Application of Multi-Tensor Tract-based Analysis (MTTA) with routine clinical diffusion MRI

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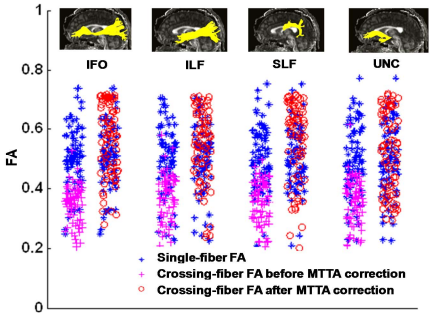
Target Audience: The developed MTTA technique can increase the sensitivity and accuracy of detecting structural changes of specific white matter tracts for clinical research of neurological, psychiatric or psychological disorders.

Purpose and Introduction: Fractional anisotropy (FA) values derived from the single tensor model are significantly underestimated at the white matter crossing-fiber regions. Single tensor FA, therefore, is biased in characterizing the white matter integrity in clinical research. Several metrics [e.g. 1-2] have been proposed to replace single tensor FA. However, they require high b and high angular resolution and cannot be used in clinical research. On the other hand, tract analysis [e.g. 3-5], in contrast to voxelwise analysis, has obtained recent attention as individual white matter tracts have more clinical significance. In this abstract, we further explored an MTTA (Multi-Tensor Tract-based Analysis) technique [6] which is capable of restoring the FA values of the targeted tract along its path while correcting the bias in single tensor FA. With the previous validation by digital phantom, we directly tested MTTA with *in vivo* diffusion MRI acquired in routine clinical research. Specifically, these routine clinical diffusion MRI data can be readily acquired within 10 minutes with clinical MR scanners and only require more than 10 diffusion orientations and b values of 1000s/mm^2. MTTA was optimized to avoid local minimum and applied to *in vivo* human brain diffusion weighted images (DWIs) to restore FA values at the crossing-fiber voxels of a selected group of white matter tracts. In addition, weighted FA at the crossing-fiber voxels was defined and proposed as an unbiased anisotropy metric to characterize white matter integrity in clinical research.

Methods: *Signal model:* A simplified Gaussian mixture model $S_i / S_0 = f_{iso} e^{-bD_{iso}} + f_1 e^{-b\overline{G_i^T}\,\overline{D_1}\,\overline{G_i}} + (1 - f_1 - f_{iso}) e^{-b\overline{G_i^T}\,\overline{D_2}\,\overline{G_i}}$ was used, where f_1 and f_{iso} are the volume fractions of the first fiber bundle and the isotropic component in the crossing-fiber voxel, b is the diffusion b value, $\overline{\overline{D_1}}$ and $\overline{\overline{D_2}}$ are the two tensors representing the first and second fiber bundles, and $\overline{G_i}$ is the ith gradient vector. Levenberg-Marquardt estimation algorithm was used for multi-tensor fitting. *Acquisition of DTI used in routine clinical research*: 10 young healthy volunteers were scanned with a 3T Philips Achieva MR system. Routine DTI data used for clinical research was acquired using a single-shot EPI sequence with SENSE parallel imaging scheme (reduction factor =2.3). DWI parameters were: in plane imaging matrix = 112× 112 with imaging resolution 2x2mm, axial slices thickness = 2.2 mm without gap, Jones 30 gradient scheme [7] with b-value = 1000 sec/mm^2. *Identification of crossing-fiber voxels for multi-tensor fitting:* Spherical harmonics (SH) decomposition was conducted for all white matter voxels first. After extensive tests for optimizing the parameters for low b (1000 sec/mm^2) clinical diffusion MRI, we have found that the voxels where multi-tensor fitting should be applied satisfy the following criteria: 1) (SH order 4) OR (SH order 2 and single tensor FA≤0.4); and 2) E_4 (energy of order 4) ≥ $0.7E_2$ (energy of order 2). These criteria ensure convergence of the multi-tensor fitting. *Tract-based FA measurement:* We traced with FACT [8] inferior frontal occipital fasciculus (IFO), uncinate fasciculus (UNC), inferior and superior longitudinal fasciculus (ILF and SLF) which are known to have crossing-fiber regions along their paths. Selection of FA1 or FA2 was determined by alignment of the orientations of eigenvectors of $\overline{\overline{D_1}}$ or $\overline{\overline{D_2}}$ to eigenvectors of surrounding voxels. *Weighted FA:* A restored anisotropy metric, weighted FA, was defined as $(f_1*FA1+f_2*FA2)/(f_1+f_2)$ to quantify the anisotropy at the voxels of crossing fibers. Weighted FA values were calculated for all crossing-fiber voxels. *Quality control to avoid local minimum in the fitting:* Let S_i be the measured signals of ith gradient direction of DWI, and S_i^f be the signal from the fitted multi-tensor model. To ensure the fitting quality, we set a fitting error metric $\sum_{i=0}^{N_{dir}} |S_i - S_i^f| / S_i / N_{dir}$, where N_{dir} is the total number of gradient directions. This metric essentially measures how close the fitted multiple tensors are to the measured diffusion profile.

