Functional Diffusion-Weighted Spectroscopy (fDWS) of the human brain at 7T

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Introduction: Conventional functional magnetic resonance imaging (fMRI) provides an indirect measurement of neuronal activity based on the blood oxygenation level-dependent (BOLD) contrast [1]. In recent years, several fMRI methods that are not based on the hemodynamic response have been suggested. These include functional magnetic resonance spectroscopy (fMRS), which follows changes in metabolism in response to activation [2], and diffusion weighted fMRI at high b-values, which explores the possibility of microstructural changes upon activation [3,4]. Here we propose a new method to investigate compartment-specific microstructural and metabolic changes related to neuronal activation: functional diffusion-weighted spectroscopy (fDWS). In this method an alternating time series of diffusion and non-diffusion weighted spectra is acquired, yielding a time-resolved series of ADC values of metabolites correlated with neuronal activation.

Methods: All measurements were performed on a 7T Philips scanner equipped with a 32-channel receive coil and a quadrature transmit head coil. Six healthy volunteers (28±6 yrs) were scanned. An initial fMRI scan (EPI, TE/TR=14/2000ms) was performed prior to the MRS studies in order to select a VOI encompassing the activated region of the primary visual cortex. The full-field visual stimulus consisted of a radial blue/yellow checkerboard flickering at a frequency of 8 Hz and was projected onto a screen and viewed through a mirror fixed on the head coil. A VOI of 12cm^3 was positioned in the activated region for functional fDWS acquisition (Fig. 1). ^{1}H spectra were acquired using a STEAM sequence with the following parameters: TE/TM/TR=45/230/2100ms, spectral width 3kHz, 2048 time points. Diffusion weighting was applied with g=5.2G/cm, Δ=245ms and δ=9ms (b = 3770 s/mm^2). A bipolar gradient scheme was employed to minimize eddy currents. Non-water suppressed spectra were also acquired for eddy current corrections. The functional paradigm comprised 24 blocks, each constituted of a 33.6s-rest period followed by a 33.6s-stimulation period. Each block contained 16 scans (8 rest + 8 activation) without diffusion-weighting and 16 diffusion-weighted scans (8 rest + 8 activation) acquired in an interleaved manner such that the functional TR was 4.2 seconds. Phase and frequency shift corrections on individual scans were performed using the residual water peak. After summation of spectra acquired under similar conditions, 4 different composite spectra (192 scans each) were produced and quantified with LCModel. ADCs of tNAA, tCr and tCho were derived for rest and activation by evaluating the averaged signal decay induced by diffusion-weighting in the two conditions and then averaged across the 6 subjects. Finally, average time courses for the diffusion and non-diffusion weighted data, as well as for the ADCs, were calculated for a single time block and averaged across subjects.

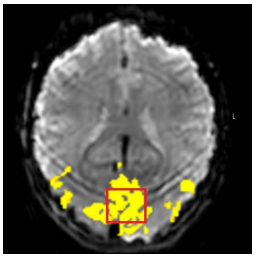

Figure 1: *Location of the VOI in the primary visual cortex, as seen on an axial EPI image from the fMRI data set.*

Results and discussion: The average ADC values of tCr and tCho were found to increase significantly during visual stimulation by about 4% (p=0.003, paired t-test) and 7% (p=0.04, paired t-test), respectively (Fig. 2). There was no significant change in the ADC of tNAA . The time courses of the tCr signal at b=0 (Fig. 3a), b=3770s/mm^2 (Fig.3b) and the tCr ADC (Fig. 4), averaged over 24 blocks and 6 subjects, were generated. Error bars were estimated from Cramér-Rao lower bound (CRLB) values provided by LCModel analyses. During stimulation, the tCr signal increased significantly, probably due to an increase in T_2. The diffusion-weighted tCr signal upon activation, however, decreases significantly (Fig. 3b). This combined effect of an increase in both T_2 and ADC of the tCr signal could possibly be attributed to the decrease in the PCr/Cr ratio during activation found in several previous studies [5,6], given that creatine, being a smaller molecule than phosphocreatine, has a longer T_2 and a higher ADC. These preliminary findings warrant further corroboration from independent measurements of diffusion coefficients of PCr and Cr, performed by a combination of ^{31}P and ^{1}H DWS measurements. Remarkably, however, changes in metabolite ADC can be exploited as a viable probe for neuronal activation, providing a tool for direct measurement of metabolic and microstructural changes upon neuronal activation.

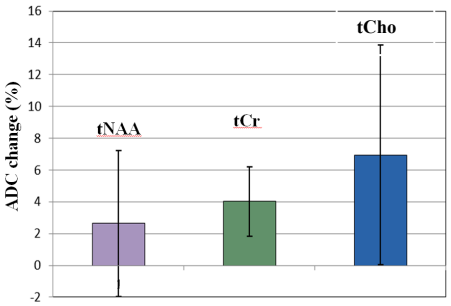

Figure 2: *Average ADC increase detected during visual stimulation for tNAA, tCr and tCho.*

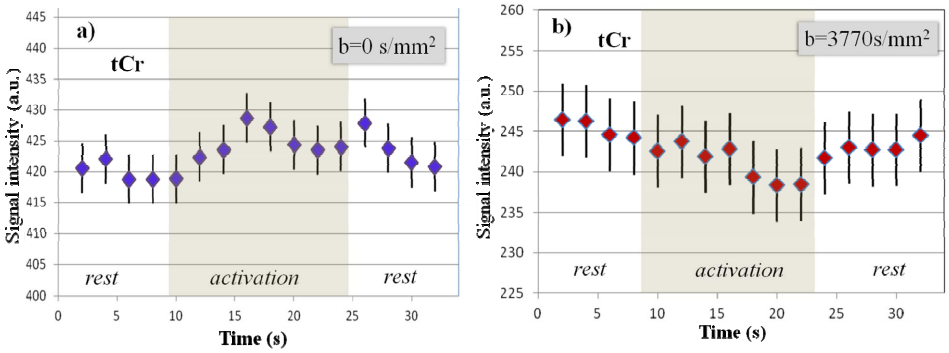

Figure 3: *Average time course of tCr signal intensity at* b=0s/mm^2 *(a) and* b=3770s/mm^2 *(b) during the functional periods of rest and activation. Two point smoothing was applied.*

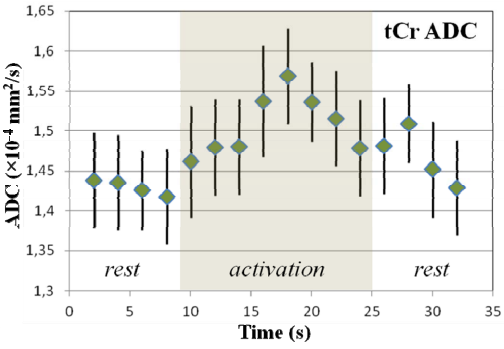

Figure 4: *Average time course of tCr ADC during the functional periods of rest and activation. Two point smoothing was applied.*

References: [1] S. Ogawa *et al*., *PNAS*, **89**, 5951–5955 (1992). [2] S. Mangia *et al*., *JCBFM,* **27**, 1055–1063 (2007). [3] D. Lebihan *et al*., *PNAS*, **103**, 8263-8268 (2006). [4] T. Aso *et al*., *Neuroimage*, **47**, 1487-1495 (2009). [5] D. Sappey-Marinier, *et al*., *JCBFM,* **12**, 584 – 592 (1992). [6] S. Xu *et al*., *NeuroImage,* **28,** 401 – 409 (2005).