A Novel MRI Technique for Quantifying Myelin in Mice Brain White Matter

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Introduction: *In-vivo* imaging of myelin could provide a tracking tool for demyelination disorders and facilitating the development of new therapeutic agents[1]. In this work we propose to use a recently reported MRI sequence, MEX, that measures a signal linearly dependent on the myelin protons fraction in the tissue[2], and uses a simple analysis procedure that can be applied in a clinical setup. The MEX sequence includes selective suppression of the water magnetization, by RF pulses and spoiling gradients, followed by a variable period (t_{LM}) in which magnetization recovery occurs[2]. Two processes dominate the observed signal: magnetization transfer between protons associated with lipid-protein molecules (myelin) and protons in the aqueous surrounding, and spin-lattice relaxation (T_1). The analysis of the image intensity dependence on t_{LM}, yields the percentile fraction of the myelin in the tissue (F), the exchange time (τ_{exc}) and T_1.

Methods: Cuprizone is a frequently used model for demyelination in mice[3]. Seven mice, fed with cuprizone and, four, fed with standard food, were imaged *in-vivo*. Animals were scanned using the proposed MEX sequence (Fig.1), on a 7T Bruker BioSpec scanner. The preparation MEX block was calibrated to ensure maximal water saturation at $t_{LM} = 10\,\mu s$, using hermite pulses adjusted to 3.3-3.7 watt, ensuring a good suppression. Following the recovery period, a standard gradient-echo imaging module was implemented. Ten different values of t_{LM} delays ranging 2.5-2500 ms were used to acquire two slices with TE/TR=3.5/3000 ms. The images were normalized by the longest t_{LM} scan, and fitted to Eq.1 using non-linear least squares in MATLAB (MathWorks, MA), assuming fast exchange.

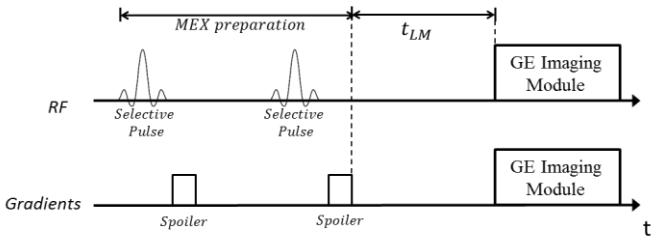

Fig. 1: MEX pulse sequence. Two selective pulses are applied at the water resosnance, each followed by a spoiler. The delay time, t_{LM}, is varied between repetitions.

$$M_{zw}(t_{LM}) = M_{ZW}^{eq}(F\left(1 - e^{t_{LM}/\tau_{exc}}\right) + (1 - F)\left(1 - e^{t_{LM}/T_1}\right)) \qquad \text{Eq. 1}$$

Three regions of interest (ROI's) were segmented: white matter (WM) in the Corpus Callosum (CC) and Internal Capsule (IC), and gray matter in the cortex (GM). The signals of the pixels within the ROI's were summed and fitted to Eq.1, obtaining fit of R^2>0.999.

Results: The signal obtained from the scans show inversion of contrast along the t_{LM} scale, where in short delays WM/GM value is greater than one, and in long delays the ratio reverts. The maps obtained the fitted parameters show significant differences in the CC between the cuprizone fed mice and the control group (fig. 2). F is reduced by 25% (P<0.05), and T_1 is higher by 37% (P<0.01). The expected effect of the cuprizone model on myelin in the CC support these results of the F values[4]. In the IC and GM we cannot detect any significant decrease in the F values, resulting in a disappearance of contrast in the brain (not shown) [3], [5].

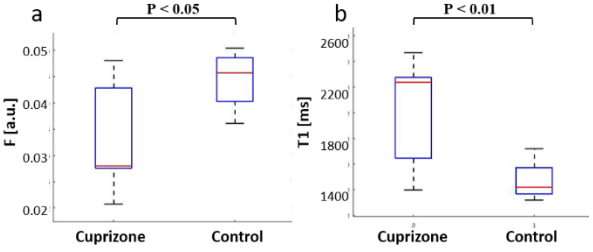

Fig. 2: (a) F, (b) T_1 parametrs for all cuprizone and control mice, averaged over the whole CC.

Conclusions: The results provide quantitative measure of demyelination in brain white matter, as demonstrated by the cuprizone model. The values of F show decreased content of myelin in the CC in cuprizone fed mice, and no changes in the in other white matter regions of the brain (IC) or in GM.

References: [1] Stikov Neuroimage(2015). [2] Eliav NMR Biomed.(2017). [3] Torkildsen, Acta Neuro. Scand.(2008). [4] Hibbits, ASN Neuro.(2012). [5] Matsushima, Brain Pathol.(2006).