA_2) / (1 - f_{iso})$. It represents the weighted anisotropy of the fitted two tensors in a single voxel. The average weighted FA map and ST FA map across different subjects were calculated after nonlinear registration to EVA single subject FA map of JHU

atlas (43) using FSL's nonlinear registration tool (FNIRT, from FMRIB's software library FSL, www.fmrib.ox.ac.uk/fsl). Weighted FA was only used to yield Fig. 5 below.

Free water component was removed for all ST FA, GFA (16–18) and GA (19) based on the approach of Pasternak et al 2009 (39) for fair comparisons in this study.

Step #1-2: TSFA for tract analysis

Tract-specific analysis—The tracts were traced using probabilistic tracking (25) (FMRIB's diffusion toolbox (FDT) of FSL). Each voxel in the traced tracts was categorized as CFR or non-CFR voxel by the approach described above. Assigning FA1 or FA2 in the voxels at CFR as TSFA was determined by the orientations of the primary eigenvectors of the two tensors. Specifically, FA_i (i = 1, 2) of the individual-tensor whose primary eigenvector aligned best to those of the surrounding non-CFR voxels ($C_p < 0.2$) (41) in the local neighborhood (a volume with 5×5×5 dimension) was selected as TSFA. The underlying hypothesis is that the fiber orientations in a tract are continuous and well aligned. The alignment of the eigenvectors was quantified by the dot product of the two eigenvectors. The best alignment of an eigenvector resulted in the higher summation of the dot product of this eigenvector and surrounding eigenvectors of non-CFR voxels.

Along-the-tract analysis—Mean and standard deviation of the anisotropy metrics at certain planes perpendicular to the traced tract were calculated and plotted.

Step #2: Digital phantom test

Test accuracy of estimating f_{iso} at CFR—A digital phantom simulating CFR voxels was created using Equation [1] to evaluate estimation of f_{iso} from $mADC$ with linear function, $f_{iso} = c1 * mADC + c2$. Single b-value is 1000 s/mm². The fiber crossing angle was fixed at 90°. SNR for this simulation was 40. The same digital phantom was also used to evaluate approach of Pasternak et al 2009 (39) on estimating f_{iso} at the CFR voxels. The known ground truth of f_{iso} was 0.2 at the CFR voxels.

Test accuracy of estimating unbiased FA_i and f_i at CFR—A digital phantom simulating a CFR voxel was generated with Equation [1] to test the feasibility of estimating unbiased FA_i and f_i (i = 1 or 2) from dual-tensor fitting. The phantom was simulated with diffusion signals acquired under a clinical research framework, i.e. relatively low b-value of 1000 s/mm² and reasonable signal-to-noise ratio (SNR) from 10 to 70. The four variables used for the phantom design and their detailed values were as follows: angle between two tensors = 10, 20, •••90, $f_1 = 0.1, 0.2, •••0.9$, FA1 = 0.2, •••0.9; FA2 = 0.2, •••0.9. To match *in vivo* human data, Jones30 gradient scheme (44) with 30 diffusion gradient directions was used to generate 30 dMRI volumes and one non-diffusion weighted image volume. Rician noise was added to the simulated signal generated from Equation [1] by adding Gaussian noise with different standard deviation to both real and imaginary part of the simulated signal in k-space (45) to understand the influence of noise on the proposed model.

Step #3: Application of TSFA to dMRI of normal human subjects and HSP patients

Normal human subjects and HSP patients—17 healthy young adults (age: 24.4 ± 3.3), 12 HSP children (age: 8.9 ± 2.1) and 11 age-matched control children (age: 8 ± 1.4) were scanned with a 3T Philips Achieva MR system at the Advanced Imaging Research Center of the University of Texas Southwestern Medical Center. 10 healthy adults (age: 17 ± 2) were scanned with a 3T GE Signa MR system at Imaging Center of the University of Texas at Austin to test the effects of scanner on the proposed technique. All healthy subjects were free of current and past medical or neurological disorders. All children were recruited from Texas Scottish Rite Hospital for Children (TSRHC). The Gross Motor Function Classification System (GMFCS) (46) measurements, used to quantify “severity” of this disease related to motor outcome, were obtained from all HSP children. All human subjects gave informed written consents approved by the Institutional Review Board.

