IN-VIVO MEASUREMENTS OF AXON RADIUS AND DENSITY IN THE CORPUS CALLOSUM USING ANOMALOUS DIFFUSION FROM DIFFUSION MRI

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Target Audience: Neuroscientists interested in brain microstructure

Purpose: The axon radius is an important property that affects nerve function, such as conduction velocity.[1,2] Mapping of axon radius and packing density provides information about the role and performance of white-matter pathways.[3,4] Innocenti et al. found that the radii of cortical axons depends both on the area of origin and target.[5] The corpus callosum comprises thicker axons projecting into motor and visual areas and thinner ones from prefrontal and parietal areas.[6-8] It has also been shown that the mean callosal fiber density has no significant correlation with callosal area.[3] MRI researchers have tried to measure axon radii along with histological investigations, however, the methods they used assume the radius of axon follows a γ distribution or a single axon radius in the models.[4,9-11] We aim to map the axon radius and density in the corpus callosum based on equations of anomalous diffusion. Our approach utilizes the previously outlined space fractional Bloch-Torrey equation.[12] Simulations were performed in a similar manner to that by Alexander et al.[4] We demonstrate that our method can measure axon radii and packing density from DWI data without a priori assumptions about the distribution of radii or angle of the fibre bundle.

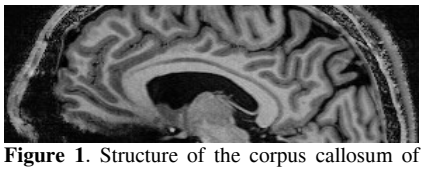

Figure 1. Structure of the corpus callosum of one human subject.

Methods: Processing pipeline: (i) a nonlinear least-squares fitting algorithm (Levenberg-Marquardt) in Matlab[12] was used for the fitting the parameters of the space fractional Bloch-Torrey model[12], catering for multiple b-values and multiple direction diffusion-weighted data; (ii) we performed constrained spherical deconvolution and probabilistic tractography using the MRtrix package to define regions of the corpus callosum projecting into different cortical regions (Figure 2); (iii) together with the fitted results from (i) and the multiple b-value multiple direction diffusion-weighted images, both axon radius and volume fraction in the corpus callosum were deduced with the aid of simulations proposed by Alexander et al.,[4] again using the Levenberg-Marquardt nonlinear fitting algorithm.

Diffusion-weighted and T1-weighted images were acquired in 10 healthy human subjects (1 female, 9 males; age, 23-66 years) on a 7T whole-body Magnetom MRI research scanner (Siemens Healthcare, Erlangen, Germany) with a maximum gradient strength of 70 mT/m at a slewrate of 200 mT/m/ms. Each subject underwent a 30-minute session. The data were acquired using a Stejskal-Tanner echo-planar imaging prototype pulse sequence: TE/TR = 86/5,900 ms, Matrix = 142, iPAT = 4, BW = 1,136Hz/pixel and 50 slices with an isotropic resolution of 1.5 mm^3 ensured coverage of the brain excluding the cerebellum. 11 b-values between 0 and 5,000 s/mm^2 in steps of 500 s/mm^2 were acquired with the signal-to-noise ratio maintained across b-values (i.e. number of diffusion directions increases with b-value, where directions were derived using the electrostatic model). The images were corrected for motion and eddy-current-induced distortions inline on the scanner using a prototype non-linear registration algorithm. We also acquired T1-weighted structural images at 0.75 mm^3 isotropic resolution. The structural images were used as a template to depict the results of our axon radius and axon density mappings. Additionally, we acquired a diffusion-weighted data set (1.5 mm^3 isotropic resolution, b-value = 3,000 s/mm^2 and 64 directions and TE/TR = 86/5,900 ms) for constrained spherical deconvolution allowing segmentation of the corpus callosum.

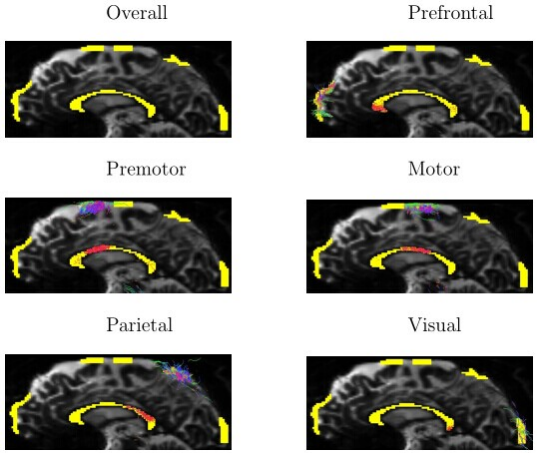

Figure 2. Callosal axon bundles from prefrontal, premotor, motor, parietal and visual areas.

Results and Discussion: Table 1 shows the comparison of axon radius between one human subject and histology data reproduced from Caminiti et al.[6] The distribution of axon radius is in good agreement with the histology result, namely "low-high-low-high". Furthermore, we were able to deduce the axon density across the corpus callosum projecting into the various cortical regions. We have performed the analysis for 10 subjects and one ex vivo imaging validated via electron microscopy. Overall, we found good agreement between our measures of axon radius and axon density with respect our measures used for validation. At the meeting we will report all of our results.

Cortical areas	Axon density	Axon radius (mm)	Histology axon radius (mm)
Prefrontal	0.18 ± 0.077	1.6735 ± 1.0715	0.5 ± 0.24
Premotor	0.29 ± 0.068	2.9417 ± 0.3050	-
Motor	0.27 ± 0.089	3.6269 ± 0.7362	0.62 ± 0.365
Parietal	0.35 ± 0.12	2.4867 ± 0.2074	0.49 ± 0.23
Visual	0.36 ± 0.12	2.7056 ± 0.4482	0.625 ± 0.32

Table 1. The comparison of axon radius between one human subject and histology data which are reproduced from Caminiti et al.[10] The trend across the regions of the corpus callosum should be compared and not the absolute values, as it is know that shrinkage occurs with histological processing.

Conclusion: After utilizing the model of space fractional Bloch-Torrey equation[12] and the simulation framework proposed by Alexander et al.,[4] we were able to measure the axon radius and density without assumptions of the distribution of axon radii or orientation of fibre bundles. This may be helpful in clinical diagnosis and monitoring, and further analysis of this data will be carried out in conjunction with medical specialists. Alexander et al.'s simulation framework is based on intra- and extra-axonal diffusion (CHARMED),[4] which may or may not apply in all white matter regions. In particular, in regions where compartmental exchange may be important. Our future work will focus on overcoming existing limitations.

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