665-WTh

MGH/HST Athinoula A. Martinos Center for Biomedical Imaging

In Vivo Human Brain Measurements of Axon Diameter Using 300 mT/m Maximum Gradient Strengths

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Introduction:

Several groups have shown the ability of q-space diffusion MRI to resolve axon diameter distributions in brain tissue:

Stanisz GJ et. al. MRM 37:103-111 (1997).
Assaf Y. et. al. MRM 59:1347-1354 (2008).
Ong HH et. al. NI 51:1360-6 (2010).
Barazany D.et. al. Brain 132:1210-1220 (2009).
Alexander DC et. al. 52:1374-1389 (2010).
Zhang H et. al. NI 56:1301-1315 (2011).

Q-space imaging techniques require strong magnetic gradients and for this reason much of the original work was carried out in small bore MRI scanners on fixed tissue or *in vivo* animals.

Axon diameter is an important structural substrate of brain function and therefore the translation of these techniques to the clinic could have a significant impact on the diagnosis and treatment of many different neurological disorders. For example:

- Axon diameter is directly related to conduction velocity[Hursch JB 1939], current magnitude and downstream synaptic branching[Salinas PC 2005].
- In amyotrophic lateral sclerosis, it is thought that large diameter axons are damaged selectively [Cluskey S 2011, Heads T 1991].
- In autism, it is hypothesized that small-diameter axons are maldeveloped [Piven J 1997].
- Smaller diameter axons are thought to be the most vulnerable to degeneration associated with aging[Marner L 2003].

It is therefore extremely exciting to see efforts being made to optimize these q-space techniques such that they may provide useful information at clinical gradient strengths (30-60 mT/m) [Alexander DC et. al. 2010].

Aim: Ultimately, we aim to aid the optimization of q-space diffusion MRI for clinical estimation of axon diameter distributions by employing a novel gradient system AS302† which is part of a new 3T system (MAGNETOM Skyra CONNECTOM† Siemens Healthcare) equipped with 300 mT/m maximum gradient strength. The connectom scanner enables exploration of a broader **"q"** and diffusion time (Δ) parameter space than was ever previously possible in humans *in vivo*. Here, we provide an initial demonstration on the connectom, targeting the well known microstructure of the corpus callosum.

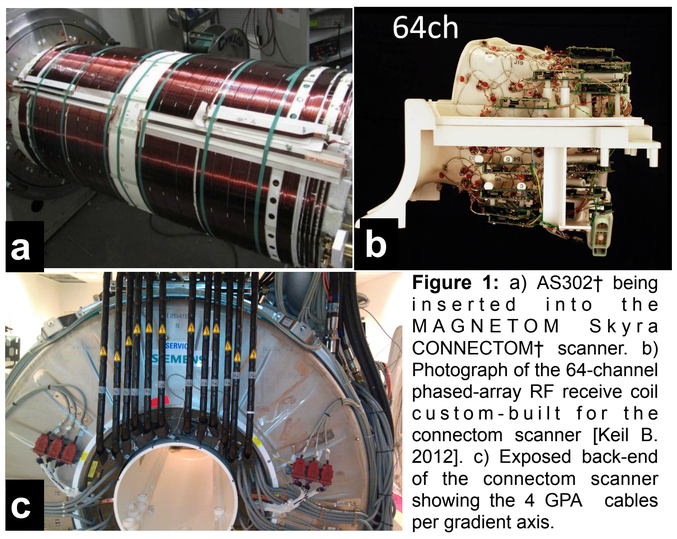
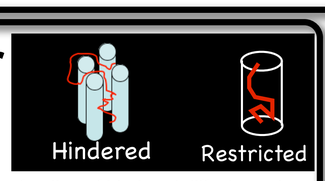


Figure 1: a) AS302† being inserted into the MAGNETOM Skyra CONNECTOM† scanner. b) Photograph of the 64-channel phased-array RF receive coil custom-built for the connectom scanner [Keil B. 2012]. c) Exposed back-end of the connectom scanner showing the 4 GPA cables per gradient axis.