Data acquisition with Philips 3T Achieva system—A single-shot echo-planar imaging (EPI) sequence with SENSE parallel imaging scheme (SENStivity Encoding, reduction factor = 2.5) was used. dMRI of healthy human subjects were acquired with the following parameters, b-value = 1000 s/mm^2 for 17 subjects and b-value = 2500 s/mm^2 for 7 subjects, TR = 9.5s, TE = 80 ms, imaging matrix = 112×112 zero filled to 256×256 , field of view = $224 \times 224 \text{ mm}$ (nominal resolution of 2 mm), Jones30 gradient scheme (44), slice thickness = 2 mm without gap, slice number = 65, axial acquisition parallel to the anterior-posterior commissure line (AC-PC). Same delta values ($\delta = 17.4 \text{ ms}$ and $\delta = 39.9 \text{ ms}$) were used for b = 1000 s/mm^2 and b = 2500 s/mm^2 . To ensure enough SNR, two repetitions were used for dMRI with b-value of 2500 s/mm^2 . The acquisition time was 5 minutes for every repetition of dMRI acquisition.

Data acquisition with GE 3T Signa system—A single-shot EPI sequence with GRAPPA parallel imaging scheme (GRAPPA acceleration factor = 3) was used. dMRI were acquired with the following parameters: b-value = 1000 s/mm^2 , TR = 16.5s, TE = 84.4 ms, imaging matrix = 96×96 zero filled to 256×256 , field of view = $240 \times 240 \text{ mm}$ (nominal resolution of 2.5 mm), 25 diffusion gradient orientations, slice thickness = 2.5 mm without gap, slice number = 60, axial acquisition parallel to the anterior-posterior commissure line (AC-PC). The acquisition time was 5 minutes. GE data was only used for along-the-tract analysis of cortico-spinal tract (CST).

Preprocessing of diffusion weighted images (DWIs)—Routine preprocessing (e.g. 12–13) was conducted. For two repetitions of high-b dMRI, we conducted an intra-session 12-parameter affine registration followed by the inter-session 12-parameter affine registration. Intra-session transformation registered all DWIs to b0 of the same session. Inter-session transformation registered b0 of the 2nd repetition to that of the 1st repetition and this transformation matrix was applied to all DWIs in the 2nd repetition.

Application of TSFA to normal subjects—With the region-of-interests (ROI) placement protocol in the literature (47), probabilistic tractography (25) was conducted to trace the left inferior fronto occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF), CST, uncinate fasciculus (UNC) and superior longitudinal fasciculus (SLF) which are

known to have CFR along their paths. Traced left UNC, IFO, ILF and SLF from Philips dMRI of 17 healthy adults were used for tract-specific analysis. The voxels of each tract from all subjects were evenly sampled. Traced left CST of Philips dMRI from 17 healthy adults and GE dMRI from 10 healthy adults was used for along-the-tract analysis. ST FA, GFA (16–18) and GA (19) along the CST were also calculated for comparison. To test the benefit of two shell dMRI with regards to the anisotropy correction, ST FA and TSFA were calculated with two shell ($b = 1000$ and 2500 s/mm^2) Philips dMRI from 7 out of 17 healthy subjects. The profiles of all these metrics along CST were plotted. In addition, mean and standard deviation of these metrics at all CST voxels were calculated to compare the consistency of these metric values inside the same tract.

Application of TSFA to clinical HSP patients—Left CST of all HSP patients and age-matched control subjects was traced with dMRI data in the native spaces. For comparison, single tensors were first fitted for whole brain voxels including the CFR voxels. The technique for estimating TSFA was applied to estimate the anisotropy of CST at the CFR voxels. Inter-subject registration from FSL was then conducted to transform biased ST FA and TSFA of all subjects to the JHU ICBM-DTI-81 template (43). The skeletonization and statistical comparisons between the control and HSP groups with TSFA or biased ST FA were conducted through tract based spatial statistics (TBSS) procedures (48).

