Intravascular contribution to the BOLD fMRI signal change: an echo time dependence study at 9.4T

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Introduction

The widely accepted BOLD contrast mechanism assumes a linear relation between the fractional signal change and the echo time during functional activation [1], which for spin-echo is expressed as: $\Delta S / S = -TE \cdot \Delta R_2$ (1). Except in large vessel areas, this relation has been shown to be a good approximation in many experiments and is widely used in calculations of ΔR_2 and ΔR_2^* [1-4]; however, an understanding of the limitation is important. A positive intercept, when ΔS/S is linearly extrapolated to TE = 0, has been observed by several research groups but the underlying mechanism remains controversial [4-6]. In order to investigate the origin of this positive intercept and also to test the validity of the linear relationship at high field for a wide TE range, we studied the dependence of the fractional signal change on SE echo time at 9.4T.

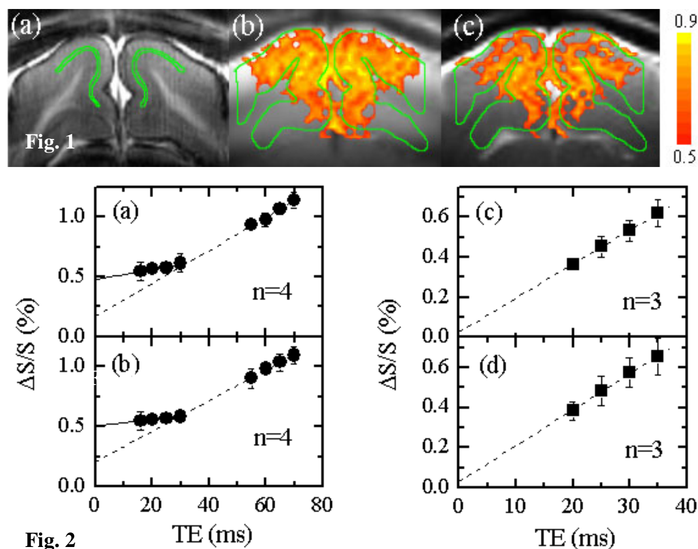
Materials and methods

fMRI experiments were performed on a 9.4T MRI (Magnex/Varian) system. Seven female adolescent cats, weighting 0.9-1.5kg, were anesthetized as previously described and scanned with a surface coil [4]. A double echo EPI sequence was used with adiabatic pulses, and two unipolar diffusion weighting gradients placed on both sides of the second 180-degree pulse. The imaging parameters were: $2\times2cm^2$ FOV, 2mm slice thickness, 64×64 matrix size, and 1.2s TR. A T_1 weighted image with 128×128 scanning matrix was obtained for anatomical reference. Two multiple TE experiments were interleaved: Short TEs of 16, 20, 25, 30ms and long TEs of 55, 60, 65, 70ms. The effective TR was 4.8s for four TE images. In diffusion weighted experiments, b=200 mm^2/s and TE=20, 25, 30, 35ms were used. For short TEs (<40ms), the zero k-space line was shifted 26-28 lines from the center to reduce the echo time. The binocular visual stimuli consisted of a drifting square wave grating (0.15 cycle/degree, 2 cycles/s). A typical stimulation paradigm includes 10 control (48s), 10 stimulation, and 10 control images. Images with the same TE were grouped together, interpolated and shifted to take into account their different time origins. For all animals, 15-20 data sets were averaged to improve the S/N. Cross-correlation coefficient (CCC) maps were calculated from a boxcar reference function for the averaged data set with typical CCC threshold of 0.5 and minimal cluster size of 5 pixels. The fractional signal changes for different TEs were calculated for two ROIs. One ROI (300–400 pixels) was obtained from all of the activated pixels of the CCC map for TE=20ms and b=0, the other (~150 pixels) was chosen at the middle of the visual cortex from the anatomic image (Fig 1a).

