In vivo mapping of myelin g-ratio in the human spinal cord

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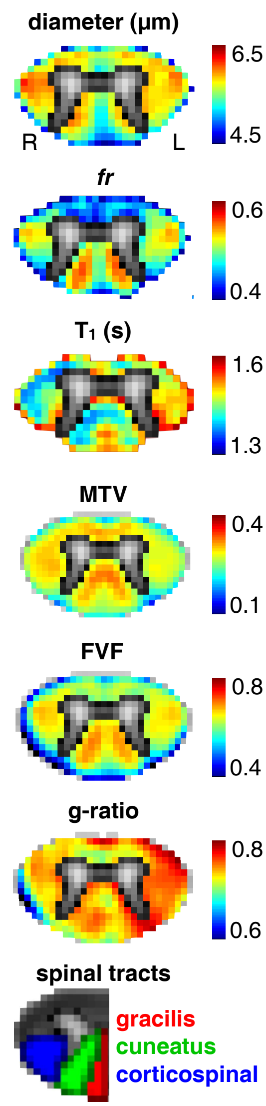
Purpose. The myelin g-ratio is the ratio of the inner to the outer diameter of the myelin sheath. As such, it provides a measure of the myelin thickness that complements axon morphology (diameter and density), with high specificity towards assessment of demyelination in diseases such as MS. Mapping g-ratio in the spinal cord has therefore great interest for the diagnosis/prognosis of several neurodegenerative diseases. Previous work shows that the g-ratio can be computed from a simple formula relating the fiber volume fraction (FVF) to the myelin volume fraction (MVF) [1]. FVF can be estimated from diffusion-weighted experiments, while MVF can be derived from myelin mapping techniques [2]. In this work, we took advantage of the 300 mT/m gradients from the *connectome* scanner [3] for estimating FVF with high accuracy using AxCaliber [4, 5]. To achieve reasonable scan time and circumvent the RF deposition issue, MVF was estimated using the macromolecular tissue volume (MTV), derived from T1 and PD mapping [6].

Methods. *Acquisition*. Experiments were performed in 9 healthy subjects (28 +/- 11 y.o., 5 males) using a dedicated high-gradient (AS302, G_{max}=300 mT/m) 3T MRI scanner (MAGNETOM Skyra CONNECTOM, Siemens Healthcare) equipped with a custom-made 60-channel phased array head/spine coil [7]. The parameters for the AxCaliber protocol were: EPI sequence, 4 slices covering C2 to C5, TR~2s (cardiac gating, 2 slices per phase), TE = 70ms, matrix = 128×128, voxel size = 0.8×0.8×5 mm^3, R=2 acceleration using GRAPPA, $G_{max} = \sqrt{2}*300 = 410$ mT/m, diffusion time Δ = {20, 20, 40, 36} ms, δ = {3, 3, 6, 6, 10} ms, slew rate = 90 mT/m/ms (downgraded), acquisition time ~ 30 min. The parameters for the MTV protocol were: gradient echo 3D FLASH, TR/TE = 20/2.74 ms, flip angle = {4°, 10°, 20°, 30°}, matrix = 192×192, R=2 acceleration using GRAPPA, same coverage and voxel size as in the AxCaliber protocol, BW=400Hz/pixel. B1 mapping was done using a segmented spin echo EPI sequence: TR/TE=3000/19ms, flip angle = {60°, 120°}, voxel size = 3×3×5 mm^3. A 3D T2-weighted fast spin echo sequence was acquired for registration to the template. *Processing of AxCaliber data*. Eddy-current distortions were corrected using the reversed gradient method [8], followed by slice-by-slice motion correction, local PCA denoising and AxCaliber fitting using Gaussian phase distribution approximation [9], yielding maps of axon diameters and restricted water fraction (*fr*). *Processing of MTV data.* Data were registered to flip angle 10° using SyN transformation [10], voxel-wise estimation of M0 and T1 were done according to [11], accounting for the B1 map obtained from the double angle method. Here we assumed coil sensitivity to be constant across the region of interest (verified from SNR map) and assumed no T_2* contribution. Average M0 in the CSF ($M0_{CSF}$) was calculated using a manual mask. MTV was then calculated as in [6]: MTV = 1 - ($M0/M0_{CSF}$). *Group analysis*. Registration of AxCaliber and MTV metrics to the MNI-Poly-AMU template [12] was done with the Spinal Cord Toolbox (http://sourceforge.net/projects/spinalcordtoolbox/). *G-ratio estimation*. FVF was calculated as in [13]: FVF = MTV+(1-MTV)*fr. Then, g-ratio was computed as in [1]: g = sqrt(1-MTV/FVF). Quantification of metrics within specific spinal pathways was achieved in the template space using the atlas of white matter tracts [14]. All processing scripts are available at https://github.com/neuropoly/spinalcordtoolbox.

Results. Fig 1 shows mapping of axon diameter, water restricted fraction (*fr*), T1, MTV, FVF and g-ratio at the C3 vertebral level. Average values within spinal tracts are listed in Table 1. Mean diameters are smaller in the gracilis, confirming previous results [4]. G-ratio in the spinal cord white matter ranged from 0.60 to 0.80 (median 0.73, mean 0.74 ± 0.06). The inter-subject coefficient of variation (COV) averaged across tracts was respectively 37%, 12%, 25% and 13% for axon diameter, T1, MTV and g-ratio.

Discussion. We demonstrate for the first time *in vivo* mapping of myelin g-ratio in the human spinal cord. G-ratio was fairly constant across the whole spinal cord white matter with an average value of 0.74, which is consistent with the reported optimal g-ratio of 0.70 [15]. Measurements of g-ratio are fairly reproducible (COV = 13%), despite some difficulties for accurately registering all subjects due to variability in gray matter morphology. It should be acknowledged that MTV is not an absolute measure of myelin; other myelin mapping techniques exist such as qMT and myelin water fraction. Similarly, FVF could be estimated using other approaches such as NODDI [9]. While *in vivo* g-ratio mapping warrants further histological validation, the proposed method is feasible in a clinically-acceptable time (~40min) and could be useful for assessing demyelination in diseases such as multiple sclerosis.



→ *Fig 1. Mapping of AxCaliber and MTV results at C3 vertebral level. Maps are averaged across subjects (n=9). The "spinal tracts" image shows the tracts that were used to compute metrics (takes into account partial volume effect).*

	Diameter (µm)	T1 (s)	MTV	g-ratio
gracilis	5.26 ± 0.80	1.38 ± 0.26	0.29 ± 0.03	0.74 ± 0.03
cuneatus	5.74 ± 0.66	1.37 ± 0.26	0.29 ± 0.04	0.75 ± 0.03
corticospinal	5.89 ± 0.52	1.40 ± 0.28	0.27 ± 0.03	0.74 ± 0.02

Table 1. Results of AxCaliber and MTV metrics averaged within tracts and across subjects.

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