Results

Digital phantom test

Accuracy of estimating f_{iso} at CFR—Left panel of Fig. 2a shows that f_{iso} in the CFR voxels using the approach of Pasternak et al. 2009 (39) (top right panel) is underestimated from the known ground truth 0.2. At non-CFR voxels, f_{iso} estimated from approach of Pasternak et al. 2009 (39) is accurate. As can be observed from right panel of Fig. 2a, f_{iso} estimated from Gaussian mixture model with two shell dMRI cluster between 0 and 0.3 and have less than a 5% bias in the CFR voxels. With f_{iso} estimated from two shell dMRI and $mADC$ obtained from single low- b dMRI at the CFR voxels of 5 subjects, a linear regression line was established as shown in the left panel of Fig. 2b. The measured points are tightly clustered around the linear line ($p < 0.0001$), making it possible to get an accurate estimate of f_{iso} directly with the linear function of $mADC$ from single shell dMRI. The phantom test shows that estimated f_{iso} values in the CFR voxels with linear function as a calibration line have less than 5% bias from the known ground truth, as shown in the right panel of Fig. 2b.

Accuracy of estimating unbiased FA_i and fi at CFR—Fig. 3a shows that the bias for estimating two anisotropy values is less than 5% for almost all cases with SNR greater than 35 (pointed by the arrows) and separation angle greater than 30 degrees. Under the similar condition, the fitting errors of volume fractions fi are less than 5% for almost all cases as shown in Fig. 3b. The known ground truth in Fig. 3a and Fig. 3b is represented by the dashed line. The fitting algorithm was tested to be robust with less than 5% error for almost all cases in the range of FA_i ($i = 1$ or 2) from 0.2 to 0.9 and volume fractions fi ($i = 1$ or 2) from 0.2 to 0.9 in the simulated voxel. For simplification, the results of several selected combinations of two tensors are shown in Fig. 3.

Comparison of the primary eigenvectors and tensors at CFR from ST model, ball-and-stick model (BSM) and the proposed technique for TSFA

As shown in the upper panels of Fig. 4, ST model cannot differentiate two primary eigenvectors corresponding to two crossing fibers at the CFR voxels. In contrast, both BSM (25) and the proposed technique for TSFA can estimate the primary eigenvectors of the crossing fibers in the CFR voxels with similar orientations. Furthermore, as shown in the lower panels of Fig. 4, our technique is capable of estimating two tensors at the CFR while neither ST model or BSM estimates two tensors.

Comparisons of weighted FA and ST FA

The upper panels in Fig. 5 show the averaged ST FA maps acquired from 17 subjects with dMRI of b-value = 1000 s/mm², and the lower panels show the average weighted FA map after applying the proposed technique to the CFR voxels with the same dMRI datasets. As indicated by the red arrows in upper panels of Fig. 5, the ST FA values were significantly lower at the CFR compared to surrounding regions, conveying biased information on WM anisotropy. The weighted FA at a crossing-fiber voxel is not specific to a tract, but reflects the corrected anisotropy of that voxel. It is clear from Fig. 5 that the underestimated anisotropy values were restored with weighted FA at the CFR and they appear more homogeneous to the anisotropy values of surrounding non-CFR voxels.

Application of TSFA to normal human subjects

Tract-specific analysis—The two columns below each tract of Fig. 6 show the FA values at the evenly sampled voxels for 17 subjects before (pink “+”) and after (red circle) applying the technique to crossing-fiber voxels. The unbiased non-CFR FA values (blue dots) from the same tracts were put in both columns as references. As can be seen in the lower panel of Fig. 6, ST FA values at the CFR (pink “+”) cluster are severely underestimated and fall below the ST FA values in the non-CFR voxels (blue dots). In contrast, TSFA at the CFR voxels (red circle) overlap with FA values at the non-CFR voxels (blue dots). It indicates that the application of the proposed technique restores the unbiased FA at the CFR, resulting in a group of consistent FA values at both CFR voxels and non-CFR voxels in the same tract.