Results and discussions

Fig. 1 shows the CCC map of a representative cat at TE=20ms (1b) and 60ms (1c) with b = 0. The green contour indicates the primary visual cortex area obtained from the anatomic image. At both echo times, the strongest activated area is mainly in the middle of the cortex, in agreement with previous SE results [4]. ΔS/S during stimulation as a function of TE at b = 0 (b = 200 mm^2/s) is plotted for the ROI with all of the activated pixels, Fig. 2a (2c), and for the middle cortical ROI, Fig 2b (2d), respectively. The error bars shows the standard error of the mean. The results from the two ROIs are very similar, indicating that the contribution from the large vessel area is small, as expected for SE. For simplicity, we only analyze the data of the middle cortical ROI, Fig 2b and 2d. Fig 2b clearly illustrates a non-linear dependence of ΔS/S on TE. Thus, simple calculation of the relaxation rate change (ΔR_2) based on equation (1) would give misleading information. Nevertheless, we divide the data points into two regimes and linearly fit the data to gain some insight. For short TEs (≤ 30ms) we get $\Delta S / S = 0.51\% + 0.025$ TE (TE in seconds, and R^2 =0.99), and for long TEs (≥55ms) $\Delta S / S = 0.21\% + 0.13$ TE (R^2 =0.99). Thus, it appears that the relaxation rate change (ΔR_2) decreases drastically from -0.13/s to -0.025/s when short echo time is used. A linear fitting to Fig. 2d (b=200 mm^2/s) gives $\Delta S / S = 0.03\% + 0.18$ TE (R^2 =0.99). This suggests that the decrease of ΔR_2 at short TE and b=0 is caused by intravascular signal which is mostly crushed out when diffusion weighting is applied.

The underlying assumption for equation (1) is that SE signal decay can be approximately described by a single transverse relaxation rate. However, BOLD signal contains contributions from both intravascular and extravascular components that have different relaxation rates, and the intravascular contribution to the fractional signal change, ΔS/S(IV), is usually not linearly dependent on TE [7]. Therefore, the linear relation in equation (1) can be valid only if ΔS/S(IV) is very small compared to the extravascular signal change, or it is nearly linearly dependent on TE, within the TE range studied. From the model in ref. [7], ΔS/S(IV) at 9.4T is negligible for TE>30ms, but increases rapidly with decreasing TE for 10ms<TE<30ms. This prediction agrees well with our results. From Fig. 2b, for long TEs (≥55ms), there is a small but not negligible positive intercept (~0.2%) by linearly extrapolating ΔS/S to TE = 0. When diffusion weighting of b=200 mm^2/s was applied, the intercept became slightly negative (about -0.1%, n=6, not shown). This suggests that the origin of this intercept is probably intravascular as well, and not an extravascular proton density increase as proposed in ref. [6]. Similar findings were reported in ref. [5] and explained as an in-flow effect. In our case the 90-degree adiabatic excitation pulse is not slice-selective, thus the in-flow effect is not expected to contribute to the fractional signal change and to the positive intercept. This has also been confirmed by our experiments (n=2, not shown) in which two repetition times were interleaved, and ΔS/S was found to be almost identical for TR=1s and TR=2s. An alternative explanation of the positive intercept is that it probably comes from the intravascular signal change of small arterioles or capillaries of the arterial side. BOLD signal is usually considered to be originated from the venous compartment. However, in small arterioles and capillaries, the baseline oxygen saturation level (70-90%) is substantially lower than that of arterial blood [8] and can slightly increase (by 0.5-2%) when CBF increases dramatically during activation [9]. This intravascular signal can cause a small positive intercept for long TEs, in a way similar to the larger intercept (~0.5%) caused by the venous BOLD signal for short TEs. In conclusion, we have found that the dependence of the BOLD fractional signal change over a wide TE range is nonlinear at the parenchyma. This is caused by the intravascular signals from the venous compartment which became significant at small TEs. The small arterioles and capillaries of the arterial side can contribute slightly to the BOLD signal as well and thus to the small positive intercept.



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