The impact of gradient strength on *in vivo* diffusion MRI estimates of axon diameter

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PURPOSE: Several methods have been developed for estimating axon diameter distributions (ADDs) and fiber density in white matter bundles.[1-4] These methods generally acquire diffusion-weighted images with a range of q-values and diffusion times. A model for intra- and extra-axonal diffusion is then fit to the data. Large q-values are needed since $1/q_{max}$ defines the ability to resolve small differences in spin displacements. The need for short diffusion times and large q-values places strong demands on MRI gradient hardware. The advent of higher maximum gradient strengths (G_{max}) on human MRI scanners[5,6] has enabled the translation of AxCaliber[1] and other axon diameter mapping methods from small animal[2] and ex vivo studies[1] to the *in vivo* human brain.[3,7] Recent simulation and *ex vivo* experimental results suggest the key role of G_{max} in detecting small diameter axons (~μm) and enhancing contrast between ADDs.[8] These results motivated us to systematically study the effect of gradient strength on *in vivo* axon diameter estimates. Here we use a novel 3T MRI equipped with G_{max}=300 mT/m to acquire data with a range of G_{max} values in the human corpus callosum *in vivo*. We find that G_{max} values below 130 mT/m result in overestimation and increased variation of the resulting ADDs, whereas applying the highest possible G_{max} improves the accuracy and precision of the estimated ADDs, thereby justifying the use of high G_{max} in *in vivo* microstructural studies.

METHODS: *Data acquisition.* Three healthy volunteers were scanned on a dedicated high-gradient (AS302) 3T MRI scanner (MAGNETOM Skyra CONNECTOM, Siemens Healthcare) (G_{max}=300 mT/m, slew rate=200 mT/m/ms) equipped with a custom-made 64-channel phased array head coil.[5] The experimental protocol consisted of sagittal 2-mm isotropic resolution diffusion-weighted spin echo EPI acquisitions with 17 slices, TE/TR=120/3000 ms, δ=8 ms, 39 different diffusion gradient increments (10–293 mT/m) and 8 averages. The data were divided into subsets representing data acquired with 4 different G_{max} (77–293 mT/m) and up to 5 different diffusion times Δ (Table 1). Diffusion gradients were applied in the *z*-direction orthogonal to the callosal fibers. Total acquisition time was 118 minutes.

Data analysis. Following the AxCaliber approach,[1] we used a model of intra- and extra-axonal compartments to estimate ADDs within ROIs drawn in the mid-sagittal corpus callosum. Instead of assuming a gamma distribution of axon diameters, we fitted to a single axon diameter as in ActiveAx.[3] A Markov chain Monte Carlo simulation was implemented to provide samples of the posterior distributions of model parameters given the data. The restricted diffusion coefficient was limited to a narrow range between 1-2 μm^2/ms, and broad uniform priors were used for the hindered diffusion coefficient, restricted diffusion fraction (i.e., axon density), and axon diameter.

Table 1: Diffusion-weighting parameters for data subsets.

Data Set	G_{max} (mT/m)	q-values in μm^{-1} (# of q-values)	$1/q_{max}$ (μm)	Diffusion times at each q-value (Δ, ms)
1	77	0.0034:0.0015:0.026 (16)	37.9	16,25,35,60,94
2	131	0.0034:0.0031:0.049 (16)	20.3	16,25,35,60,94
3	212	0.0034:0.0046:0.072 (16)	13.8	16,25,35,60,94
4	293	0.0034:0.0061:0.1 (16)	10.0	16,25,35,60,94
5	293	0.045 to 0.1 (16)	10.0	16,25,35,60,94
6	293	0.0034 to 0.1 (39)	10.0	16,25,35
7	293	0.0034 to 0.1 (39)	10.0	35,60,94
8	293	0.0034 to 0.1 (39)	10.0	16,25,35,60,94

RESULTS: Figure 1 shows histograms of samples drawn from posterior distributions on axon diameter for the data subsets in Table 1 obtained with different G_{max} and Δ. The ADDs obtained with G_{max}=77 mT/m had larger mean axon diameters compared to ADDs obtained with G_{max}≥131 mT/m. The mean axon diameter and variance of the posterior distribution decreased with increasing G_{max}. Posterior distributions obtained with high q and short Δ were skewed toward smaller axon diameters, whereas data acquired with low q and long Δ were biased toward larger diameter axons. The pixel-wise axon diameter and density maps in the mid-sagittal plane of the corpus callosum obtained using the entire dataset showed smaller diameter and more tightly packed axons in the genu and splenium compared to the body (Figure 2).

