Diffusion Properties of Metabolites in the Corpus Callosum at 7T: White Matter Microstructure and Metabolite Compartmentation

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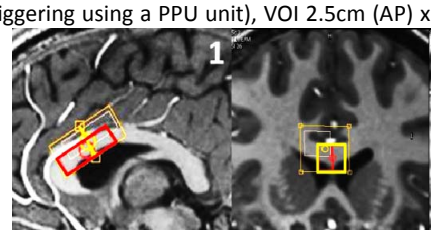
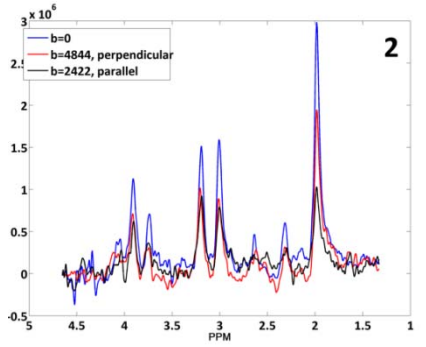
Introduction: Diffusion weighted spectroscopy (DWS) provides compartment-specific microstructural information about metabolites in brain [1-3] and in muscle [4] and thus offers unique access to the variation of compartmental geometries on the microanatomical level, and potentially to compartment-specific changes upon disease. Here we investigated in detail the diffusion of brain metabolites in a well-organized white matter fiber bundle, the corpus callosum (CC), at 7T. The results indicate a clear difference in compartmentation among metabolites and raise interesting questions when results are fitted to conventional models of diffusion in given geometries, relevant to the interpretation of the more sensitive but less specific diffusion weighted imaging.

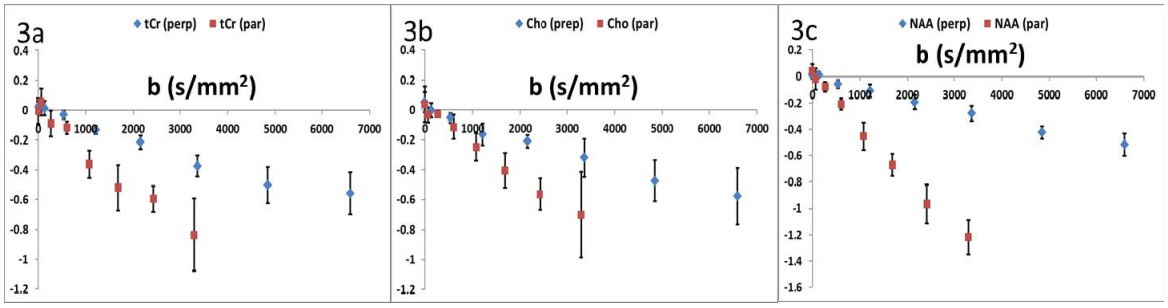
Methods: Scans were performed on a 7T Philips Achieva scanner equipped with quadrature transmit head coil and a 32 channel receive coil array. 11 subjects were scanned – 7 of them for obtaining information on N-acetyl-aspartate and N-acetyl-aspartyl-glutamate(tNAA) and 4 for total Choline compounds (tCho) and creatine+phosphocreatine (tCr). Separate sessions were necessary because of the chemical shift difference between the tNAA and the tCho + tCr (center frequency set at 3.1PPM), which shifts the volumes of interest (VOI) several millimeters apart. A PRESS sequence with bipolar gradient diffusion scheme was used :TE/TR = 121ms/3 cardiac cycles (cardiac triggering using a PPU unit), VOI 2.5cm (AP) x 1cm (RL) x 0.8cm (FH), angulated to include the rostral body and anterior body of the corpus callosum (Witelson segments A3-A4 and part of A2, see figure 1). Acquisition parameters: BW=3000Hz, #points=1024. A total of 720 individual scans with 15 conditions: two diffusion directions and 7 gradient amplitudes + one scan at b=0. Directions chosen were parallel to the fibers in the CC (left-right) and perpendicular to the fibers (at 45 degrees between AP and FH). Diffusion parameters were δ=34ms, Δ=60.5ms and gradient strengths of 3.5-31.5mT/M for a single gradient, resulting in maximum b-values of 3297 s/mm^2 (parallel) and 6594 s/mm^2 (perpendicular). Individual scans were corrected for phase and frequency fluctuations based on the phase/frequency of the residual water and then averaged. An independent non-water suppressed data set was acquired for eddy current correction and analysis of the water diffusion in the same VOI (data not shown). Quantification of the data was then performed with LCmodel [5]. All other post-processing work used in-house MATLAB® routines (Mathworks, Natick, MA).





Results and discussion: Typical diffusion weighted spectra zoomed on the region of the metabolites analyzed here are shown in figure 2. These spectra are taken from the set acquired for the tCho-tCr, and although the NAA here is not optimally acquired, the spectrum is representative of the same findings observed when the center frequency is set to NAA. The attenuation of the NAA signal when the DW gradients are parallel to the fiber orientation is much stronger than that in the orientation perpendicular to the fibers, whereas the difference is much less marked in the case of the tCho and tCr. Plots of the normalized attenuation for the three metabolites for the entire group are shown in figure 3. The table summarizes the ADC values parallel and perpendicular to the fibers, and the ratio between them as a measure of diffusion directionality. NAA, a primarily neuronal/axonal constituent, shows, as expected, the most marked directionality, with a ratio of above 5 between the two ADC values. The results shown here for diffusion of NAA are in excellent agreement with those for diffusion of NAA in bovine optic nerve [6, 7], which show similar findings in the range of b-values explored here. However, when the NAA data are fitted to a model of diffusion in cylindrical pores [8] with realistic distribution of inner axonal diameters, the angular distribution of axons needed to properly fit the data is about 40°, much higher than expected for this particular VOI, which extends only 5mm on each side of the medial line (simulation data not shown here). These data suggest a re-examination of simple compartmentation models of NAA in white matter, in order to better evaluate the microscopic arrangement of axons, which may differ from the average properties measured with DTI, and for exploring the interaction between transverse relaxation and restricted diffusion, which may strongly affect the measured values of ADC(perp) in the case of highly relaxing boundaries. The diffusion of tCho and tCr is expectedly less directional, and their larger ADC(perp.) and lower ADC(par) compared to those of NAA attest for a significant fraction in cell bodies (e.g. glial cells), where the typical length scale is significantly larger than that of a typical axonal diameter.

	ADC(Perp) μm^2/ms	ADC(Par) μm^2/ms	ratio
tCho	92.8±6.9	222.0±23.0	**2.39**
tCr	95.0±4.1	263.1±15.7	**2.77**
tNAA	79.3±3.3	410.3±12.9	**5.17**



References: **1.** Nicolay, K., et al., NMR Biomed, 2001. 14(2): p. 94-111. **2.** Upadhyay, J., et al., Magn Reson Med, 2007. 58(5): p. 1045-53. **3.** Ellegood, J. et al.,, Magn Reson Med, 2006. 55(1): p. 1-8. **4.** de Graaf, R.A., A. van Kranenburg, and K. Nicolay, Biophys J, 2000. 78(4): p. 1657-64. **5.** Provencher, S.W., Magn Reson Med, 1993. 30(6): p. 672-9. **6.** Assaf, Y. and Y. Cohen, NMR Biomed, 1998. 11(2): p. 67-74. **7.** Assaf, Y. and Y. Cohen, J Magn Reson, 1998. 131(1): p. 69-85. **8.** van Gelderen, P., et al., J Magn Reson B, 1994. 103(3): p. 255-60.