Diffusion-Weighted MR Spectroscopy feasibility in clinical studies at 3 T : the effect of reducing the acquisition time investigated by bootstrapping

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Target audience: Clinicians interested in adding diffusion-weighted spectroscopy in multimodal clinical studies, MR spectroscopists.

Purpose: Diffusion-weighted MR Spectroscopy (DW-MRS) allows to measure the diffusion properties of intra-cellular metabolites in-vivo[1], and in recent years it has been proved a powerful tool to investigate brain tissue microstructure and function in both healthy and disease[2,3,4]. Thanks to the specific compartmentation of different metabolites in different cell types, DW-MRS provides additional information to that derived by diffusion tensor imaging, since in contrast water is present in all tissue compartments, and may help to differentiate between different physiological or pathological mechanisms affecting different cells types. However, due to the low concentration of brain metabolites, the applicability of DW-MRS in clinical protocols may be prevented by the long acquisition times often required by this technique. In this study, we simulated the variability of the apparent diffusion coefficients (ADCs) of total n-acetylaspartate (tNAA), total creatine (tCr) and choline compounds (tCho) associated with different acquisition schemes of different durations, and propose a short and efficient acquisition protocol to be used in clinical application.

Methods: A single VOI diffusion-weighted PRESS sequence[5] was implemented for a 3T whole-body Siemens scanner equipped with a 32 channel receive coil. A full data set was acquired in the parietal white matter (WM) of two healthy volunteers with the following parameters: VOI =15(RL)x25(AP)x20(HF)mm^3 (***Fig.1a***) - diffusion time 60ms, gradient pulse duration 30 ms, TE/TR 120ms/3 cardiac cycles, spectral width 2kHz, sample points 1024, scan time 22 minutes. A bipolar scheme was employed to minimize eddy currents. Diffusion gradients were applied in three orthogonal directions with 3 increasing gradient strengths – with positive and negative polarity acquired in an interleaved way to minimize the coupling with the background gradients - corresponding to the b values b1=350, b2=1400, b3=3100s/mm^2. For each condition, including b=0s/mm^2, 26 spectra were acquired. Residual water peak was used to perform phase and frequency corrections on individual scans before summation. The geometrical average of the signal intensities estimated for the two gradient polarities was calculated. Metabolite ADCs were estimated from mono-exponential fits of the signal decay induced by the diffusion weighting. Re-sampling was performed using bootstrapping (1000 iterations) to estimate the mean and standard deviation of the ADC for each metabolite. For a given acquisition scheme, an acquisition was simulated by drawing with repetition the averages on each condition. Each average can be considered independent of each other, since frequency and phase drift corrections were performed on single scans. The ADC average values and their variability as a function of the acquisition time was investigated varying the number of averages (26, 20, 16 and 13 for the non-diffusion weighted condition and the double for the other conditions) using the following acquisition schemes: **(a)** 3 directions and 3 b values b1,b2,b3 (duration from 22 to 11 min), **(b)** 3 directions and only b3 (from 8 to 4 min), **(c)** one direction and b3 (from 4 to 1.5 min, Fig). **(d)** As in (c) but considering the same number of averages for b0 and b3 (from 2.4 to 1.5 min). Finally, spectra were acquired in 8 healthy volunteers using scheme (c) with 26 averages for b0 and b3 (scan time = 4 min), in order to evaluate the inter-subjects variability.

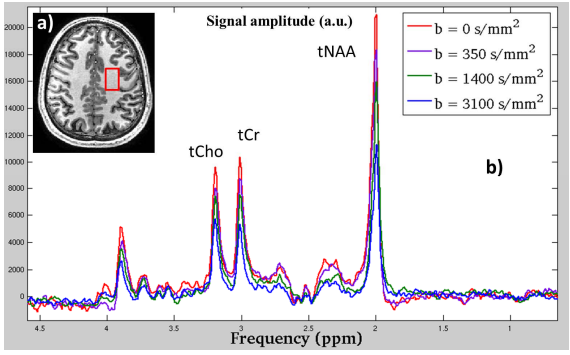

Fig.1: a) Location of the VOI in the parietal WM. b) Examples of spectra acquired at different diffusion-weighted conditions.

