Characterization of Spin Echo and Stimulated Echo BOLD Contrast for functional MRI of the Rat Brain at 4.7 T

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Introduction: For functional MRI (fMRI) at high B_0, spin echo (SE) based pulse sequences have attracted increasing interest because of minor image distortions and better regional specificity as compared to T_2^* based sequences as well as the improved temporal resolution as compared to perfusion based fMRI methods (1-6). Exchange and/or diffusion based models have been developed to describe signal changes in SE fMRI experiments at different B_0 and to support the optimization of pulse sequence (7,8). Data characterizing the dependence of T_2 on the refocusing interval τ_{180} showed that T_2 still decreases at rather long τ_{180}. Therefore, we compared SE images with stimulated echo (STE) images to examine whether activation induced signal changes can be increased by choosing an appropriate mixing time (TM) in STE based sequences. The measurements were performed using SE or STE variants of echo planar imaging (EPI) and ultra fast low angle RARE (U-FLARE). As the image contrast of SE- or STE-U-FLARE inherently has negligible T_2' contributions, it was possible to determine whether the effects observed in SE/STE-EPI images are due to remaining T_2' contributions caused by static B_0 inhomogeneities and the rather long train of gradient echoes.

Experimental: *NMR Hardware and animal model:* All experiments were performed on a 4.7T/40cm Biospec system (Bruker, Germany) equipped with self-shielded gradients (170mT/450µ s). A saddle-type resonator was used for RF transmission and an 18 mm surface coil for signal reception. Wistar rats (200-300 g) were initially anaesthetized with 1.5% halothane in a 70%/30% mixture of N_2O/O_2. After 10 minutes, α -chloralose (40 mg/kg) was administrated intraperitoneally. The animal was fixed in a stereotactic head holder. The respiration rate of the animal and rectal temperature was monitored and the body temperature was maintained using a warm water blanket (37 °C +/- 1 °C). Two electrodes were positioned subcutaneous in the left or right forepaw. All fMRI experiments were performed using two periods of electrical stimulation (square pulses, 0.3 ms, 1.5 Hz, 2 mA) either of the right or left forepaw bracketed by three 30s periods of rest. The animals were positioned using FLASH images (TR=200ms, TE=6ms, 128^2 matrix, FOV 32*32 mm^2, 2 mm slice) and fMRI was performed in a 2 mm slice. The slice position (~5mm posterior to the rhinal fissure) was optimized (+/-0.5mm) based on maximum fMRI signal changes.
Pulse sequences: SE ($90°_{Gz}$-$180°_{Gy}$-[EPI readout]) and STE ($90°_{Gz}$ - $90°_{Gy}$ - [EPI readout]- 90° - [EPI readout]) variants of EPI with asymmetric readout gradients were implemented using the following parameters: FOV: 48(x, read)*24(y, PE) mm^2, matrix size: 64(x)*32(y), slice thickness: 2mm, interecho spacing: 1.5 ms, TE_{min}=56ms. The repetition time TR was 3s for SE-EPI and 3s+TM yielding a constant relaxation delay. The first two RF pulses were spatially selective to select the slice (z) and allow a small FOV in phase encoding (y) direction. The third 90° pulse in the STE sequence was not spatially selective to avoid in-flow/out-flow effects when comparing the images from the primary spin echo (prSE) and the stimulated echo. Additionally, SE and STE variants of displaced U-FLARE were implemented with the following parameters: FOV: 48(x, read)*48(y, PE) mm^2, matrix size: 64*64, slice thickness: 2mm, 135° Gaussian refocusing pulses, interecho spacing: 5ms, TE_{min}=36ms. Of course, in STE-U-FLARE, images of the prSE and the STE may not be acquired simultaneously, but in subsequent measurements. In all experiments, the spoiler gradients were minimized to suppress diffusion effects in external gradients (e.g., in STE-EPI b<50 s/mm^2 for TM=200ms.).
Data processing: The images were calculated using sine-bell apodization and 2D FFT. The signal evolution was analyzed in each pixel without any averaging, additional filtering or motion correction. Difference images were calculated from the mean values in the two stimulation and the three rest periods, neglecting the first three images of each period to avoid transition effects. The statistical significance of signal changes was determined by a paired t-test.