DISCUSSION: We present the first comprehensive empirical study from a clinical MRI system equipped with 300 mT/m gradients that demonstrates the effect of gradient strength on *in vivo* axon diameter estimates in humans. Our results suggest that an optimal q-space sampling scheme for estimating ADDs should incorporate the highest possible gradient strengths and draw from as wide a range of gradient strengths and diffusion times as possible with proportionate sampling from different regimes of q and Δ. The smaller variance of ADDs at higher G_{max} agrees with findings from recent simulations and *ex vivo* experiments.[8] Histological results validate the trends in axon diameter and packing seen in different regions of the corpus callosum.[9] The results support an interpretation of ADD maps as axon-diameter-weighted images instead of quantitative maps of axon diameter, which depend on the selection of q and Δ.

CONCLUSION: This work shows the importance of high G_{max} for *in vivo* axon diameter estimation in humans. The improvement in axon diameter estimates that we demonstrate from increasing G_{max} will inform protocol development and encourage the adoption of higher gradient systems for use in human scanners.

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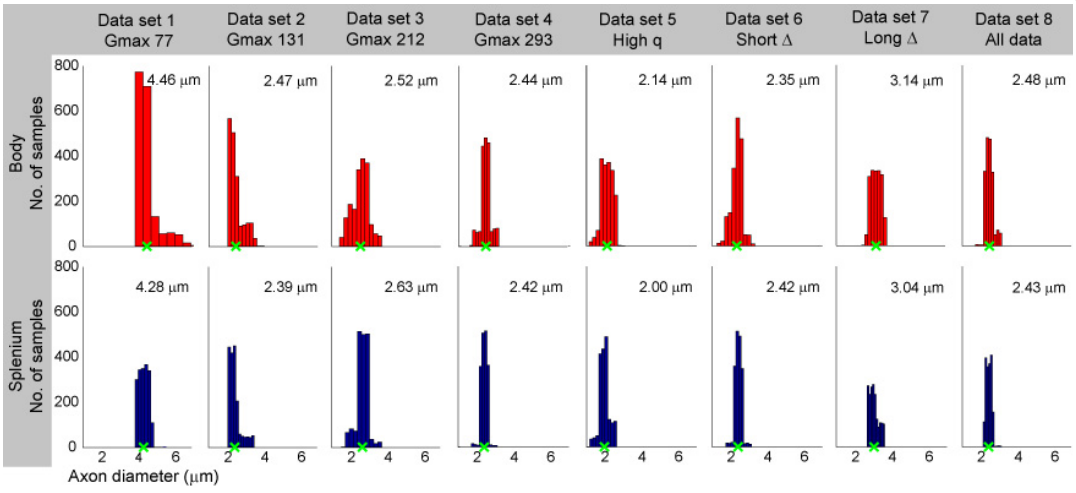

Figure 1: Posterior distributions on axon diameter with mean values (green x's and numerical values in the top right of each histogram) in the body and splenium of the corpus callosum for averaged data from 3 human subjects.

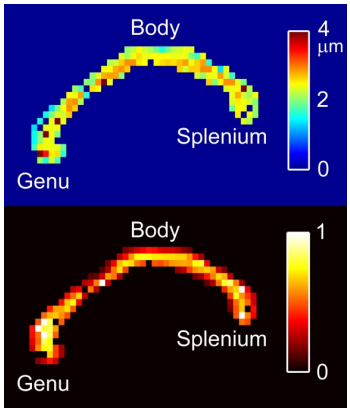

Figure 2: Pixel-wise estimates of mean axon diameter (top) and axon density (bottom) in the corpus callosum of a single subject.