Theory: AxCaliber

Assaf Y. et. al. MRM 59:1347-1354 (2008).



$$\mathbf{q} = \frac{\gamma}{2\pi}\int_0^t \mathbf{G}(t)dt = \frac{1}{2\pi}\gamma\mathbf{G}\delta$$

E (q, Δ) = Signal at a given q-value and difusion time (Δ).

f_h = fraction of hindered diffusion spins.
f_r = fraction of restricted diffusion spins.

$$E(\mathbf{q},\Delta) = f_h \cdot E_h(\mathbf{q},\Delta) + f_r \cdot E_r(\mathbf{q},\Delta)$$

Hindered diffusion is Gaussian:
Υ=gyromagnetic ratio of 1H, δ=diffusion gradient duration, g=diffusion gradient amplitude.

$$E_h = \exp(-\gamma^2\delta^2 g^2 D_h(\Delta-\delta/3))$$

Signal contribution from spins restricted within axons with a distribution of diameters (a_i) . J_i'=bessel functions of the nth-order, β_{nk} = arguments that result in zero crossings of the bessel functions.

$$E_r = \sum_i \frac{f_i}{\pi a_i^2}\cdot\left[\sum_k 4\exp[-\beta_{0k}^2 D_r\Delta/a_i^2]\times\left[\frac{(2\pi q a_i)J_0'(2\pi q a_i)}{(2\pi q a_i)^2-\beta_{0k}^2}\right]\right.$$

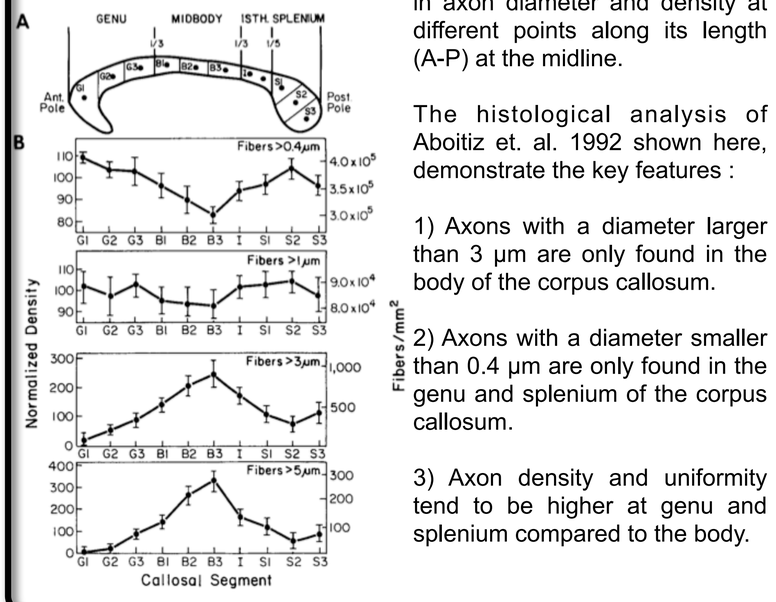
$$\left. + \sum_{nk} 8\exp[-\beta_{nk}^2 D_r\Delta/a_i^2]\times\frac{\beta_{nk}^2}{\beta_{nk}^2-n^2}\times\left[\frac{(2\pi q a_i)J_n'(2\pi q a_i)}{(2\pi q a_i)^2-\beta_{nk}^2}\right]\right]$$

Weights (w_i) of different axon diameters modeled by a gamma-function with parameters α, β.

$$w_i(\alpha,\beta) = \frac{a_i^{\alpha-1}e^{-a/\beta}}{\beta^\alpha\Gamma(\alpha)}$$

Corpus Callosum Microstructure

Figure below reproduced from:
Aboitiz F. et. al. Brain Research 598: 143-153 (1992).



The corpus callosum provides an excellent testing bed for microstructural measures due to the well-established differences in axon diameter and density at different points along its length (A-P) at the midline.

The histological analysis of Aboitiz et. al. 1992 shown here, demonstrate the key features :

1) Axons with a diameter larger than 3 μm are only found in the body of the corpus callosum.

2) Axons with a diameter smaller than 0.4 μm are only found in the genu and splenium of the corpus callosum.

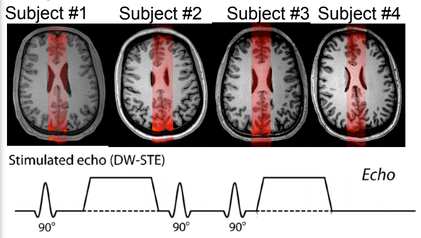
3) Axon density and uniformity tend to be higher at genu and splenium compared to the body.

