Microscopic anisotropy in the fixed spinal cord from dPFG and qMAS diffusion weighted imaging compared to DTI

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TARGET AUDIENCE: Diffusion weighted imaging (DWI) is a powerful technique for studying the central nervous system (CNS) and can reveal information on a variety of disease pathologies. More sensitive techniques are helpful both to investigators looking to quantify pathology and to clinicians in detecting disease states.

PURPOSE: Diffusion tensor imaging (DTI) has provided tremendous insight to CNS microstructure using the derived parameters of fractional anisotropy (FA) and diffusivities (mean, axial, and radial). However, DTI is limited by assumptions of coherent macroscopic nerve fiber organization. Recently proposed techniques including the double pulsed field gradient[1] (dPFG) and q-vector magic angle spinning[2] (qMAS) sequences aim to circumvent these limitations and more accurately resolve microscopic anisotropy from macroscopic organization[3]. We implemented and applied these two sequences to fixed spinal cord and compared the derived microstructure measures to FA obtained from the conventional pulsed gradient spin echo (PGSE).

METHODS: Formalin-fixed cervical spinal cords from three normal healthy female Sprague-Dawley rats were imaged in a 9.4T Bruker horizontal bore BioSpec imaging system with a custom 1 cm diameter solenoid transceiver coil. For both sequences, the TR/TE (3000/42 ms), resolution (0.104 mm^2; 96x96 matrix), and slice thickness (1 mm) were identical. The dPFG sequence consisted of two bipolar diffusion sensitizing gradient pairs applied either parallel or orthogonal to one another within a single acquisition. 60 directions were employed for both the parallel and orthogonal direction sequences based on the orientational invariant scheme by Jespersen et al[1]. Gradient duration (δ) of 6.5 ms and separation (Δ) of 8 ms per pair achieved a b-value of 1200 s/mm^2. The total scan time was 8:12 hrs. DTI parameters and the measure of microscopic anisotropy, Fractional Eccentricity (FE), were derived as described by Jespersen et al[1]. The qMAS sequence consisted of a standard PGSE coupled with a rotation of the q-vector about the magic angle between the diffusion gradients in order to achieve isotropic diffusion weighting. 15 parallel PGSE directions and 15 qMAS directions were employed. Diffusion gradient duration (δ) of 4 ms and separation (Δ) of 32.66 ms were used to achieve 4 b-values (600, 1200, 1800, 2400 s/mm^2). The total scan time was 8:24 hrs. The diffusion tensor and kurtosis were fit to the data to calculate FA, MD, MK, and microscopic fractional anisotropy (μFA) as described by Lasič et al[2]. Additionally, subsets of the dataset were used to determine the effects of reduced numbers of b-values or isotropic averages on the resulting parameter estimates.

RESULTS: A comparison of an FA map to the maps of microstructure derived from the dPFG and qMAS sequences, parameterized as FE and μFA, respectively, is shown in Fig. 1 and quantified in Fig. 2. FA, FE, and μFA all demonstrate high anisotropy in the white matter, as expected. Whereas FA is considerably lower in the gray matter, FE and μFA exhibit only a small reduction in the gray matter compared to the white matter. Furthermore, the reduction in FA observed in the ventral white matter where ventral nerve fibers exit the spinal cord is not evident in the maps of FE and μFA, which demonstrates their insensitivity to fiber crossings. Additional analysis (not shown) demonstrated that the number of isotropic averages in the qMAS could be reduced to as few as five and yield similar estimates of μFA as the full dataset (without modification of SNR). Likewise, the number of b-values could be reduced to two and still provide similar estimates of μFA.

DISCUSSION: As seen in Figure 1, the dPFG and qMAS diffusion encoding methods methods have been successfully applied to fixed tissues to calculate microstructure. Although the spinal cord has a less complicated macroscopic arrangement than the brain, it still serves as a good model that may benefit from improved sensitivity and specificity of DWI methods. Both the dPFG and the qMAS may be important in this regard. Measures of microscopic anisotropy derived from both the dPFG and qMAS exhibit similar behavior in the spinal cord, with values being markedly greater in the gray matter than the white matter compared to FA. A histologic measure of microscopic anisotropy is needed to confirm these observations. One primary difference between the dPFG and qMAS is their efficiency. Within an identical total acquisition time and identical resolution, the qMAS sequence allowed collection of multiple b-values. Additionally, the number of b-values and number of averages for the qMAS could be further reduced without a considerable reduction in the accuracy of the parameter estimates. These are important considerations for greater efficiency and improvements in image resolution for *in vivo* and clinical implementation in which shorter acquisition times are necessary.

CONCLUSION: We showed that the dPFG and qMAS sequences are able to be successfully applied to the CNS and allow calculation of values for microscopic tissue structure. Both techniques provide better microstructure determination than widely used DTI-based fitting methods. Furthermore, the increased efficiency of these scans, especially the qMAS, should allow the information to be collected in a shorter amount of time. Thus, these have significant investigative and clinical implications for better understanding CNS pathology and warrant consideration for future imaging applications.

REFERENCES: **1**. Jespersen S, et al. NMR Biomed. 2013; **2**. Lasič S, et al. FrontPhys. 2014; **3.** Jespersen S, et al. FrontPhys. 2014;

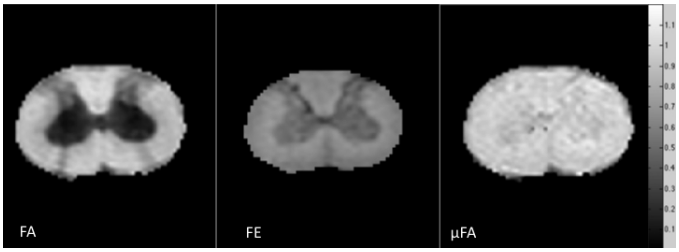

Figure 1. Microstructure maps for FA, FE, and μFA calculated from PGSE, dPFG, and qMAS sequences respectively.

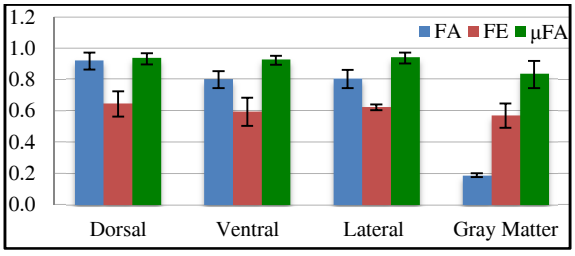

Figure 2. Average microstructure values for spinal cord segmented into dorsal, ventral, and lateral white matter and gray matter sections. Error bars show standard deviations (n=3).