Quantitative measurement of functional cerebral blood volume changes with multi-echo fMRI at 7T

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INTRODUCTION: Functional magnetic resonance imaging (fMRI) at high fields has proven advantageous because of its high signal-to noise ratio (SNR) and higher spatial resolution. Multi-echo experiments[1] at 7T have been shown to further increase the sensitivity of fMRI methods. While efforts are underway to develop novel methods such as vascular space occupancy (VASO)[2] and arterial spin labeling (ASL)[3] to measure the hemodynamic components of the BOLD response separately, it is difficult to take advantage of these methods at high fields due to the longer longitudinal relaxation times (T1s) of the various tissues in the brain and the confounding BOLD effects due to a short *T2** at 7T. In this study, we tested the use of multi-echo fMRI at 7T to contrast and compare conventional BOLD response with signal changes at TE = 0 ms which are expected to be a function of cerebral blood volume (CBV) only. Regional saturation technique (REST) slabs were used to eliminate the effect of fresh spins[4] due to inflow.

MATERIAL AND METHODS: *Experiment:* Multi-echo fMRI data were acquired on a 7T Philips® Achieva scanner with and without regional saturation technique (REST) slabs to compare the effect of inflow on *R2*, S_0* and BOLD response. 6 subjects were imaged and analyzed with the following fMRI protocol for a right handed button press motor task: TFE sequence, *TR/TE* =28/1.5:4: 24.5 ms, dynamics = 72 (dynamic scan time = 6 s), resolution = 2.5 x 2.5 x 2.5 mm^3 per slice (total 10 slices), matrix = 96 x 96 x 10. 60 mm thick, REST slabs were placed 15 mm below the imaging volume. 6 echo data were acquired with and without REST slabs in random order for each subject. Physiological data was collected using bellows for respiration and pulse-oximeter for cardiac cycle measurements. *Analysis:* Physiological noise correction was performed using retrospective image-based correction (RETROICOR)[5]. BOLD data at TE = 19.5 ms were evaluated using a general linear model (GLM) analysis with FEAT in FSL[6]. Preprocessing steps included motion correction, baseline drift removal, high pass filtering and smoothing (5 mm). The smoothed multi-echo data were fit to a simple mono-exponential $S = S_0 e^{-TE \times R2^*}$ using customized MATLAB scripts to estimate voxel-wise values S_0 and *R2** for the entire imaging volume at all 72 dynamics. Functional runs for S_0 and *R2** were calculated and evaluated with similar FEAT analysis as for the BOLD data. Spatial and temporal characteristics of BOLD, S_0 and *R2** were investigated. Time-courses and % signal changes in regions, common to all three activation maps were compared. *Simulation study:* The steady state signal intensity in the parenchyma for the TFE sequence is given by $S = \frac{S_0 \sin\alpha(1-E1)e^{-TE/T2}}{1 - E1\cos\alpha + E1E2 - E2\cos\alpha}$ where $E1 = e^{-TR/T1}$, $E2 = e^{-TR/T2}$.

We separate S into 2 components: pure grey matter (GM) and blood. The total signal is $S = S_t\, e^{-TE/T2(tissue)} + S_b\, e^{-TE/T2(blood)}$. We define $S_0 = S_t + S_b$ where $S_b = \xi C_b M_{0b}$ and $S_t = (C_p - \xi C_b)\, M_{0t}$[2]. C_b = water density of blood (ml water/ ml blood), $C_p = C_t + \xi C_b$, water density of parenchyma (grey matter+ blood), C_t = water density of grey matter, ξ is the vascular occupancy and increases to ξ' with increased CBV at activation during the task. M_{0b} and M_{0t} denote the steady state longitudinal magnetization of blood and grey matter respectively. Assuming a 5% baseline CBV, with C_b, C_p calculated by Lu et al.[2,7], and utilizing T1/T2[8] of GM and blood at 7T, percentage signal change i.e. $\Delta S_0/S_{0@rest}$ was simulated as a function of CBV change. Experimental values of $\Delta S_0/S_{0@rest}$ were overlaid on the graph.

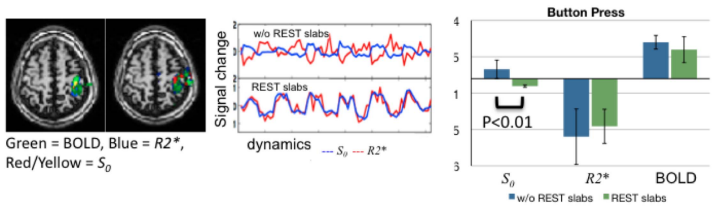

Figure 1*: Multi-echo fMRI with and w/o REST slabs*

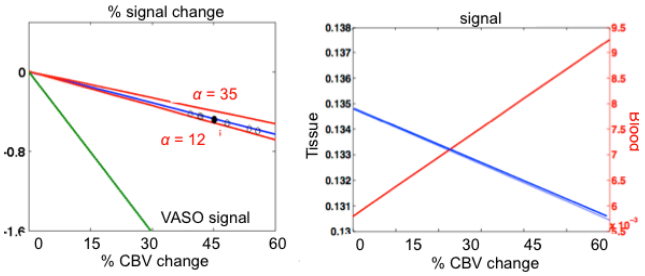

Figure 2*: Left: Simulation of signal changes with CBV Blue – based on current experiment, red – different flip angles, green - VASO . Right: Signal change in the tissue and blood w.r.t. CBV*

RESULTS AND DISCUSSION: ***Figure 1*** shows experimental results for multi-echo fMRI with and without the use of REST slabs. Time courses for S_0 and *R2** during functional activation clearly show the activation and rest pattern followed in this task. Changes were positive in the absence of REST slabs and significantly negative when rest slabs were used. REST slabs did not alter *R2** or BOLD responses significantly. ***Figure 2*** depicts the simulation results obtained for the above derived signal changes. Note that at the inversion time of blood, the above equation simplifies to the VASO equation for CBV change during functional activation. The VASO signal changes shown in the figure, assume no BOLD effects at 7T. The small angle approximation can only be used for α<15°, which increases the sensitivity of the method to CBV changes as shown in the simulation results. The figure also shows the decrease in tissue signal intensity and increase in the blood signal intensity, corresponding to increase in CBV. However, the blood signal intensity is much lower than the tissue signal intensity in the parenchyma at TE = 0, causing the overall signal change to be negative. Our experimental values correspond to a CBV change of about 45%. The computed CBV changes are larger than those observed with other MR methods and PET, potentially due to noisy estimation of S_0, the assumption that the parenchyma is just a 2 compartment model (neglecting CSF), and the use of parenchyma partition coefficient for pure tissue. When subjects were separated based on caffeine intake, subjects with no caffeine (n=2) intake showed 9.09% more S_0 change compared to subjects with caffeine intake(n=4) with this method. Caffeine is known to have a vasodilatory effect and may potentially cause the decreased response, measured here. This also may in part contribute to the increased BOLD effect (70%) in caffeine drinkers, seen in other studies.

CONCLUSION: We demonstrate the feasibility of employing multi-echo fMRI for measuring functional CBV changes at 7T. Multi-echo fMRI therefore can, not only provide BOLD and *R2** with high CNR but also information about CBV changes, allowing a more detailed understanding of the hemodynamic response of the brain to stimuli from a single fMRI experiment.

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