Along-the-tract analysis—Fig. 7 shows the differences among TSFA, ST FA, GFA and GA (Fig. 7a and 7c); differences of TSFA from dMRI of Philips scanner and dMRI of GE scanner (Fig. 7a and 7c) and differences of TSFA with single and two shell dMRI (Fig. 7b and 7d) along the CST. The traced CST is shown in red color at the top of Fig. 7. Fiber crossings of CST and corpus callosum occur at the corona radiata part of CST. The ST FA values at that location are smaller, shown as a dip in the CST profile (blue line) and pointed by the orange arrow in Fig. 7a and Fig. 7b. TSFA (red line in Fig. 7a and red bar in Fig. 7c), GFA (gray line in Fig. 7a and gray bar in Fig. 7c) and GA (black line in Fig. 7a and black bar in Fig. 7c) show more homogeneous CST profile, compared to ST FA (blue line in Fig. 7a and blue bar in Fig. 7c). Among all metrics, TSFA has the best tract profile homogeneity with the smallest standard deviation to mean ratio (Fig. 7c) based on all anisotropy values along the CST. Also shown in Fig. 7c, the mean of GA along the CST is quite similar to that

of TSFA along the CST, while the standard deviation of GFA along the CST is similar to that of TSFA along the CST.

It can be seen in Fig. 7a and 7c that TSFA is insensitive to the dMRI from different scanners and different gradient orientations. Specifically, TSFA/ST FA profile (orange/dark blue line in Fig. 7a) and their mean/standard deviations (orange/dark blue bar in Fig. 7c) from dMRI of the GE scanner with 25 diffusion gradient directions is similar to those from dMRI of the Philips scanner with 30 diffusion gradient directions.

By comparison of TSFA results from two shell ($b = 1000$ and 2500 s/mm²) and single shell ($b = 1000$ s/mm²) dMRI in Fig. 7b and 7d, the TSFA profiles along the CST with single shell and two shell dMRI appear to be similar in Fig. 7b while the ST FA profile along the CST is significantly lower with two shell dMRI than that with single shell dMRI.

Application of TSFA to the clinical HSP case

Fig. 8 demonstrates the improvement of detecting biomarkers inferring disruption of WM microstructure in the clinical HSP case. The red clusters in Figs. 8a and 8b indicate the regions of significantly lower FA in the HSP patient group compared to those of control group before and after anisotropy correction, respectively. ST FA could only identify a single disrupted location (cluster #1) in lower CST shown in Fig. 8a. Due to the fiber crossing, the disrupted location in upper CST (cluster #2) cannot be revealed in Fig. 8a. With TSFA, the cluster #2 is revealed in Fig. 8b besides cluster #1. Fig. 8c shows that averaged TSFA at the cluster #2 are significantly correlated to the clinical GMFCS scores, revealing additional clinical imaging biomarkers.

Discussion

In this study, we presented a technique for estimation of TSFA, corrected for the effects of free water and crossing-fiber geometry, and adapted for tract analysis. This technique has low requirements on dMRI data acquisition and is readily used for single shell dMRI data with 25–30 diffusion encoding directions. In addition, the proposed technique is easy to implement and the postprocessing is computationally efficient. The digital phantom studies and tests with clinical diffusion MRI jointly suggest that this technique is robust for estimating unbiased per-tract anisotropy values after free water correction and can increase sensitivity in detecting WM microstructural abnormality at the CFR when applied to clinical research. The proposed technique is therefore a technique to get closer to an efficient, workable solution acceptable in a clinical setting. The whole package for TSFA will be made available in a public website.

The motivation of this study is to provide a convenient tool estimating unbiased TSFA at CFR for radiologists, psychiatrists, neurologists and other clinicians who use FA from dMRI in their routine clinical research. For them, there is a strong need to improve anisotropy measurements at CFR for tract analysis without altering their dMRI sequences.