Discussion:

The *in vivo* human q-space diffusion MRI estimates of axon diameter distributions using the connectom scanner are in excellent correspondence with literature, not only at the group and ROI level but also on a pixel-wise basis. Specifically, we see smaller diameter axons at the genu and splenium (~0.5 μm) and larger diameter axons at the body (~7 μm) and this result is consistent across all four subjects. Future work will aim to test the effects of potential confounds such as brain pulsation, partial volume effects and orientation discrepancies by implementing cardiac gating, higher spatial resolution and models that consider orientational variation. Finally, we aim is to compare the effect of gradient strength on the axon diameter estimates in order to help inform protocol development for clinical gradient strengths.

Methods: Acquisition

17 sagittal slices at the midline of the corpus callosum.



- TE/TR=54/3100ms, R=2, 2 mm isotropic
- 5 diffusion times (Δ = 38 - 123 ms) x 17 gradient strengths (30-272 mT/m), (b-values = 400 - 10,000 s/mm²), diffusion-encoding along S-I orientation
- 12 averages each
- Acquisition time = 57 min.

Methods: Post-processing

Motion Correction:
- Image registration of b=0 images interspersed every 12 images were used to correct for bulk motion between scans using FLIRT (www.fmrib.ox.ac.uk/fsl)

Eddy Current Correction:
- DWI averages were acquired with alternating polarity.
- Opposite polarity DWI pairs were registered one to the other, constraining for the expected translations, dilations and shears and then the "half-way" transform was calculated and applied.
- The motion correction and eddy current correction transformations were applied in a single step so as to prevent further blurring.

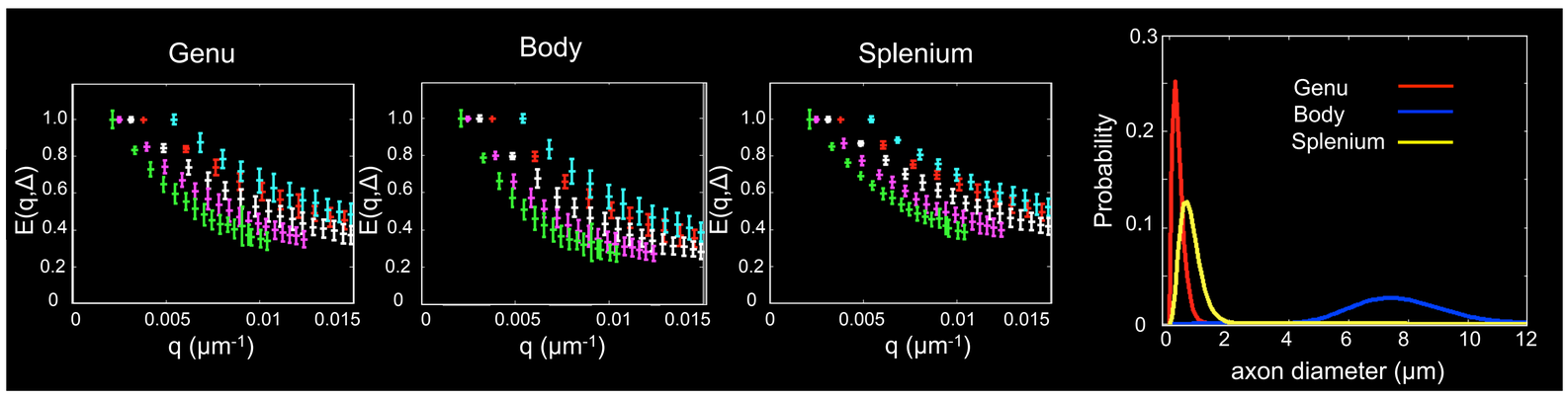
Methods: Model-fitting

- The AxCaliber model (Assaf Y. et. al. 2008) was fit simultaneously to all data points using in-house Matlab (MathWorks, Natick, MA) code using a nonlinear least-squares routine (Levenberg-Marquardt minimization).