Results and Discussion: Despite using spontaneously breathing rats, activation induced signal changes were clearly observed in all animals, with only minor motion artifacts in some images. In the center of activated regions, the relative signal change $(I_{stim}-I_{rest})/I_{rest}$ in the SE-EPI experiment was about 3-5% at TE=56ms. The relative signal changes increased with increasing TE up to 11 % at TE=140ms (cf., Fig.1). A similar behavior was observed in SE-U-FLARE images, where the relative signal changes increased from 2% at TE=36 upto 6.5% at TE=136ms. However, a direct comparison with the EPI results is not possible because of the inherent T_1/T_2 weighting of U-FLARE images.
In the STE-EPI measurements, similar signal changes were observed in the images of the prSE as expected. However, the images of the STE, acquired at the same TE=56ms and with TM values of 100-500ms yielded significantly larger relative signal changes as well as improved statistical significance as compared to the prSE data, despite the reduced signal intensity (cf. Fig.2). The ratio between the relative signal changes, i.e. $[(I_{stim}-I_{rest})/I_{rest}]_{STE}/[(I_{stim}-I_{rest})/I_{rest}]_{prSE}$, was 1.3-1.8. This ratio did not increase systematically with increasing TM. For most animals, the ratio did not increase furthermore for TM>200ms.
Increased relative signal changes were also observed in STE-U-FLARE images as compared to prSE-U-FLARE images, thus indicating that the observed effect does not result from specific properties of SE/STE-EPI (e.g. remaining T_2' contributions). The reason why the relative signal changes are higher in STE images than in prSE images remains still unclear. Both the effect of increased T_1 values (accompanying increased T_2 values) in the stimulated regions or changed diffusion processes [9] (in case the "long-echo limit" is not valid for the used TE) seem to be compatible with the described observations.

Conclusion: As the increased relative signal changes in STE images (compared to prSE) do not compensate for the inherent 50% SNR loss of STE as compared to SE images at a given TE, an increased statistical significance in fMRI studies cannot be achieved. However, the findings are of interest because (a) STE based fMRI with its high temporal resolution can be beneficial, (b) STE experiments may help to evaluate models describing fMRI signal changes, and (c) diffusion studies based on STE experiments where both echoes (prSE, STE) are used for images with different b-values [10] should be carefully evaluated to avoid misinterpretations.

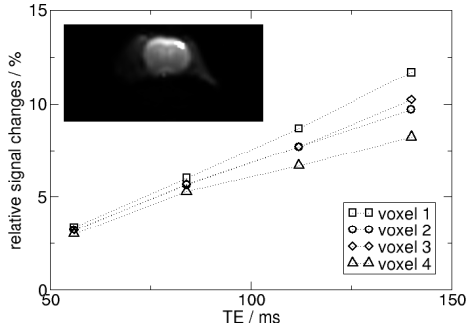

Fig.1: $(I_{stim}-I_{rest})/I_{rest}$ vs. TE determined for four pixels in the center of the activated region, and SE-EPI image (TE=56ms) with stimulated area ($p<10^{-6}$) overlaid in white.

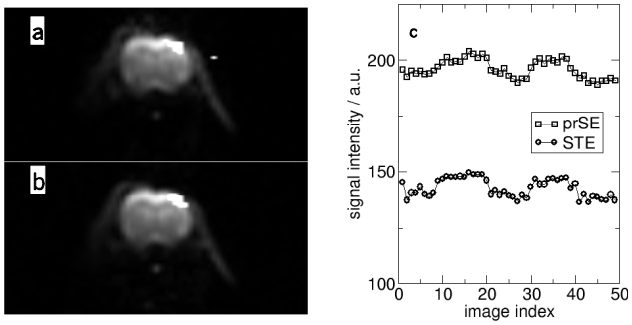

Fig.2: STE-EPI images of the rat brain using (a) the prSE and (b) the STE with the activated area ($p<10^{-6}$) overlaid in white. (c) time course of the signal intensity in a voxel in the center of the the activated region by the prSE and the STE signal.

References: [1] J.M.E. Oja et al., MRM 42, 617(1999). [2] S.-P. Lee et al., MRM 42, 919(1999). [3] T.Q. Duong et al., MRM 48, 589(2002). [4] E. Yacoub et al., MRM 49, 655(2003). [5] T.Q. Duong et al., MRM 49, 1019(2003). [6] G. Nair et al., MRM 52, 589(2004). [7] J.H. Jensen et al., MRM 44, 144(2000). [8] R.A. Brooks et al., MRM 45, 1014(2001). [9] A. Darquie et al., PNAS 98, 9391(2001). [10] U. Goerke et al., Proc. ISMRM 2004, p.1240.