Digital phantoms were used for evaluating estimated f_{iso} , FA1, FA2, $f1$ and $f2$ in the CFR voxels. A linear function of $mADC$ from single shell dMRI was used to compute f_{iso} in the

CFR voxels. The resultant f_{iso} was shown to be accurate when compared to two shell dMRI (Fig. 2). In addition, FA_i and f_i ($i=1$ or 2) were estimated with high accuracy after free water correction with wide range of SNRs and combinations of individual-tensor FA values, fractions of each tensor and angles between the two tensors covering most CFR situations (Fig. 3). With human dMRI data, the consistency of the TSFA at the CFR to the ST FA value at the non-CFR voxels, shown in Fig. 6 and Fig. 7, demonstrates the effectiveness of TSFA. Such consistency of anisotropy at the CFR and non-CFR voxels can be also appreciated with weighted FA map shown in Fig. 5. TSFA can be reliably applied to dMRI data acquired from scanners of different manufacturers. Fig 7a showed that the estimation of FA along-the-tract is similar across the scanners of different manufacturers and yielded similar profile along the CST for acquisition with 25 or 30 diffusion gradient directions. TSFA in HSP brains revealed the disrupted CST location which has significant clinical correlation and could not be identified with ST FA (Fig. 8).

At least two shell dMRI, besides b_0 , is required (28) to estimate f_{iso} in the CFR voxels. However, typical dMRI in clinical studies is usually acquired in less than 5 minutes with a single shell of $1000s/mm^2$ and 25–60 diffusion gradient orientations. f_{iso} has been estimated using a single shell dMRI by imposing equal f_1 and f_2 from both the tensors (29). However, f_1 and f_2 are different in most CFR voxels (3). To estimate f_{iso} with single shell dMRI, we developed and tested a method using a linear function of $mADC$ for *a priori* calculation of f_{iso} . This linear function has been validated with a digital phantom (Fig. 2b) and could serve as a calibration line for estimation of f_{iso} . The three-compartment Gaussian mixture model in Equation [1] was simplified into the two-compartment model by *a priori* calculation of f_{iso} without sacrificing the validity of the three-compartment model used for estimating TSFA. Our own study (31) and another independent study (28) have shown that two tensors can be reliably fit with two-compartment model using a single shell dMRI after appropriate constraints (e.g., the constraints shown in Appendix). The number of gradient directions to fully characterize the crossing fibers can be estimated from spherical harmonics (SH), $N=1/2*(l_{max}+1)(l_{max}+2)$, where l_{max} is the maximum SH order. For crossing of two fibers or two tensors, l_{max} is 4 which results in $N=15$. Practically more than 15 gradient directions are needed to improve the two-tensor fitting.

The proposed technique is unique in estimating two anisotropy values corresponding to two crossing fibers after free water elimination at the CFR voxels. Dual-FA values within a single voxel are difficult for voxelwise analysis. However, dual-FA values can be readily used for tract analysis, as illustrated in Fig. 1. It is important to note that the binary volumes of the crossing tracts will overlap with each other at the CFR voxels, if they are compressed into one volume. Two tracts need to be separated at the CFR voxels. With tract analysis, each of the TSFA values at the CFR voxels all over the entire brain is associated with a specific tract (Fig. 1). Fiber orientations of the surrounding non-CFR voxels will be used to determine which tract is associated with one of the two TSFA values. TSFA can be readily integrated into the tract statistics (6–9), tract morphometry (10–11) and tract metric analysis (12–15) developed recently. On the other hand, the weighted FA map shown in Fig. 5 helps to conduct the whole brain voxelwise comparison as two anisotropy values are integrated

into one weighted FA for each CFR voxel. Such scheme of a weighted average of two per-tract metric at CFR has been used recently for another novel measure at CFR (49).