- Restricted diffusion coefficient (Dr) fixed to: 1.4 μm²/ms.
- Four parameters to fit: hindered fraction (fh), hindered diffusion coefficient (Dh), α and β defining gamma distribution.
- Starting values : f_h=0.1, D_h=2.5um2/ms, α=12, β=0.4
- Lower Bounds : f_h>0.05, D_h>1.8μm²/ms, α>2, β>0.1
- Upper Bounds: f_h<0.95, D_h<3μm²/ms, α<50, β<1.0

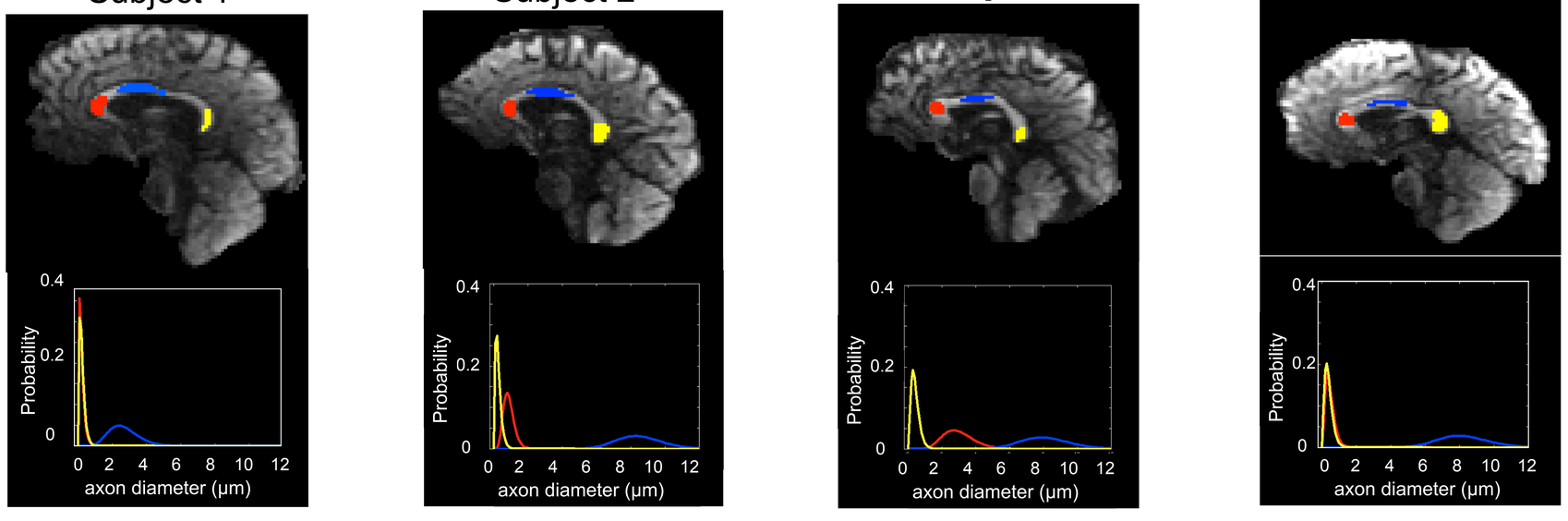
Results: Group ROI Analysis

Diffusion Times: + Δ = 38 ms, + Δ = 47 ms, + Δ = 57 ms, + Δ = 87 ms, + Δ = 123 ms

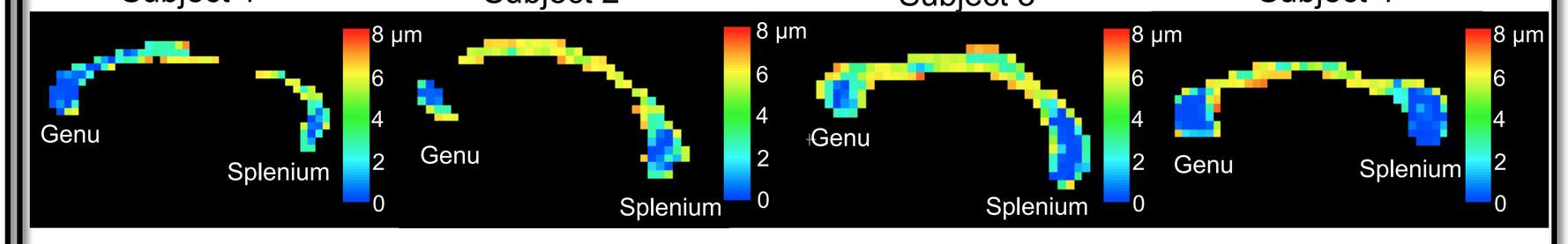


Error bars = standard deviation across 4 subjects.

Results: Individual ROI Analysis



Results: Pixel-Wise Calculation: Axon Diameter Maps



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† 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.