Results: ***Fig.1b*** shows examples of spectra acquired with the longest acquisition protocol in one subject for different diffusion-weighted conditions. The metabolite mean ADCs estimated with schemes (a) (***Fig.2a***, tNAA: filled red symbols, and tCho: open red symbols. tCr data not shown) and (b) (***Fig.2a***, blue symbols) remain stable by decreasing the employed number of averages. The corresponding percentage standard deviation (SD) increases smoothly down to acquisition times of about 4 minutes (***Fig.2b***). A small bias towards higher ADCs is observed when considering only one b value, as expected due to the non mono-exponentiality of the signal decay. Slightly higher variability in the mean ADCs can be observed for schemes (c) and (d) (***Fig.2a*** green symbols), which is nevertheless much smaller compared to the associated SD, which tends to increase drastically below the 4 minutes acquisition. Due to the relatively big size of the VOI, possible anisotropic effects in metabolite diffusion can be neglected and each gradient direction can be considered equivalent[6]. Acquisition schemes (c) and (d) do not show significant differences among each other. ***Table 1*** shows the three metabolite mean ADCs estimated from 8 healthy subjects. The mean ADCs are consistent to those derived from the simulation, and both the mean ADC and the inter-subject variability are in agreement with literature findings[5].

Table 1

	ADC (μm²/ms)	SD (%)
tNAA	0,16 ± 0,04	24
tCr	0,14 ± 0,04	32
tCho	0,13 ± 0,05	37

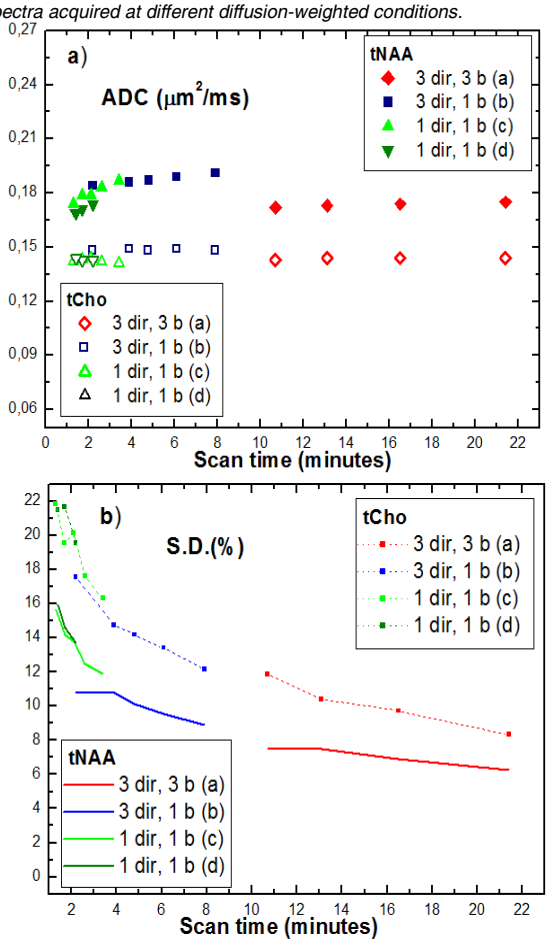

Fig.2: a) ADCs estimated for tNAA (filled symbols) and tCho (open symbols) for different acquisition schemes. b) Corresponding percentage standard deviations.

Discussion and conclusion: DW-MRS can be performed at 3T in less than 5 minutes in an isotropic VOI of the size ~7cc, which makes it possible to include DW-MRS in clinical protocols. The variability of the metabolite ADCs estimated for this acquisition time is around 10% for tNAA which is not very far from the 7% found for the 22 min acquisition. Further reductions drastically increase the variability in particular for tCho. Further analysis is required to evaluate the robustness of the acquisition with respect to movement and repositioning in scan-rescan analysis. In terms of possible applications of this sequence, multiple sclerosis, ischemia and brain tumor represent pathologies in which possible differences in metabolite diffusion may shed light into physiological mechanisms which differentially affect different cell types in these diseases.

References: [1] K Nicolay et al, NMR Biomed, **14**, 94 (2001). [2] I Ronen *et al*, Brain Struct Funct, **219**, 1773 (2014). [3] Wood et al, J Neurosci, **32**, 6665(2012). [4] F Branzoli et al, MRM, **69**,303 (2013). [5] Kan et al, MRM, **67**, 1203 (2012) [6] Branzoli et al, NMR Biomed, 27, 495 (2014).