In Vivo Human Brain Measurements of Axon Diameter Distributions in the Corpus Callosum using 300 mT/m Maximum Gradient Strengths

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INTRODUCTION. Axon morphology is closely related to important functional attributes of white matter pathways such as conduction velocity. Diffusion MRI q-space measurements have previously been used to quantify axon diameter distributions in *ex vivo* tissue specimens[1-3] and *in vivo* rat brain[4] using high performance small bore scanners. Translation of these q-space axon diameter measurement techniques to *in vivo* human studies has been impeded by the limited gradient strengths currently available on clinical MRI scanners (G_{max} = 40mT/m) that are insufficient to adequately sample the necessary range of q-values and diffusion times. Recently, a technique for estimating an axon diameter index, a', for specific axon diameters determined *a priori* to the acquisition has been demonstrated in the *in vivo* human brain using a standard clinical gradient strength of 40 mT/m[5,6]. This a' contrast provides limited sensitivity to smaller axons due to the gradient limitations and lacks distribution information. In this work we use a gradient system designed to achieve ultra-high gradient strength (G_{max} = 300 mT/m) on a 3T clinical MRI scanner. We present non-invasive *in vivo* human brain measurements using G_{max}=220 mT/m to measure the full axon diameter distribution in the corpus callosum as determined by the AxCaliber method.

METHODS. Two volunteers were scanned using a novel gradient system AS302† which is part of a new 3T system (MAGNETOM Skyra CONNECTOM†, Siemens Healthcare) capable of up to 300 mT/m and switching rate of 200 mT/m/ms. The slew rate was de-rated during the diffusion encoding to prevent physiological stimulation. A custom-made 64-channel phased array coil was used for signal reception. The experimental protocol consisted of a series of sagittal 2mm isotropic resolution DW-STE-EPI acquisitions with 12 slices (no gap), TE/TR =57/3000 ms, δ = 15.3 ms, 16 diffusion gradient increments (20 – 220 mT/m), 5 averages. The maximal b-value (at the longest diffusion time) was 10,000 s/mm^2. The diffusion gradients were applied along the z-direction (perpendicular to the fibres of the corpus callosum) in the mid-sagittal plane. The experiment was repeated for five different diffusion times 28, 38, 48, 78 and 118 ms. Total acquisition time was 51 minutes. The AxCaliber[2] method was used to estimate axon diameter distributions within hand-drawn ROIs in a single slice in the mid-sagittal plane in the splenium, body and genu of the corpus callosum (Fig. 1d).

The AxCaliber model was fit simultaneously to all data points at all diffusion times using in-house Matlab (MathWorks, Natick, MA) code that employs a nonlinear least-square routine (utilizing Levenberg-Marquardt minimization). Following previous demonstrations of the AxCaliber method in *in vivo* rat brain[4], the diffusion coefficient of the restricted component was fixed to 1.4 μm^2/ms. Therefore, we fit for the 4 parameters used in the AxCaliber model: the hindered diffusion fraction (f_h), the hindered diffusion coefficient (D_h) and α and β parameters that describe the gamma function used to model the distribution of different axon diameters. Note that we modeled only two components and therefore the restricted fraction (f_r) is equal to 1-f_h. Initial conditions/lower bounds/upper bounds were set to: f_h = 0.5/0.0/1.0, D_h=1/0.01/100μm^2/ms, α =12/2/50, β =0.4/0.1/10. Axon diameter (a) values used in the fit were: 0 < a < 50 μm.

RESULTS. The signal attenuation vs. q data, measured over a range of different diffusion times, show significant differences between the ROIs in the body of the corpus callosum relative to the splenium or genu (Fig.1a-c). The axon diameter distributions from the AxCaliber analysis are shown in Figure1e. Parameter estimates from the AxCaliber analysis are shown in Table 1. Inline with literature[7] we observe larger axon diameter in the body of the corpus callosum compared to the genu or splenium. The fraction of extra-axonal spins (f_h) was also estimated to be greater at the body of the corpus callosum (0.86 vs. 0.55 or 0.54).

Table 1:

Parameter	Genu	Body	Splenium
a (μm)	4.1	6.0	4.1
f_h	0.55	0.86	0.54
D_h (μm^2/ms)	2.4	5.5	2.7
α	13.6	37.6	13.9
β	0.32	0.16	0.32

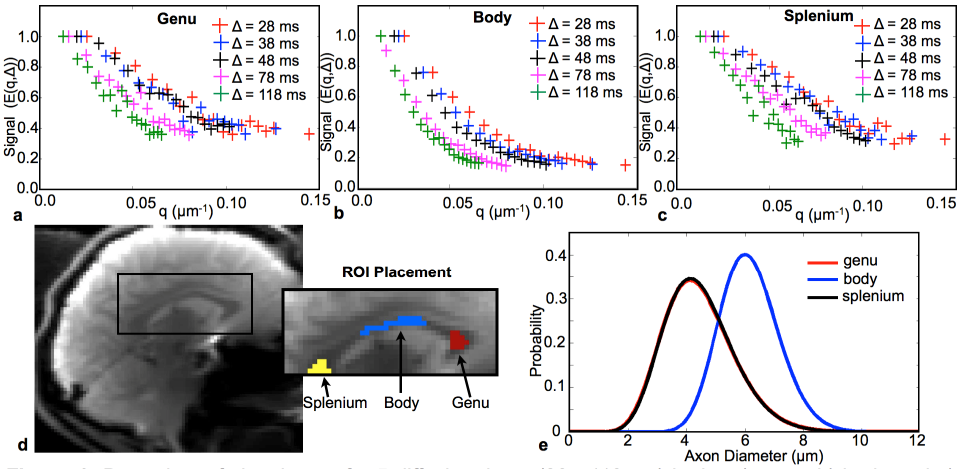

Figure 1: Data plots of signal vs. q for 5 diffusion times (28 - 118 ms) in the a) genu, b) body and c) splenium of the corpus callosum. d) ROI placement. e) Axon diameter distributions estimated for each ROI using the AxCaliber framework.

DISCUSSION We have demonstrated the AxCaliber technique for the first time in the *in vivo* human brain. The methodology used here follows closely from prior demonstrations of the AxCaliber technique in fixed tissue and *in vivo* rat brain, which have been extensively validated through comparisons to histology. Our work used gradient advances that provide the ability to translate techniques developed and validated in animal models to clinic use. Minor sequence modifications are expected to enable sampling of an even broader range of q-values and diffusion times and increase the sensitivity and accuracy of the axonal diameter estimates. The ability to non-invasively measure axon diameter distributions in the *in vivo* human brain opens a vast spectrum of applications in basic neuroscience and clinical applications.

† *Works in Progress. The information about this product is preliminary. The product is under development and is not commercially available in the U.S. and its future availability cannot be assured.*

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