There are several limitations of the proposed technique. Free water fraction, f_{iso} , was estimated from $mADC$ by assuming fixed coefficients i.e. $f_{iso} = c1 * mADC + c2$ which leads to at most an approximate estimate of f_{iso} . Nevertheless, it is a more appropriate estimation of f_{iso} that reflects local tissue diffusion properties compared to the fixed value used previously (23). Although previous studies have suggested prevalence of two-fiber crossings among all the fiber crossings in the brain voxels (e.g. 25, 50–51), there are brain voxels that have more than two-fiber crossings (52). It should be noted that this technique was not designed to resolve crossing of three or more fiber bundles. By imposing certain constraints on the Gaussian mixture model, it is possible to estimate three primary eigenvectors using a single shell dMRI (27, 33). To estimate three full tensors (for measuring three anisotropies), 20 (18 for three tensors and 2 for $f1$ and $f2$) independent variables need to be estimated. Even after constraints, 20 independent variables could only be reduced to 10 and the phantom tests showed that we could not reliably estimate these 10 variables. In order to reduce the number of independent variables for better nonlinear fitting, assumptions such as equal largest eigenvalues for the two tensors (28) may not best fit the underlying WM fiber architecture. The assumptions on the equal largest eigenvalues (28) were proposed for better nonlinear fitting, but prevented this technique from being used for estimating other important metrics such as axial (AxD) or radial diffusivities (RD) at the CFR. Although AxD and RD of the fibers in combination with FA may better infer the underlying microstructures (5, 53), it is impossible to estimate individual unbiased AxD and RD accurately with single shell dMRI (28). We have conducted phantom study to show that AxD and RD can be accurately estimated by removing the assumption of equal largest eigenvalues and incorporating two shell dMRI acquisitions which has also been confirmed by another independent study (30). Further validation of TSFA at CFR could be conducted by scanning the optic chiasm, a known crossing-fiber structure, with different resolutions. Such investigation is beyond the scope of this study. Besides Gaussian mixture model that can be readily applied in routine clinical research, spherical harmonic decomposition (SHD) techniques have also been used to provide tract-specific metrics (54–55) such as peak FA. Nevertheless, peak FA is considered as a different metric from two FAs estimated from Gaussian mixture model and the biological meaning of peak FA is not yet clear. Finally, our phantom test (Fig. 3) shows that SNR=35 is required for a good fitting of two tensors. Clinical dMRI acquired from 3T scanners at $b=1000s/mm^2$ can achieve such a SNR, but may need repetitions of dMRI acquisitions from 1.5T scanners to enhance SNR.

Conclusion

A technique estimating TSFA, corrected for the effects of free water and crossing-fiber geometry at CFR, has been developed and tested with digital phantom and dMRI data acquired in routine clinical research. TSFA is suited for tract analysis. Unbiased TSFA of dual-tensors and high accuracy of estimated f_{iso} was demonstrated with digital phantom analysis. The underestimated FA at the CFR of the major WM tracts was effectively restored and found to be consistent with the ST FA at the non-CFR of the same tracts. Application to

HSP showed potential of TSFA to reveal additional imaging biomarkers highly correlated to clinical motor function scores.

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APPENDIX: constraints and algorithm used to fit D_1^- and D_2^-

$\overline{D_1}$ and $\overline{D_2}$ of Equation [1] are formulated from their eigenvalues $E_1 = \text{diag}[\lambda_{11}, \lambda_{21}, \lambda_{31}]$, $E_2 = \text{diag}[\lambda_{12}, \lambda_{22}, \lambda_{32}]$ and rotations R_1, R_2 by $\overline{D_i} = \overline{R_i^T} E_i \overline{R_i}$. Rotation around x, y and z

axes is given by $\overline{R}_i = \overline{R}_{x(\alpha_1)} \overline{R}_{y(\alpha_2)} \overline{R}_{z(\alpha_3 \pm \alpha_4)}$, $i=1,2$ for $\overline{D}_1$ and $\overline{D}_2$ respectively, where α_k , $k=1,2,3$, represent the orientation of the plane in which the principal eigenvectors of the two tensors reside and α_4 is the angle between the two primary eigenvectors of $\overline{D}_1$ and $\overline{D}_2$ (28).