Results: *White matter tract FA measurement:* Upper panel in Fig. 1 shows the traced IFO, ILF, SLF and UNC (yellow fibers) overlaid on a representative sagittal FA image, respectively. The two columns below each tract in the lower panel of Fig. 1 show the FA values at the evenly sampled voxels for 10 subjects before (pink "+") and after (red circle) applying the MTTA technique to crossing-fiber voxels. The same unbiased single-fiber FA values (blue asterisks) from the same tracts were put in both columns as references. As can be seen in the lower panel of Fig. 1, FA values estimated using single tensor model on crossing-fiber voxels (pink "+") are severely underestimated as compared to those from single-fiber voxels (blue asterisks). In contrast, MTTA-corrected crossing-fiber FA values (red circle) overlap with those from single-fiber voxels (blue asterisks). It indicates that the application of MTTA well restores the FA at the crossing-fiber voxels, resulting in a group of FA value consistent in the same tract. *Weighted FA:* Top panel in Fig. 2 shows the averaged single-tensor FA from 10 subjects using single tensor model and the bottom panel shows the averaged weighted FA from the same 10 subjects after applying MTTA technique on the voxels of crossing-fibers. As can be seen from the top panel in Fig. 2, the FA estimated using single tensor model is significantly underestimated at the regions of crossing-fibers indicated by the red arrows. Substituting the underestimated single tensor FA by the weighted FA at the crossing-fiber regions renders a more homogeneous anisotropy map in the bottom panel.



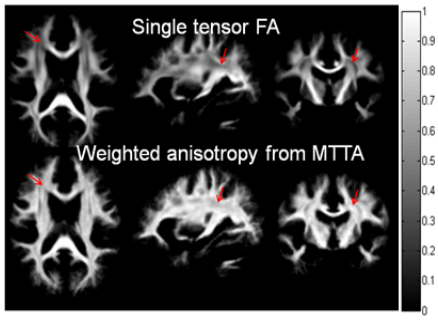


Fig. 1 (left): Single-fiber FA, crossing-fiber FA before and after MTTA correction for sampled voxels (lower panels) of individual tracts (upper panels).

Fig. 2 (right): Single tensor FA (upper panels) and weighted anisotropy from MTTA (lower panels) averaged from 10 subjects. The red arrows point to some typical regions with underestimated single tensor FA due to fiber crossing. Compared to single tensor FA, weighted anisotropy from MTTA provides unbiased measure of white matter integrity at the crossing-fiber regions in the entire brain.

Discussion and Conclusion: In this study, we have demonstrated that MTTA technique can be used to effectively correct the biased FA for the tracts that have crossing-fibers with diffusion MRI acquired for clinical research. In addition, the proposed weighted FA can be a potential unbiased metric characterizing white matter integrity at the crossing-fiber region. MTTA technique was optimized to avoid local minimum during the fitting. For all the crossing-fiber voxels applied with MTTA, fitting error metric less than 0.05 was achieved, indicating high quality of fitting convergence. The previous digital phantom study [6] suggested that MTTA fitting error is greater than 5% if crossing angle is less than 30 degrees. Under such circumstances, multi-tensor fitting was simply not initiated in our program. In summary, the MTTA technique has a great potential to correct the underestimated FA of the targeted tract from diffusion MRI routinely used in clinical research. ***References:*** [1] Tuch (2004) MRM 52,1358. [2] Zhan et al (2010) Neuroimage 49, 1357. [3] Yushkevich et al (2008) Neuroimage 41, 448. [4] O'Donnell et al (2009) Neuroimage 45, 832. [5] Goodlett et al (2009) Neuroimage 45, 5133. [6] Mishra et al (2011) ISMRM 4656. [7] Jones et al (1999) MRM 32, 515. [8] Mori et al (1999) Ann Neurol 45, 265. ***Acknowledgement:*** This study is sponsored by NIH EB009545.