Measurement of apparent diffusion coefficients (ADC) and ^{1}H transverse relaxation times (T_2) of human brain metabolites and water: insights on white matter microstructure

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Introduction: The dependence of MR-measured apparent diffusion coefficients (ADCs) of molecules in biological tissues on a controllable, acquisition-specific timescale allows measurement of the characteristic length scales of tissue compartments and it has been recognized as a powerful mechanism for deriving information on tissue microstructure [1]. Metabolites are generally considered to be confined mainly in intracellular compartments and to exchange at a slower rate than water molecules between microscopic pools, making them better probes for compartmentalization in neural tissues [2,3] and therefore providing higher specificity in studying brain tissue microstructure and pathology. In addition, because of the differing molecular environments modulating dipolar interactions among proton spins, each micro-anatomical pool may also be characterized by a different ^{1}H transverse relaxation rate ($1/T_2$) [4]. The interaction between relaxation and diffusion characteristics has been thoroughly studied in porous media [5] and in excised nerves [4,6]. In this study, for the first time the interaction between relaxation and diffusion was studied for both water and metabolites in the human brain in vivo at 7T.

Methods: Scans were performed on a 7T scanner (Philips, Best, the Netherlands) equipped with a 32-channel receive coil and a quadrature transmit head coil (In Vivo, Florida). A single voxel, diffusion-weighted STEAM sequence was used to measure the diffusion of water and of the metabolites tNAA, tCr and tCho (not all data shown here). Two data-sets were obtained, from 7 young healthy volunteer each (29 ± 8 years), using two different diffusion times (Δ). Sequence parameters for the two protocols were: Δ = 246/44ms, TM = 230/14ms, δ = 10/24ms, TR = 3 cardiac cycles (triggering using PPU), spectral width 3kHz, 1024 sample points. Diffusion gradients were applied in 3 standard quasi-orthogonal directions with 5 increasing gradient strengths chosen in the range 0-3.6G/cm in order to obtain identical b-values of 0, 285, 1140, 2570, and 4575s/mm^2 in both data-sets. A bipolar gradient scheme was employed to minimize eddy currents. Spectra were acquired for three echo times TE = 40/63, 90, 160ms with an increasing number of averages in order to keep similar SNR for each scan. A VOI of 30x20x19mm^3 was positioned in parietal WM. The residual water peak was used to perform phase and frequency corrections on individual spectra before summation. Non-water suppressed spectra were also acquired to derive water diffusion and relaxation properties as well as for eddy current corrections.

Results and discussion: The water and metabolite normalized signals as a function of b-value show a non-monoexponential trend (Fig.1b), reflecting, among other factors, the presence of physical restriction hindering the diffusion of molecules. In order to extract the ADC values, the curves were fitted to a stretched-exponential model $S(b)/S(0)=\exp[-(b\cdot ADC)^{\beta}]$, which describes diffusion-weighted signal decay as a continuous distribution of sources decaying at different rates [7]. At the long diffusion time Δ = 246ms the ADC of water is significantly lower at longer TE values (Fig. 1a), suggesting that the slow diffusing component, mainly associated with intra-cellular water, has a longer T_2 than the fast diffusing component in the extra-cellular space. The $1/T_2$ decrease on increasing diffusion weighting at long Δ (Fig.2a) is also consistent with this hypothesis and corroborates previous findings obtained in frog sciatic nerve [4]. The estimated value for the stretching-factor β was in the range 0.5-0.6, indicating strong deviation from "pure" Gaussian diffusion. Surprisingly, the ADCs of tNAA, tCr (Fig. 1c) and tCho were found to decrease with increasing TE, while transverse relaxation becomes slower at high b-values (Fig.2b), suggesting that the slow diffusing components have a longer T_2. β increased with TE and was in the range 0.6-0.9. In contrast, for Δ = 44ms no significant dependence of ADC on TE was observed for either water or metabolites and β was very close to 1 for all metabolites. The results for the interaction between relaxation and diffusion in metabolites is evidently more complicated than that of water, especially given the absence of an extracellular pool for the metabolites, and may need to be modeled by including some form of compartmentalization in axons and glia, with exchange between "bound" and "free" states affecting both metabolite relaxation rates and diffusion.

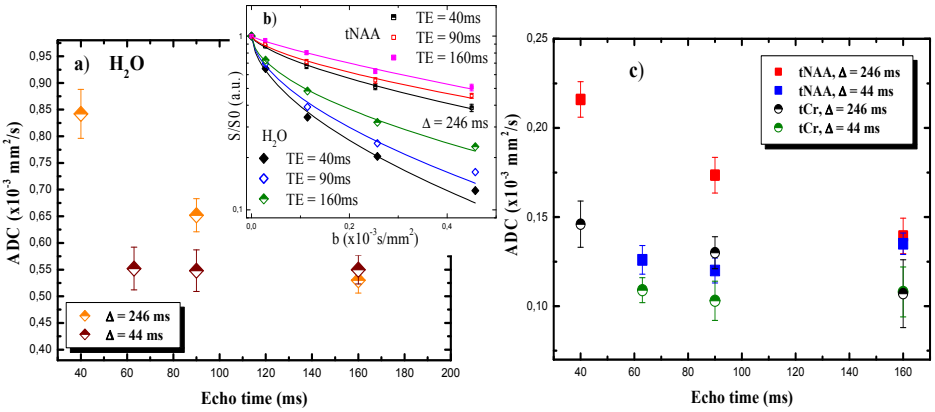

Fig.1: Water (a), tNAA and tCr (c) ADCs measured as a function of echo time for two different diffusion times Δ. ADCs have been estimated from fits to stretched exponentials of normalized signal decay plotted as a function of b-value, as shown in (b) for water and tNAA data at long Δ.

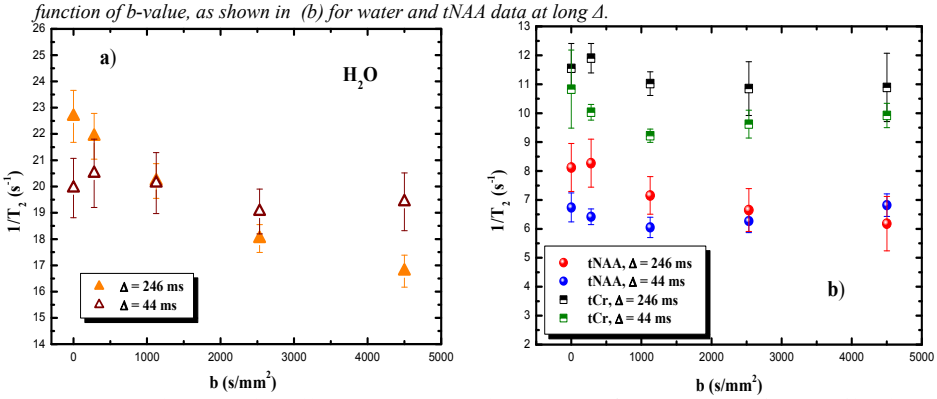

Fig.2: Water (a), tNAA and tCr (b) proton transverse relaxation rates $1/T_2$ measured as a function of b-value for two different diffusion times Δ.

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