In vivo estimation of axon diameter in the human spinal cord using 300 mT/m gradients

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Target audience: Physicists, clinicians (radiologists, neurologists), neuroscientists.

Purpose: The composite hindered and restricted model of diffusion (CHARMED) was shown to be useful for modeling micro-structure of white matter pathways. Combined with AxCaliber[1] framework, one can retrieve white matter micro-structural information, such as axon diameter. This technique is optimized by increasing the gradient strength above the 40-60mT/m available in current clinical systems. We recently demonstrated the feasibility to map axon diameter distributions in the human corpus callosum using 300mT/m human gradients[3]. Here we further our developments and demonstrate *in vivo* mapping of axon diameter in the human spinal cord. Given the difficulties associated with spinal cord diffusion-weighted MRI, we used state-of-the-art methods, including highly parallelized coil array, reduced FOV and template-based analysis.

Material and Methods: *Data acquisition*. Experiments were performed on 5 healthy subjects (mean age 28 +/- 11, three males). Data were acquired on a 3T MRI system (MAGNETOM Skyra, Siemens Healthcare, Germany) equipped with a *Connectom Gradient* (AS302) capable of up to 300 mT/m along each axis and a slew rate of 200 mT/m/ms. The slew rate was derated during the diffusion encoding to prevent physiological stimulation. A custom-made 60-channel phased-array head/neck receive coil was used. Diffusion-weighted data were acquired with a single shot EPI sequence. Q-space was sampled in the plane perpendicular to Z (direction of spinal tracts) along four opposite directions: XY, -XY, X-Y and -X-Y. Parameters were: TR ≈ 2s (cardiac gated), δ = 8ms, $G_{max} = \sqrt{2} * 300 = 410$ mT/m, diffusion time Δ = 20/35/50 ms, TE = 65/70/85ms (minimized for each Δ), voxel size = 0.8×0.8×5 mm^3. Four slices were prescribed between C1 and C4, in the middle of each vertebral body to ensure good B_0 homogeneity. Gradients were played at inverse polarity every two volumes to correct for eddy current distortions. Total acquisition time was around 30 min. Subject motion was corrected using interspersed b=0 volumes. The density of q-space sampling was linearly increased towards high-q to overcome the loss of SNR and to be more sensitive to smaller axon diameters. *Data processing*. The AxCaliber method was implemented in Matlab. The model fitting uses a non-linear least square routine (using trust-model-reflective optimization), with a maximum of six iterations. Although we could obtain consistent results of axon diameter gamma distribution (see Fig 1), single axon diameter within each voxel as in ActiveAx[4] was found to be more robust and hence was used to generate maps of axon diameters. The final stage consisted in registering spinal cord images to a template[5,6] using a diffeomorphic transformation tool (ANTS). Spinal pathways were manually isolated based on anatomical atlases of the white matter.

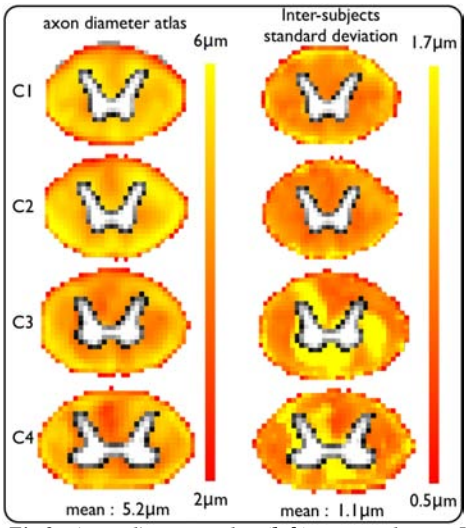

***Fig.2**: Axon diameter atlas (**left**) averaged over 5 patients and the corresponding inter-subject dependence (**right**).*

Results: Signal decay curves showed different patterns for each tract and could be correctly fitted with the CHARMED model (see Fig 1). Average axon diameter distributions showed consistent values in the gracilis (3.2 μm), rubrospinal (4.3 μm) and cutaneous tracts (5 μm). Note that values in the right and left tracts were similar, suggesting good reproducibility of the technique. The map of mean axon diameter, generated using the ActiveAx approach is shown in Fig 2. These maps were generated by averaging the 5 subjects after registration to the template. The standard deviation across subjects suggests fairly good inter-subject reproducibility of axon diameter mapping. Local spots of high variance ~1.7 μm are seen at levels C3 and C4 and might be due to large physiological noise due to cardiac pulsation[7].

