Diffusion Relaxation Correlation Spectroscopy at Ultra Short Echo Times Reveals Two Major Compartments in Human Cadaver Brain White Matter

B. Dhill1, M. Gratz2, and R. Turner1

1Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, 2Faculty of Physics and Geosciences, Department of Interface Sciences, University of Leipzig, Leipzig, Germany

Introduction: MR measurements of water diffusion have been widely used in recent years to identify neurological abnormalities and to characterize white matter fibre tracts. Although diffusion-weighted signal for brain tissue decreases exponentially for low b-values (<2000 s/mm²), at larger b-factor it is clearly apparent that diffusion is not mono-exponential [1]. This multi-exponential decay may arise from multiple water compartments with slow exchange. However, while efforts continue to correlate fit parameters with physical parameters [2], multi-exponential water diffusion in brain tissue is still poorly understood [3].

The diffusion weighted signal obtained with a Stejskal-Tanner spin echo DWI measurement is \( T_e \) weighted. For a sample with \( n \) different water compartments, \( S = S_0 \sum (P_i T_{2i} \exp(-TE/T_{2i}) \exp(-bD_i)) \). Therefore, the problem of characterizing water dynamics in brain tissue should be regarded as two-dimensional, requiring a wide range of echo times in order to discriminate the compartments, and the shortest possible diffusion time to allow a short echo time and to reduce inter-compartment exchange. In this study we performed Diffusion Relaxation Correlation Spectroscopy (DRCOSY) measurements with very short diffusion time (\( \Delta = 1.2 \) ms). This was made feasible in human cadaver brain tissue by the use of an NMR spectrometer with exceptionally powerful gradients.

Method: Figure 1 shows the schematic of a DRCOSY sequence, where a Stejskal-Tanner[4] spin-preparation module is followed by a CPMG train without any new excitation.

Five formalin-fixed, excised specimens of human corpus callosum were cut exactly to fit the NMR tube, with fibre orientation in the axial direction. Experiments were performed in a homebuilt Figris NT 125 MHz NMR spectrometer equipped with gradient of up to 35 T/m in z-direction[5]. The parameters used were: Delta (\( \Delta \)) = 1.2 ms, gradient pulse duration (\( \delta \)) = 0.5 ms, first echo (\( T_E \)) = 2.4 ms, CPMG echo interval (\( \tau \)) = 0.5 ms. Diffusion gradients were incremented linearly from 0.1 T/m to 28 T/m with intervals of 0.7 T/m (maximum b-value = 11.365 s/mm²). Eight averages and 6 repetitions were measured. Prior to measurement sample was checked for internal gradients by comparing CPMG attenuation with different echo intervals(t).

The first-echo diffusion data were first analyzed using a conventional bi-exponential fit and CPMG train from the smallest diffusion parameter with physical parameters [2], multi-exponential water diffusion in brain tissue is still poorly understood [3].

Results: Bi-exponential fitting of the diffusion data resulted in two distinct components \( D_{fast} \) ranging from 0.11 \( \mu m^2/\)ms to 0.67 \( \mu m^2/\)ms and \( D_{slow} \) (0.1--0.05 \( \mu m^2/\)ms) with relative fractions \( F_{fast} \) (0.56--0.42). Biexponential fit of CPMG train also gave a faster relaxing component \( T_{2fast} \) (25.5--18.2 ms), and a slower relaxing component \( T_{2slow} \) (140--95 ms), and fraction of the fast relaxing component ranged from 0.53--0.61.

Two Dimensional Laplace transform also resulted in two distinct peaks, with an order of magnitude difference in both diffusion and \( T_e \) relaxation properties (Figure 2). Surprisingly, the faster component was associated with a faster \( T_e \) relaxation, counter to the common assumption that faster diffusion, characteristic of more mobile water molecules, would be associated with slower \( T_e \) relaxation.

Conclusion: Correlating diffusion and relaxation in a single experimental setup allows us to discriminate multi-compartmental water in the brain tissue without assuming an inherent relation between diffusion and relaxation properties of water in these compartments. Although both diffusion and \( T_e \) relaxation are related to the mobility of water molecules, whereas \( T_e \) relaxation reflects rotational dynamics of the molecule, diffusion is related to the translational motion. We hope that further studies on different brain tissues with this method will allow us to distinctly separate the different water components present and help understand the biophysical basis of diffusion NMR.

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