# Low frequency OGSE improves axon diameter imaging in monkey corpus callosum over simple PGSE method

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**TARGET AUDIENCE:** Researchers studying brain microstructure, especially axon diameter.

**PURPOSE:** Axon diameter statistics provide information about the function and performance of white matter pathways. Hence imaging axon diameter could provide insight into basic brain operation as well as neuronal diseases that alter axon diameter distribution. Majority of current methods for diffusion imaging of axon diameter use Pulsed Gradient Spin-Echo (PGSE) sequence. However, various authors suggest that Oscillating Gradient Spin-Echo (OGSE) offers benefits over PGSE for imaging pore sizes. Here we compare PGSE and OGSE approach on a monkey corpus callosum, and investigate whether OGSE indeed improves estimation of the smallest axon diameters.

**METHODS:** PGSE approach is called ActiveAxPGSE [1,2], combining PGSE protocol optimization and model fitting to estimate tissue parameters. Here we define ActiveAxOGSE approach, which differs in that it uses trapezoidal OGSE sequences and an extra parameter, number of lobes N [6]. Optimal N can take any real value, and N=1 is the PGSE case. *Protocol Optimisation.* OGSE protocol was optimized for white matter model following procedure in [1,4]. PGSE protocol was optimized following [1] and presented in [3]. Both had 360 measurements each divided into 3 (PGSE) and 5 (OGSE) HARDI shells and with additional b = 0 measurements (Figure 1). A-priori model parameters for the optimization were: Gmax=300mT/m, volume fraction f=0.7, intrinsic diffusivity $d_{||}=1.7\times10^{-9}m^2s^{-1}$ and apparent diffusion coefficient $d_{\perp}=1.2\times10^{-9}m^2s^{-1}$ as used in [2,3] for ex vivo.

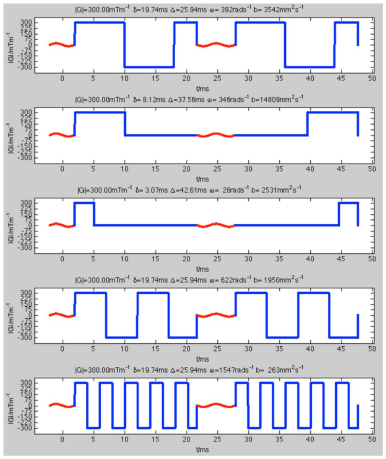

**Figure 1** Optimised OGSE protocol

*MRI data.* We used an experimental 4.7T MRI scanner with a slew rate of 2000T/m/s. Three sagittal slices covering the mid-sagittal plan of the corpus callosum were acquired with voxel size of isotropic 0.5 $mm^3$ (NEX=6). For comparison with ActiveAxPGSE we used the same normal young perfusion fixated Vervet monkey brain (32 months of age) as was used in [3] and imaging setup as in [8]. The animal was handled and cared for according to a protocol approved by the local ethics committee. *Fitting.* A white matter model was fitted using a three-stage fitting procedure as outlined in [2,3]. The final stage included Markov Chain Monte Carlo (MCMC) that created a posterior distribution from which the mean axon diameter index is calculated. The CC was subdivided into ten regions as described in [7].

**RESULTS AND DISCUSSION:** Figure 1 shows the optimized OGSE protocol. The optimized OGSE protocol consists of both PGSE waveforms (N=1) and OGSE waveforms (N>1). Figures 2 and 3 show the results of fitting the model into the data. Figure 2 shows the estimated axon diameters and their posterior distributions from voxels sampled along the corpus callosum from genu (in red) to splenium (in blue). The characteristic low-high-low trend is present in the estimates, with highest estimates in the mid-body, for both PGSE (A) and OGSE (B). The OGSE diameter estimates are very similar in size in mid-body. However, interestingly, estimated diameters from OGSE data are lower by more than a micron in the genu and splenium regions and agree more closely with EM [7, 9]. Note that some voxels in the OGSE data were affected with Gibbs ringing and were hence removed from the analysis (mid area). Figure 3 shows estimated diameters for all the voxels in the midsagittal corpus callosum. The OGSE estimations are significantly lower than the PGSE estimations in the genu and splenium regions. Simulation data using these optimized protocols and single, and mixture of radii, model samples confirm these results (data not shown) and also shows that the variance on the estimated model parameters using OGSE is smaller than just using PGSE.

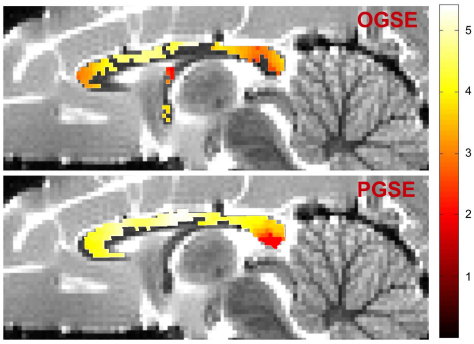


**Figure 3** Axon diameter estimates for the whole of corpus callosum for optimized OGSE (top) and PGSE (bottom).

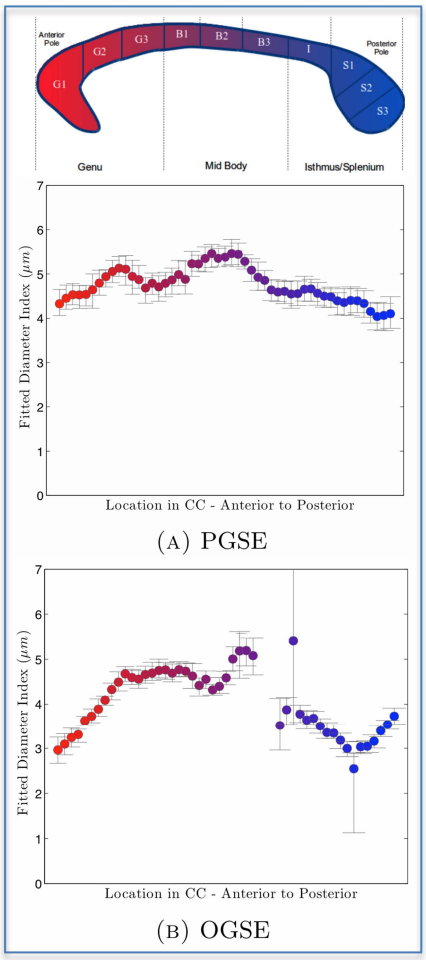


**Figure 2** The well known low-high-low axon diameter trend for both PGSE (A) and OGSE (B) optimized protocols. OGSE estimates are considerably lower in genu and splenium, suggesting better sensitivity to smaller axon diameters.

**CONCLUSION:** We show that adding an additional parameter into the optimization procedure (number of lobes N), and hence obtaining an optimized OGSE, rather than the PGSE protocol, increases sensitivity to smaller axon diameter. Additionally, the optimized OGSE waveforms are of low frequency which is a novel finding since much of the literature suggests that high frequency OGSE increase sensitivity to small pore sizes. Low frequency OGSEs are easy to implement and run on standard scanners, and also significantly reduce the gradient heating and deal better with eddy currents than PGSE sequences. Future work will look into applications on clinical scanners.

**REFERENCES**

[1] Alexander et al MRM 2008; [2] Alexander et al. NeuroImage 2010; [3] Dyrby et al MRM 2013; [4] Drobnjak et al JMR 2009; [5] Drobnjak et al JMR 2011; [6] Drobnjak et al Microp Mat 2013; [7] Lamantia J Comp Neur 1990; [8] Dyrby et al HBM 2011; [9] Dyrby et al ISMRM 2014