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. 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 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° 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 ; $\Delta\delta$ = 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 $\alpha$ and $\beta$ 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):

$$E_{total}(f, E, T_1) = f E_0 \left(1 - 2 e^{-\frac{T_1}{T_H}}\right) + f E_r \left(1 - 2 e^{-\frac{T_1}{T_R}}\right)$$

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 $T_1$ 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, $a=\beta$ (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 various 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.