The Measurement of the Axon Diameter Distribution in White Matter using Diffusion MR Methods

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Introduction

High b value diffusion weighted imaging (DWI) combined with q-space analysis enables one to measure dimensions of some cellular compartments (1-2). More recently q-space methods were combined with diffusion tensor imaging (DTI) in a composite hindered and restricted model of diffusion (CHARMED) MRI framework from which several microstructural parameters could be measured (3-4), including maps of the volume of restricted water molecules in the intra-axonal space. CHARMED MRI was subsequently shown to be clinically feasible (5). In this work the CHARMED framework was used to measure the axonal diameter probability density function (ADPDF) of excised nerves fascicles. This is a critically important histological feature, since it is known to be important in development, disease, and degeneration, and otherwise cannot be determined without biopsy. Here, the model of restricted diffusion of water in the intra-axonal space is extended to include the contributions of the measured signal arising from axons of different inner diameter. By acquiring DWIs with diffusion gradients applied orthogonal to the axon's axis, and using multiple diffusion times, it is possible to estimate the ADPDF. We tested this approach using computer simulations, and here demonstrate it using DW data acquired on porcine optic and sciatic nerves specimens.

Methods

Experiments were performed on a 7T MRI system (Bruker, Germany). Porcine optic and sciatic nerves were freshly excised and placed in an NMR tube. High b value DW spectra were acquired with the following parameters: TR/TE=3000/166ms, δ=2.5ms, G_{max}=120 Gauss/cm, number of averages was 8, the diffusion time, Δ, was varied from 20ms to 150ms in eight increments. Diffusion gradients were applied only perpendicular to the nerve axis with 16 increments in gradient amplitude per diffusion time. The entire DW data set consisted of 128 spectra with a total duration of 51 minutes.

Data analysis was done by extending the CHARMED approach described in (3-5). CHARMED combines contributions of hindered diffusion arising from the extra-axonal spaces, and restricted diffusion arising from the intra-axonal spaces. Diffusion parallel to the fibers (and within them) is free and modeled by the 1-D Stejskal-Tanner equation. Diffusion perpendicular to the fibers (and within them) can be modeled using the theory of Neuman et al. (6) in which it is assumed that the diffusion gradients are constant, similar to the case in clinical scanners (i.e., $\Delta \approx \delta$). In this work we used a modified formula for restricted diffusion in cylinders suggested by van-Gelderen (7) that includes the effect of shorter pulses (i.e. $\Delta > \delta$). Experimental data was fitted to the model using in-house Matlab© code that employs a non-linear least-square routine (utilizing Levenberg-Marquardt minimization). Free parameters were the volume fractions of the hindered and restricted water pools, the diffusivities of the hindered and restricted pools (perpendicular to the fibers) and the ADPDF modeled by a two-parameter gamma-variate probability density function (pdf). Initial conditions that limit the predicted ADPDF were needed to obtain adequate convergence of the fitting routine.

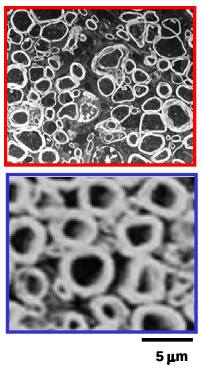

Figure 1

Results

Sciatic and optic nerves have distinct morphologies (Figure 1) that are mirrored in their signal decays and diffusion time dependence. Figure 2 shows the signal decay for the sciatic and optic nerves at different b (or q) values. Note that the signal decay for the sciatic nerve is much more pronounced than the one for the optic nerve. Figure 2 also depicts the fitted signal using the modified CHARMED (see lines in Figure 2) as well as the fitted residuals.

Figure 3 show histograms of the histologically measured ADPDF for the optic (left in red) and sciatic (right in blue) nerves. Note that the mean axonal diameter is much larger in the sciatic nerve than in the optic nerve (more than 4 µm vs. ~1µm). Green lines depict the ADPDF extracted by CHARMED which are in excellent agreement with the histologically derived histograms.

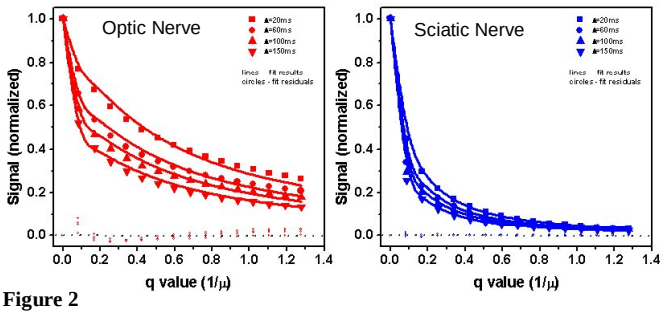

Figure 2

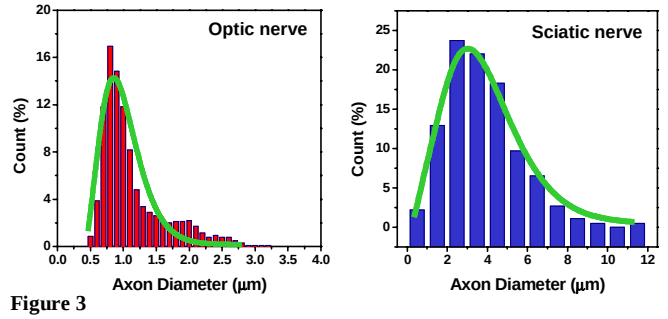

Figure 3

Discussion and Conclusions

Measurements of axon density, axon diameter, and myelin content have been previously unavailable *in vivo* noninvasively. Diffusion MRI, which detects micron-scale translational motion *in vivo*, provides new opportunities to probe such features of neuronal microstructure. By extending the CHARMED MRI methodology, we were able to measure the axon diameter probability density function (ADPDF) in porcine optic and sciatic nerves. Future work will entail implementing this methodology *in vivo* to study brain white matter pathways in the central nervous system (CNS), and peripheral nerves in the PNS to extract this important distribution without requiring a tissue biopsy.

References

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