Diffusion tensor MR Spectroscopy to assess microstructural changes in patients with multiple sclerosis

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Background and Objectives: Microstructural damage is present in all brain compartments of patients suffering from multiple sclerosis (MS) whatever the disease stage (Kutzelnigg et al, Brain 2005). To assess non invasively and more specifically such diffuse microstructural changes, we developed a diffusion tensor ^{1}H MR spectroscopic sequence in order not only to map concentrations of brain metabolites, but also to determine their diffusion characteristics (mean diffusivity and fractional anisotropy). These parameters were compared between healthy controls and MS patients.

Methods: MR explorations were performed on a 3T Verio system (Siemens, Erlangen Germany) using a 32-element proton head coil. We examined six patients suffering from relapsing-remitting MS (32.5 yo ± 10.8) and 9 healthy controls (29.4 yo ± 6.3). A home-made single voxel diffusion-weighted STEAM sequence was designed (IDEA, figure 1) and then applied *in vivo* to measure the diffusion parameters of brain metabolites including N-Acetylaspartate (NAA) at 2.01 ppm, creatine compounds (Cr) at 3.02 ppm and choline compounds (Cho) at 3.2 ppm. The diffusion sequence parameters were TR=2000ms, TE=61ms, TM=30ms, 128 averages, voxel size = 15x15x15mm^3 (3.37mL), 2048 points, bandwidth 1kHz. For each subject, two brain regions were explored: one voxel was located in the splenium of corpus callosum (white matter); the second voxel was located in the thalamus (grey matter). For each brain region, seven spectra were acquired: 1 spectrum at b=0s/mm² and 6 spectra at b=1322s/mm² acquired in the six different directions ([-1 -1 0], [-1 0 -1], [0 -1 -1], [1 -1 0], [1 0 -1], [0 1 -1]) corresponding to the diffusion sensitizing gradient diffusion (Figure 2). MR spectroscopic data were analyzed using dedicated software developed on IDL (CSIAPO, Le Fur et al. MAGMA 2010). Peak areas of NAA, Cr and Cho were measured using the AMARES approach (Vanhamme L et al. J Magn Reson 1997). Relative concentrations of metabolites were derived from the b=0s/mm² spectra by dividing the peak area by the sum of all metabolites. Diffusion coefficients were determined for each direction and MD and FA of each metabolite were computed. Data from patients and controls were compared using Mann-Whitney U-tests. Correlations between metabolite levels and diffusion characteristics of metabolites were tested for each group using Spearman rank tests (patients and controls).

Figure 1 **Diffusion weighted STEAM sequence**

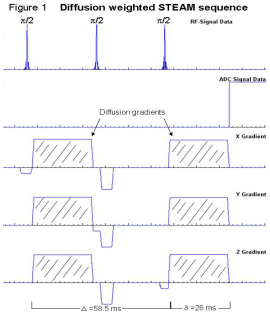
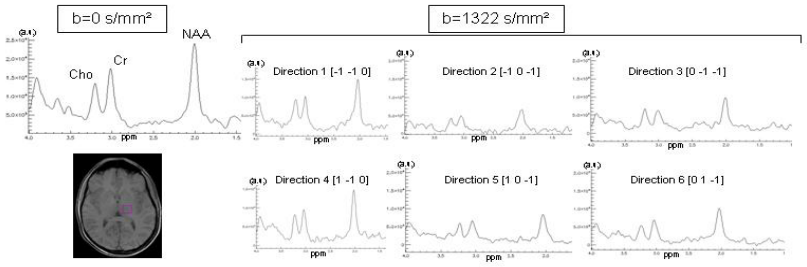


Figure 2 **Example of spectra acquired in the thalamus**



Results: Comparing patients to controls, we observed a significant decrease in relative NAA levels and a significant increase in relative Cho levels in the splenium of corpus callosum while no differences were evidenced in the thalamus (Figure 3). Concerning the diffusion characteristics, trends of increased MD were found in the thalamus of patients for NAA (p=0.086), Cr (p=0.063) and Cho (p=0.086) (Figure 4). In addition significant negative correlations were observed in the thalamus for each subgroup, between the relative Cho levels and the FA of Cho (Controls p=0.036; rho = -0.79; Patients p=0.041, rho = -0.83).

Figure 3 **Metabolites concentration in splenium of corpus callosum**

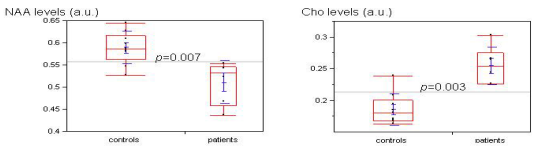
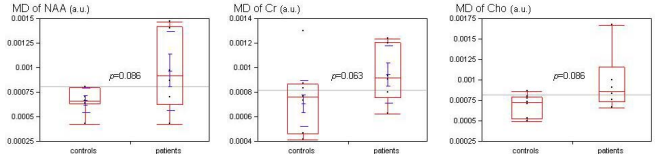


Figure 4 **Mean diffusivity of metabolites in thalamus**



Discussion and Conclusion: These results first demonstrated dissociation between the relative concentrations and the diffusion characteristics of metabolites. For example the abnormal relative concentrations of NAA and Cho within the splenium were not accompanied by abnormal MD and FA of these metabolites. In contrast, MD of all metabolites appeared more sensitive in patients to demonstrate subtle microstructural changes within the thalamus while relative concentrations of metabolites were normal. Second, the negative correlation between Cho levels and FA within the thalamus stressed the point that the increased Cho levels and decreased FA may reflect destructuration of the myelin matrix in MS patients. In conclusion, this preliminary study clearly demonstrates the feasibility of the diffusion tensor MR spectroscopic technique *in vivo* by assessing diffusion properties of specific metabolites. This should lead to better detect, quantify and monitor the pathological processes involved in MS.