Monitoring De- and Re- Myelination MR Spectroscopy Surrogate Markers in the Mouse Brain at 9.4 T

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Background Proton MR spectroscopy (^{1}H-MRS) is frequently used to augment the sensitivity of MRI with metabolic specificity. The main surrogate markers monitored by ^{1}H-MRS are the N-acetylaspartate (NAA) which is exclusive to neuronal cells, the mixture of free and phosphor-creatine (Cr) reflecting cell energetics, and the composite of free and phospho-choline (Cho) which reflects membrane turnover. Unfortunately, increases or declines in their levels are rarely definitive of the underlying process. For example, a decline in NAA may reflect neuronal dysfunction (which may be recoverable) or loss, which is permanent. Likewise, elevated Cho may indicate membrane destruction or recovery or even an admixture of the two processes. There has been precious little direct validation, *i.e.,* direct quantitative pathological verification, of the underlying molecular processes steering the MR observed behavior of these surrogates. The goal of this study was to validate the nature of the MRS surrogate markers in a known model of de- and re- myelination in a mouse brain and verify these observations with pathological validation.

Methods 23 mice were placed on a 0.2% (w/w) cuprizone diet, known to yield up to 90% demyelination in 5 weeks. After 5 weeks on this diet, 10 mice returned to normal feeding for 4 (n=4) or 7 (n=6) weeks. All mice were followed with MRI, magnetization transfer (MT) imaging and ^{1}H-MRS exams at baseline, 4, 9 and 12 weeks. All MR studies were performed on a 9.4-Tesla vertical system (Bruker, Wissembourg) using a mouse-head coil. MT imaging used coronal T2-RARE (offset=5 kHz, $\mathbf{B_1}$=1.5 μT, TR/TE=6000/6.2 ms). The MT ratio of the corpus callosum and striatum were calculated using MTR = (1- M_S / M_O) ×100, where M_S and M_O are the magnitude of the MR signal with and without MT saturation. For ^{1}H-MRS, a TR/TE=6000/9 ms PRESS was used to excite two 8.1μl single voxels: One (3×0.9×3 mm^3) over the corpus callosum, as shown in Fig. 1 and the other (1.64×1.64×3 mm^3) on the striatum. After each MR session (week 4, 9 and 12), some mice were sacrificed for histopathology which used myelin basic protein (MBP), marker for myelin, glial fibrillary acidic protein (GFAP) for astrocytes and amyloid precursor protein (APP) for acute axonal damage.

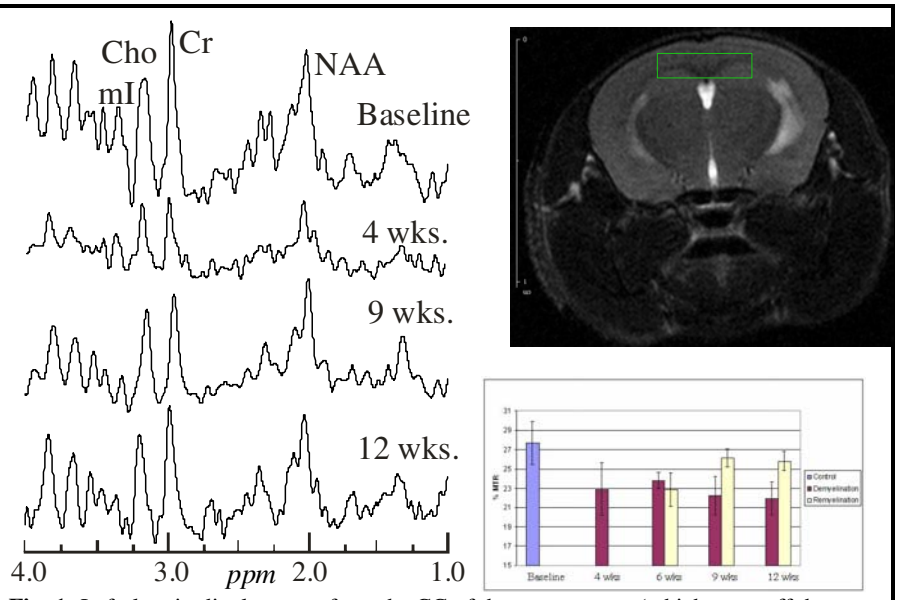

Fig. 1: Left, longitudinal spectra from the CC of the same mouse (which went off the diet at 5 wks) at baseline, 4, 9 and 12 weeks. Note the metabolic loss (wk. 4) and its subequent recovery. Top, right, the MRI of that mouse (baseline) showing the positioing of the VOI. Bottom, right, MTR from CC of all the the mice in the study at the indicated time points. Note the MTR loss and recovery pattern similar to the MRS.

Results and Discussion The spectra in Fig 1 show the longitudinal evolution of the metabolites for the same mouse, and MTR in the corpus callosum (CC) of all mice in the study. Note that, as expected, maximum MTR and metabolic losses were observed at the known nadir of myelination in mice on this diet. The subsequent recovery to (almost) normal baseline MTR value and of the metabolic levels upon cessation of cuprizone feeding, indicates that these losses reflect primarily dysfunction and *not* (permanent) losses.

References 1. Merkler D, *et al.* NMR Biomed 2005; 18(6):163-171. 2. Song SK, *et al.* Neuroimage 2005; 26(1):132-140. 3. Yu O, *et al.* Magn Reson Imaging 2004 ; 22 :1139-1144.