Quantitative histological validation of fiber orientation distributions based on high-angular resolution diffusion imaging

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INTRODUCTION

Diffusion tensor imaging (DTI)[1] is increasingly used in clinical and research settings to resolve fiber directionality in tissues and to visualize major white matter tracks in the brain. A well known problem with DTI is the inherent inability to resolve crossing fiber trajectories (neural architecture with more than one principal direction) due to the partial volume effect. A number of promising methods have been proposed for resolving multi-directional fiber trajectories at the voxel-level, including diffusion spectrum imaging[2], spherical deconvolution[3], and Q-ball imaging[4]. These novel multi-directional diffusion methods have been validated using unidirectional tissue measurement, phantoms, or computer simulations, but direct quantitative assessment of the correlation with underlying neuroarchitecture is missing. We here provide a quantitative comparison of ex-vivo diffusion MRI-derived fiber orientation distributions (FODs) with histological FODs of myelinated fibers from fixed rat brain tissue.

METHODS

An anesthetized adult male Sprague-Dawley rat was euthanized by transcardial perfusion with 4% paraformaldehyde. The isolated brain was immersed for 4 weeks in a 4°C 1mM GdDTPA solution, and positioned in a in a sealed plastic tube filled with Fomblin liquid[5]. High-angular diffusion scans were acquired on a 4.7T Bruker scanner, using a 3 cm solenoid receiver coil. Images were obtained with 265 µm isotropic voxels, matrix = 64x64x128 and 514 q-space directions (max b-value 30,000). The brain was sectioned at 50 µm on a freezing microtome at an angle closely matching the tomographic images. One in four sections was stained for myelin using a modified Woelcke[6] procedure. High-resolution mosaic images were obtained through a 40x objective using a motorized Olympus Bx52 microscope running Neurolucida software. Regions of interest containing only in-plane fiber orientation were selected on basis of histological examination and absence of through-plane variance in the fitted diffusion tensor (DT). Multiple MRI detectible anatomical landmarks were used to define corresponding anteroposterior levels before linearly registering section images to corresponding diffusion slice images. For each voxel in a region of interest, all myelin stained fibers observed within a grid of 4 sample frames were plotted as vectors. Histological FOD estimates were obtained by computing the angular histogram of the plotted fiber vectors, and diffusion MRI-derived FOD estimates were obtained using regularized linear decomposition with empirical basis functions (EBF-FOD).

RESULTS

In a region with a clear unidirectional neuroarchitecture (corpus callosum), containing horizontally oriented commissural fibers, the DT and EBF-FOD measurements both correlated well with the histological measurements (average Pearson correlation coefficients = 0.833; SD = 0.016 for DT, and 0.979; SD = 0.032 for EBF-FOD). In a region containing mainly bi-directional in-plane crossing fiber orientations (deep grey and white layers of the superior colliculus, Fig.), DT estimates correlated poorly with the histological measurements (average Pearson correlation coefficients of 0.34; SD = 0.26), while the EBF-FOD estimates correlated substantially better (average Pearson correlation coefficient = 0.861, SD = 0.075).

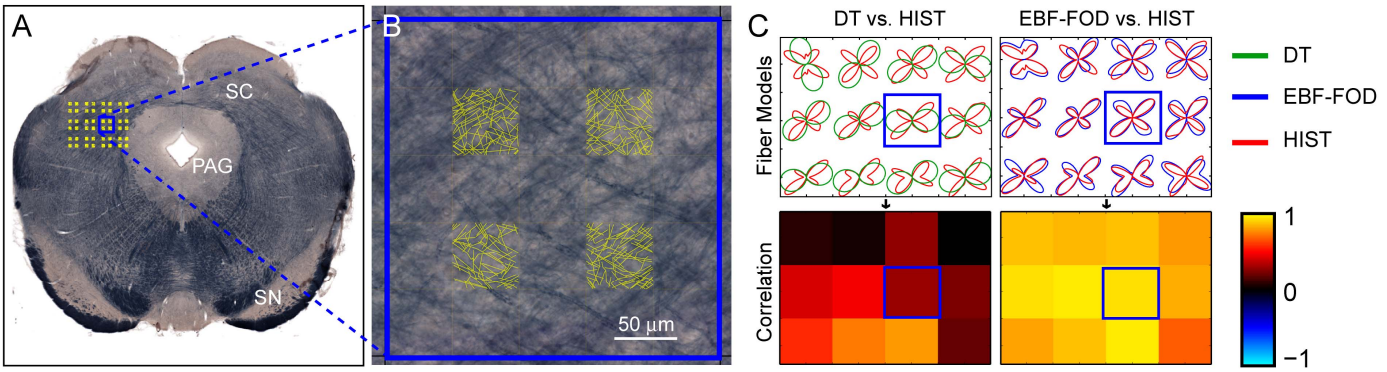

Fig. (A) Myelin stained brain stem section with 4x3 voxel region of interest in the deep layers of the superior colliculus. (B) In each voxel myelinated fibers were plotted in four sample grids. (C) Fiber distribution models and correlation plots showing correspondence of the DT and EBF-FOD models with histological FOD measurements. Blue frames indicate corresponding voxels across panels. PAG, periaquaductal gray, SC, superior colliculus, SN, substantia nigra.

DISCUSSION/CONCLUSIONS

White matter tractography methods based on the diffusion tensor model assume that the principle eigenvector of the diffusion ellipsoid is a good approximation to the local fiber orientation. Here we show that at least in some anatomical regions, this assumption is invalid as the tensor geometry does not reflect the underlying neuroachitecture of the tissue. In addition, we show that FOD estimates obtain using empirical basis function linear decomposition from high-angular resolution diffusion datasets correlate remarkably well with FOD estimates derived from histological sections. Our findings provide the first quantitative histological validation of diffusion-derived estimates of multidirectional myeloarchitecture, potentially suitable for subsequent validation of different multi-directional diffusion reconstruction algorithms.

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REFERENCES

1. Basser PJ, Mattiello J, LeBihan D. Biophys J 1994; 66:259-267.
2. Wedeen VJ, Hagmann P, Tseng WY, Reese TG, Weisskoff RM. Magn Reson Med 2005; 54:1377-1386.
3. Tournier JD, Calamante F, Gadian DG, Connelly A. Neuroimage 2004; 23:1176-1185.
4. Tuch DS. Magn Reson Med 2004; 52:1358-1372.
5. D'Arceuil H, de Crespigny A. Neuroimage 2007; 36:64-68
6. Woelcke M. J Psychol Neurol 1942; 51:199-202.