Constraints

The free water fraction, f_{iso} , was calculated *a priori* using a linear regression equation from $mADC$ with details in step #1–1 in methods. The diffusivity of the isotropic component, D_{iso} , in the voxel is assumed constant at $3 \times 10^{-3} \text{ mm}^2/\text{s}$ (39). Extra constraints include assuming the same axial diffusivity for the two tensors and equal two smaller eigenvalues for each individual tensor (28). With the above-mentioned constraints, the 13 independent variables in Equation [1] are reduced to 8 independent variables, namely λ_{1i} ($i=1,2$), λ_{2i} (equal to λ_{3i}), λ_{22} (equal to λ_{32}), a_1 , a_2 , a_3 , a_4 , fl .

Algorithm

1. The initial parameters are obtained as follows: Fit single tensor model to the measured signal in the CFR voxel and obtain the eigenvalues (λ_{1s} , λ_{2s} and λ_{3s} , where s denotes single tensor). Initialize λ_{1i} and λ_{2i} ($i=1,2$) as $\lambda_{1i} = \lambda_{1s}$ and $\lambda_{2i} = \lambda_{3s}$. The angles between the primary eigenvector and x, y and z axes are used to initialize a_k , $k=1,2,3$, respectively. The initial guess of the separation angle of the two tensors, a_4 is obtained from $\arctan(\lambda_{2s}/\lambda_{1s})$. The initial guess of fl is 0.6.
2. Fit the 8 independent variables by solving Equation (1) using Levenberg-Marquardt algorithm.
3. Test for the goodness-of-fit by calculating the similarity between the fitted dual-tensors and the measured diffusion profile with a fitting error metric $\left(\sum_{i=0}^{N_{dir}} \left(|S_i - S_i^f| / S_i \right) \right) / N_{dir}$, where N_{dir} is the total number of gradient directions, S_i is the measured signal of i th gradient direction of dMRI, and S_i^f is computed from the fitted dual-tensor model. Exit the algorithm if the fitting error is less than 0.05 and iteration not equal to 1.
4. If iteration=1 or the fitting error in the current iteration is less than that in the previous iteration, perturb the solution from step #2 randomly and use the perturbed solution as revised parameters, repeat steps #2–#3.
5. If iterations equal to 100 and the fitting error is greater than 0.05, update the current voxel as non-CFR voxel and exit.

Figure 1.

Diagram of tract analysis. Low FA value (0.3) at the red voxels from single tensors in (a) can be corrected by dual-FA values from dual-tensor fitting after free water correction in (b). Each of dual-FA values is associated with a unique blue or green tract. For tract analysis, the crossed fibers (red voxels in (a) and (b)) in a single data volume can be separated into two tracts (blue and green tract in (c)) in multiple data volumes, each of which contains only one tract (c). Tract profile can also be obtained (c). Different colors of ellipsoids indicate diffusion tensors of two unique tracts. The corrected dual-FA values (0.6 and 0.7) at the red voxels in (a) and (b) belong to two different tracts.

Figure 2.

(a) Left and right panel shows f_{iso} in the CFR voxels estimated with Pasternak et al., 2009 approach (39) from single shell dMRI and Gaussian mixture model from two shell dMRI. Color bar encodes values of f_{iso} . (b) Left panel shows significant linear relationship between f_{iso} estimated from two shell dMRI and $mADC$ from single shell dMRI in the CFR voxels of 5 normal brains. Right panel shows f_{iso} estimated from $mADC$ of single shell dMRI with the linear equation obtained from left panel of (b).

Figure 3.

(a) Estimation of FA1 and FA2 of two crossing-fiber components at different SNR and separation angles (40, 50 and 80 degrees) after free water elimination. Left, middle and right panels represent different combinations of ground truth FA1 and FA2. (b) Estimation of $f1$ at different SNR and separation angles (40, 50 and 80 degrees) with two typical combinations of FA1 and FA2 in the upper and lower panels. Dashed lines are true FA values (a) and true $f1$ (b). Arrows indicate the SNR above which the fitting becomes accurate and stable.

Figure 4.

