A combined acquisition of T_1 and AxCaliber can link between axon diameter and myelination

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Introduction: AxCaliber is a diffusion MRI method that models the axon diameter distribution[1]. While being sensitive to variations in axon diameter, this method does not measure another micro-structural property of the white matter: the myelin. In traditional analysis of white matter electron microscopy images, it is common to relate these two properties (axon diameter and myelin thickness) by calculation of the g-ratio (the ratio between in the inner and outer diameters of the axons). The longitudinal relaxation time, T_1, is considered to be a marker of myelin water fraction as water T_1 in white matter is highly influenced by membrane and lipid contents. Previously, we have shown[2] that IR-DTI can differentiate between fibers based on their T_1 properties. In this work we set to explore the T_1 properties of axons at different sizes by combined acquisition of T_1 and AxCaliber utilizing inversion recovery diffusion weighted imaging (IR-DWI) pulse sequence on the rat corpus callosum (CC). It is assumed that larger axons with thicker myelin will exhibit shorter T_1.

Methods: A fixed rat brain was scanned on a 7T/30 Bruker Biospec system equipped with a 400 mT/m gradient unit. While the traditional AxCaliber acquisition comprise multiple diffusion weighting in multiple diffusion times, for IR-AxCaliber, an adiabatic 180^O pulse was added prior to the diffusion weighted stimulated-echo echo-planar-imaging pulse sequence. Resulting an enormous dataset that include multiple inversion times (TI) for the traditional AxCaliber framework. The scanning parameters were as following: TR/TE = 2750/19 ms ; Δ/δ = 11,20,40,60,100/3.2 ms ; inversion times = 150, 225, 300, 350, 425, 500 and 850 ms ; 16 diffusion gradient increments (linearly from 0 to 320 mT/m). The diffusion gradients were applied in one direction, perpendicular to the fibers within the CC in the mid-sagittal plane, with a total of 560 IR-DWI measurements.

AxCaliber is a parametric approach that fits several parameters: the volume fraction of the restricted compartment (FR), the diffusion of the hindered compartment (Dh) and α and β parameters of gamma distribution, which are used to measure the axon diameter distribution.

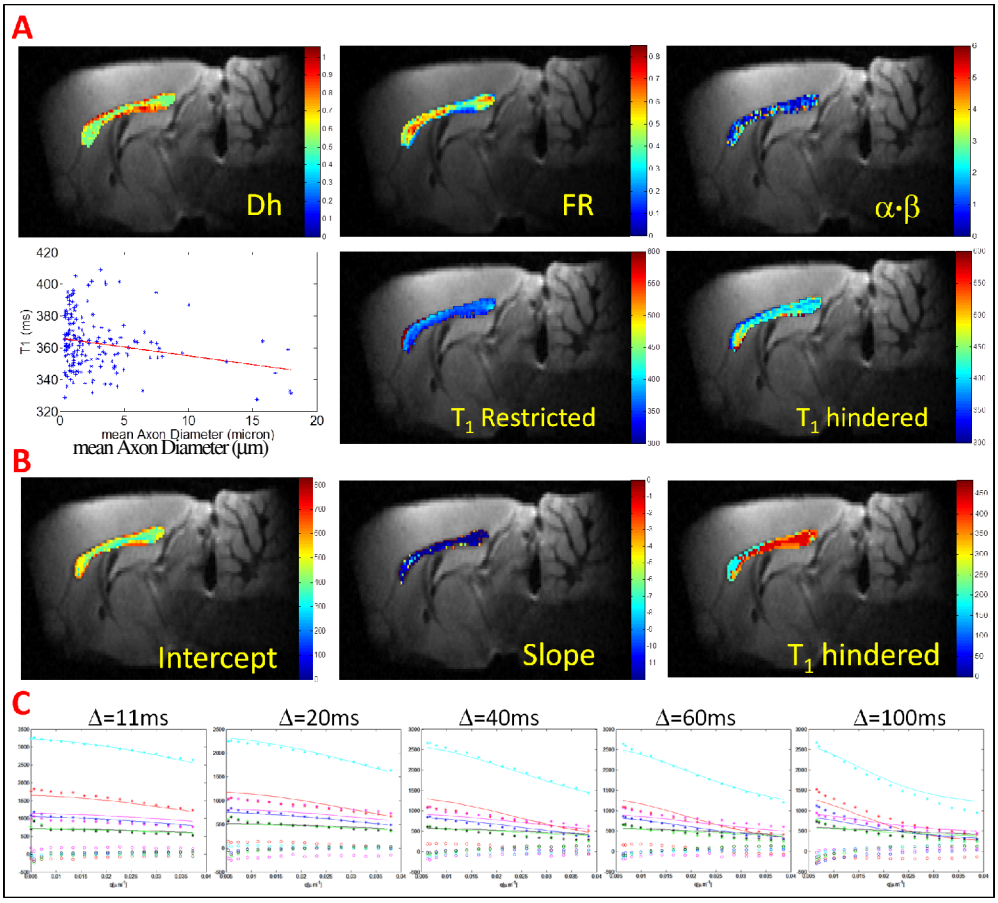
Analysis and Results: The IR-AxCaliber analysis incorporated additional parameters for T_1 calculation, while assuming that the hindered and restricted compartments have distinct T_1 characteristics (see Equation):

$$E_{total}(f,E,T_1) = f_h E_h\left(1-2e^{-\frac{TI}{T_{1h}}}\right)+f_r E_r\left(1-2e^{-\frac{TI}{T_{1r}}}\right)$$

Since the correlation between T_1 property and the axonal size is known, we examined several approaches:

(1) we examined whether a single T_1 could be used to describe the two compartments, by incorporating T_1r and T_1h (hindered and restricted respectively). Fig. A shows the fitted parameters superimposed on B0 image, where Dh, FR and the estimated expected value, $\alpha*\beta$ (i.e., the mean axon diameter) show similar estimations for the CC parts as the traditional AxCaliber. T_1r and T_1h maps display distinct T_1 characteristics for the two compartments, where T_1r values are lower than T_1h, as expected from a more highly myelinated population. Moreover, We found a negative correlation ($p<0.001$) between the mean axon diameter and T_1r maps, which indicates that bigger axons have higher degree of myelination.

(2) Consequently, we replaced T_1r with a linear equation as a function of the axon diameter (addition of slope and intercept indices to IR-AxCaliber model). Fig. B presents the results of this analysis, where T_1h remains stable as in section 1 (~400ms). The slope index was mostly homogenous across the CC concluding that similar relation exists for all voxels, and the difference is derived from the intercept. Hence the intercept and T_1r of section 1, show similar information, where the intercept values are obviously shifted a bit higher. Fig. C demonstrates qualitatively the goodness of fit of IR-AxCaliber model of section 2 to the IR-DWI intensity and the error, where each plot shows the multiple TIs across q values for a certain diffusion time.



Conclusions and Summary: Combined acquisition of T_1 and AxCaliber enables further insight into white matter micro-structure as it links between axons at different size and their T_1. This kind of combined acquisition and analysis allows to estimate the effect of myelin content on T_1 and its relation to axon diameter. The results of this work demonstrate that MRI allows to probe white matter tissue micro-structure providing invaluable high details that so far could be extracted only by invasive techniques.

References: [1] Assaf et.al MRM (2008); [2]Barazany and Assaf *ISMRM* (2012)