q-space Analysis of Diffusion Measurements in Myelinated and Non-Myelinated nerves: Restriction vs. Exchange.

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Introduction: Diffusion-weighted (DW) MR is a powerful tool for the investigation of microscopic structure of tissue in health and disease. The non-Gaussian character of water self-diffusion in tissue gives rise to non-monoexponential diffusion signal attenuation as a function of b-value, and it is has been argued that the main contribution to the deviation from Gaussian diffusion is due to the geometric restriction imposed by the cell membranes. In this work we collected and performed q-space analysis[1] on diffusion-weighted MR data from three different types of well-characterized mammalian nerves: sciatic, optic and vagus nerves obtained from adult Rhesus monkeys. These nerves differ greatly from each other in several aspects that affect water diffusion: axonal diameter, myelination and axonal density. The most surprising finding was that with the exception of the optic nerve, the RMS of the displacement probability function measured for the nerves showed *no signs of restriction* in the range of diffusion times used in the experiments (13-400ms). Moreover, the displacement probability RMS values for the vagus and the sciatic nerves were similar through the whole range of diffusion times, inspite of *almost an order of magnitude* difference in axonal diameter. Additional diffusion related quantities (fractional anisotropy and D_{slow}/D_{fast}) are calculated as well, and discussed in the frame of the cytoarchitectonics of the nerves and the possible major role of transmembrane permeability[2].

Materials and Methods: experiments were performed on an 8.9cm bore 500MHz Bruker Avance spectrometer equipped with a microimaging setup (max. gradient strength 100g/cm). RF coil was a solenoid of 5mm diameter and 1.5cm length with the symmetry axis perpendicular to the Z axis. Pulse sequence used was diffusion-weighted STEAM sequence with TE=10ms, δ=6ms, Δ=13, 50, 100, 200 and 400ms and 128 gradient strength values from 0 to 80g/cm (max. q-value = 2043 cm^{-1}). Gradients were applied in parallel (∥) and perpendicular (⊥) to the nerves. Data was processed using MATLAB®.

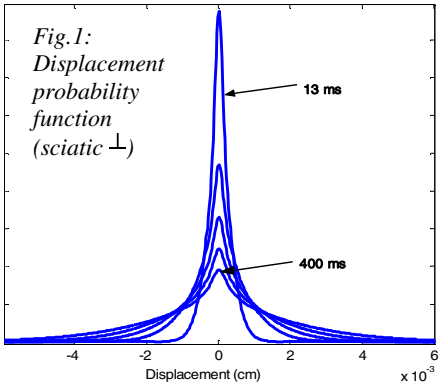
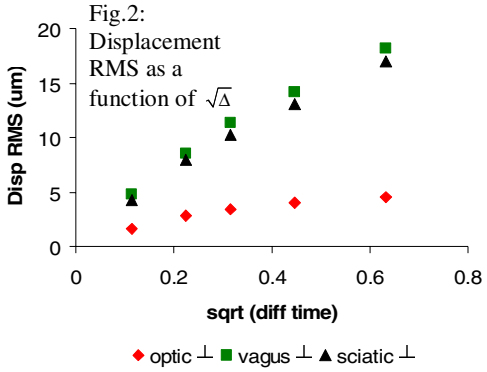


Fig.1: Displacement probability function (sciatic ⊥)

Results and Discussion: Figure 1 shows typical displacement probability functions obtained from the diffusion experiments. Displacement RMS values, equivalent to the full width at half maximum (FWHM) of the distribution functions, were calculated for all functions obtained from the three nerves. In figure 2, the displacement RMS for the experiments with the gradients applied in perpendicular to the nerves, is plotted against the square root of the diffusion time. Although in the case of the optic nerve there is a strong deviation from linearity, the curve does not reach a stable value, and reaches beyond the typical axonal diameter of the optic nerve, less than 1μm. In the case of the vagus (diam. ~ 1μm) and the sciatic (diam. ~7μm) nerves, the trend is closer to linear, and seems to be unbounded. The displacement RMS values measured in parallel and in perpendicular to the nerves were used to calculate the fractional anisotropy (FA) for the three nerves, shown in figure 3. FA increases for both the sciatic (mostly myelinated) and vagus (mostly non-myelinated) nerves, whether the closely packed, fully myelinated optic nerve shows an initial decrease and then a stable FA, possibly indicating that a non-gaussian diffusion process is also present in the measurement in parallel to the nerve. A plausible explanation for the behavior seen in Fig. 2 is that transmembrane water exchange plays a major role, surprisingly even at relative short diffusion times (13ms), also in myelinated nerves. It is thus concluded that the interplay between the geometry (axonal diameter, packing density) and water exchange rate have both a major impact on diffusion measurements in the nervous system, and that the impact of demyelination on diffusion-derived parameters such as FA and ADC acts through both the extra-axonal geometric changes as well as through increase in membrane permeability.

Fig.2: Displacement RMS as a function of $\sqrt{\Delta}$



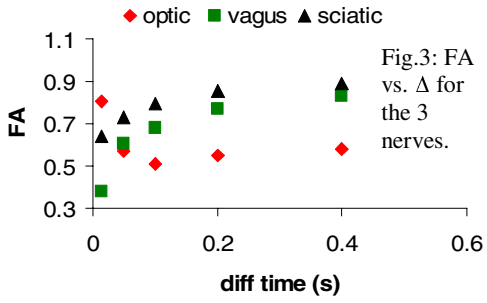


Fig.3: FA vs. Δ for the 3 nerves.

References: [1] Cory, D.G. and A.N. Garroway, Magn Reson Med, 1990. **14**(3): p. 435-4; [2] Sukstanskii, A.L.,et al., J Magn Reson, 2004. **170**(1): p. 56-66.