A coronal FA map of a healthy subject with the CFR voxels highlighted by the white box is shown in the upper left corner. Top panels show single eigenvector from ST model and the two primary eigenvectors obtained from ball-and-stick model (BSM) (25) and the proposed technique for TSFA at the CFR voxels from left to right. Bottom panel shows the estimated single tensor from ST model and BSM and estimated two tensors from the proposed technique for TSFA from left to right. Eigenvectors and tensors are overlaid on FA maps in both top and bottom panels.

Figure 5.

ST FA (upper panels) and weighted FA (lower panels) averaged from low b DWI from 17 subjects. The red arrows point to some typical regions with apparently lower ST FA due to fiber crossings. Compared to ST FA, weighted FA provides an unbiased measure of FA at CFR in the entire brain.

Figure 6.

Upper panels show traced IFO, ILF, SLF and UNC overlaid on a representative sagittal ST FA image, respectively. Below each tract, crossing-fiber anisotropy values before (pink “+”) and after (red circles) anisotropy correction for sampled voxels at the CFR are shown in left and right columns, respectively. The identical blue dots representing unbiased ST FA values from non-CFR voxels of the same tracts were put in both columns as references.

Figure 7.

(a) Metric profiles of TSFA, ST FA, GFA and GA along the CST; (b) Metric profiles of TSFA and ST FA from single shell and two shell dMRI; (c) Mean and standard deviation of the anisotropy metrics along the CST corresponding to panels (a); (d) Mean and standard deviation of the anisotropy metrics along the CST corresponding to panels (b). CST separated into segments of midbrain, internal capsule and corona radiata and overlaid on sagittal FA images is shown at the top panels for anatomical guidance. Results shown in (a) and (c) are from both Philips and GE scanner. Results shown in (b) and (d) are from Philips scanner only.

Figure 8.

Cluster(s) of voxels with significantly ($p < 0.001$) lower FA in HSP patients compared to controls in left CST are shown in red with ST FA (a) and TSFA (b). 3D reconstructed brain (gray) and CST (yellow) are shown in (a) and (b) as anatomical reference. Cluster #2 appeared with TSFA and significant ($p < 0.001$) linear relationship between averaged TSFA in cluster #2 and GMFCS of 12 HSP patients was found in (c).

Table 1

Literature review of Gaussian mixture model used to estimate dual-tensors at the crossing-fiber regions (CFR). Each study is denoted by a separate symbol and the legends are shown on the right side of the table. Entries for the parameters are marked if the study explicitly estimates the listed parameter. $v_{1,1}$ and $v_{1,2}$ represent the primary eigenvectors, f_1 and f_2 represent the fractional contribution and FA1 and FA2 represent the fractional anisotropy for tensor 1 and tensor 2, respectively. f_{iso} represent the free water fraction in the CFR voxel. b represent the b-value. SS dMRI: single shell diffusion MRI, w/o: without.

Year	SS dMRI	$v_{1,1}$	$v_{1,2}$	f_{iso}	f_1 w/o f_{iso}	f_2 w/o f_{iso}	FA1 w/o f_{iso}	FA2 w/o f_{iso}	f_1 with f_{iso}	f_2 with f_{iso}	FA1 with f_{iso}	FA2 with f_{iso}	Tract- specific FA	TSFA
2014	■	■	■	■	■	■	■	■	■	■	■	■	■	■
2013	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
2012	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2012	✱	✱	✱	✱	✱	✱	✱	✱	✱	✱	✱	✱	✱	✱
2010	□	□	□	□	□	□	□	□	□	□	□	□	□	□
2010	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2010	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇	◇
2009	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2008	△	△	△	△	△	△	△	△	△	△	△	△	△	△
2008	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧	✧
2007	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
2006	■	■	■	■	■	■	■	■	■	■	■	■	■	■
2005	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
2005	○	○	○	○	○	○	○	○	○	○	○	○	○	○
2003	▣	▣	▣	▣	▣	▣	▣	▣	▣	▣	▣	▣	▣	▣
2002	●	●	●	●	●	●	●	●	●	●	●	●	●	●