Discussion: This study provides for the first time *in vivo* mapping of axon diameters in the human spinal cord using the AxCaliber technique. We observed a mean axon diameter of 5.2 μm with a within-voxel variability of 1.1 μm between subjects. When comparing our distributions with that ones from *ex vivo* rat studies[2], average sizes of tract groups relative to each other seem consistent, with the gracilis, rubrospinal and cuneatus tracts having increasing axon diameters. These trends need to be validated with *ex vivo* human samples. This study was made possible with the 300 mT/m gradient system. However, methods that can estimate useful axon features were recently investigated with lower gradient strengths[4], notably in the spinal cord[8]. Future studies will compare the different approaches from *in vivo* measurements. AxCaliber and other single-fiber-based methods seem the most relevant for spinal cord studies due the assumption of coherently oriented fibers, hence providing time-efficient q-space sampling. Despite the use of cardiac gating (acquisition window set to 700ms), physiological noise seemed to confound results, as assessed by comparing back-and-forth gradient directions (data not showed). The inter-subject variation in axon diameter mapping could be explained by physiological noise, as well as anatomical variations in the location of white matter tracts, as suggested by previous studies focusing on gray matter shape[5].

Conclusion: This study demonstrates the feasibility to estimate axon diameter distribution in the *in vivo* human spinal cord using 300 mT/m gradient strength. This opens the door to clinical applications in diseases such as multiple sclerosis, amyotrophic lateral sclerosis (ALS), and spinal cord injury, for which axon microstructure is a relevant biomarker of early diagnosis or prognosis.

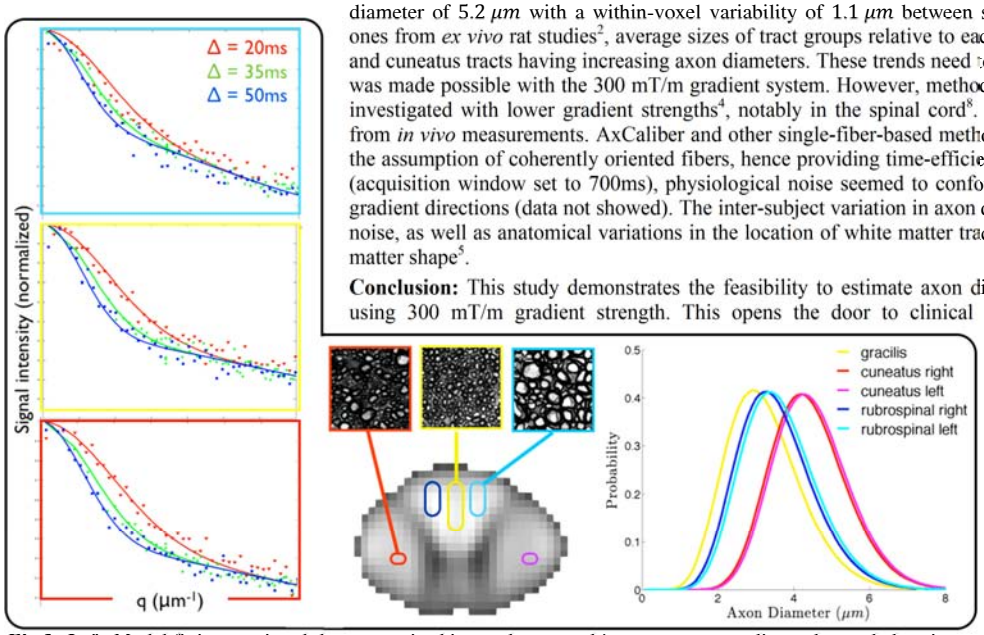

***Fig.1**: **Left**. Model fitting on signal decay acquired in one human subject on corresponding color-coded regions. **Middle**. Average DWI at b-values ∈ [5000, 13400] s/mm^2. For qualitative comparison, zoomed windows show axon histology in a rat spinal cord[2]. **Right**. Results of axon diameter distribution in the corresponding regions.*

References: **1.** Assaf, Y. et al., MRM 59, 1347-1354 (2008). **2.** Chin, C. L. et al., MRM 52, 733-740 (2004). **3.** McNab, J. A. et al.,, NeuroImage 80, 234-245 (2013). **4.** Alexander, D. C. et al., NeuroImage 52, 1374-1389 (2010). **5.** Taso, M. et al., Magma (2013). **6.** Fonov, V. S. et al., ISMRM, 1119 (2013). **7.** Piché, M. et al., Magn Reson Imaging 27, 300-310 (2009). **8.** Grussu, F. et al., MRM (2013).

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