Quantifying the BOLD Contribution in CBV-Weighted fMRI at 9.4T

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INTRODUCTION: In fMRI employing iron oxide contrast agent, there are two competing factors that contribute to the fMRI signal: one is the BOLD effect, and the other is the superparamagnetic effect of iron oxide. At high field, the BOLD contamination can be a significant component in CBV-weighted fMRI. Recent studies (1-3) demonstrated that iron oxide contrast agent can improve the sensitivity and specificity of the fMRI signal. However, several questions remain: 1) what is the optimal iron dose in CBV-weighted fMRI? 2) how much does BOLD contribute to CBV-weighted fMRI signal? 3) How much does intra- and extra-vascular BOLD effect contribute to spin echo fMRI signal? This work is intended to address these questions using a rat forepaw electric stimulation model.

THEORY AND METHODS: Mandeville et al. (4) investigated the contrast-to-noise ratio (CNR) in CBV-weighted fMRI. We extend this work to include the BOLD effect. Change in transverse relaxation rate (ΔR_2 for SE and for ΔR_2*GE) during functional challenge can be expressed as:

$$\Delta R_2 = \Delta R_{2\ IRON} + \Delta R_{2\ BOLD} \quad [1]$$

where $\Delta R_{2\ IRON} = k \cdot \Delta V$. Here k is a constant related to contrast agent concentration in plasma, and ΔV is blood volume change during functional challenge. $\Delta R_{2\ IRON}$ and $\Delta R_{2\ BOLD}$ are changes in transverse relaxation rates induced by iron and BOLD effect, respectively. $\Delta R_{2\ BOLD}$ includes extra-vascular ($\Delta R_{2\ BOLD,\ Ex}$) and intra-vascular ($\Delta R_{2\ BOLD,\ In}$) components:

$$\Delta R_{2,\ BOLD} = \Delta R_{2\ BOLD,\ Ex} + \Delta R_{2\ BOLD,\ In} \quad [2]$$

Assuming noise remains the same before and after contrast agent administration, CNR can be expressed as:

$$CNR = S_0 \exp[-TE(R_0 + k \cdot V_0)] \cdot \exp[-TE \cdot (k \cdot \Delta V + \Delta R_{2BOLD}) - 1]$$

$$\approx S_0 \exp[-TE(R_0 + k \cdot V_0)] \cdot [TE \cdot (k \cdot \Delta V + \Delta R_{2BOLD})] \quad [3]$$

Here S_0 is CNR at $TE = 0$. V_0 and R_0 are baseline blood volume and transverse relaxation rate, respectively. Optimizing CNR relative to k leads to:

$$k = [\Delta V / (TE \cdot V_0) - \Delta R_{2BOLD}] / \Delta V \quad [4]$$

$$CNR_{max} \approx S_0 \exp[-TE(R_0 + k \cdot V_0)] \cdot [\Delta V / V_0 - TE \cdot \Delta R_{2BOLD}] \quad [5]$$

Equations 4 and 5 reveal that optimum CNR can be achieved by minimum TE and high dosage of contrast agent. In practice, however, it is ideal to use the least amount of contrast agent, provided the BOLD contribution is negligible. By modulating contrast agent dosage, and assuming ΔV and $\Delta R_{2\ BOLD}$ remain the same in separate experiments, equations 1 and 2 can be employed to quantify BOLD contribution in CBV-weighted fMRI. Specifically, at the ith experiment, with a contrast dosage of k_i, equation 1 can be written as:

$$\Delta R_{2\ i} = k_i \cdot \Delta V + \Delta R_{2\ BOLD,\ Ex} + \Delta R_{2\ BOLD,\ In} \quad [6]$$

T_2 of venous blood is only about 9 ms at 9.4 T (5). After administrating contrast agent at an iron does of 5 mg/kg, we measured it to be less than 5 ms. At a TE of 30 ms, blood signal has essentially decayed away. As a result, the intra-vascular BOLD contribution ($\Delta R_{2\ BOLD,\ In}$) is negligible at high dose of contrast agent, and equation [6] reduces to:

$$\Delta R_{2\ i} = k_i \cdot \Delta V + \Delta R_{2\ BOLD,\ Ex} \quad [7]$$

We define BOLD contribution in CBV-weighted fMRI as following:

$$\text{BOLD \%} = |\Delta R_{2\ BOLD}| / (|\Delta R_{2\ BOLD}| + |\Delta R_{2\ IRON}|) \quad [8]$$

By changing the concentration of contrast agent in blood (k_i), and measuring $\Delta R_{2\ i}$ during functional challenge, we can calculate $\Delta R_{2\ BOLD,\ Ex}$ based on Eq. 7. BOLD contribution in CBV-weighted fMRI can be readily quantified using Eq. 8.

Using the $\Delta R_{2\ BOLD,\ Ex}$ value derived above, we can further quantify intra- and extra-vascular components in BOLD fMRI. This was done by measuring total transverse relaxation rate change ($\Delta R_{2\ BOLD}$) in a separate experiment without contrast agent, and calculating the extra-vascular BOLD contribution using the following equation:

$$\text{BOLD}_{Ex}\ \% = \Delta R_{2\ BOLD,\ Ex} / (\Delta R_{2\ BOLD}) \quad [9]$$

Experiments were conducted on a Bruker 9.4T scanner. Six male SD rats (250~300 g) were anesthetized using α-chloralose with an initial dose of 50 mg/kg followed by an additional dose of 50 mg/kg each hour. The animals were mechanically ventilated. Rectal temperature, end tidal CO_2, O_2, arterial blood pressure were continuously monitored and kept within normal ranges. Electric stimuli were delivered to rat forepaw using a Grass 88 stimulator with pulse duration 3 ms, frequency 3 Hz and current intensity of 3mA. Scan parameters: four-shot EPI, FOV = 3.5 cm, slice thickness = 1.5 mm, TR = 1 sec per shot, TE = 30 ms for spin echo and 15 ms for gradient echo. The stimulus paradigm was a block design consisting of three cycles of 1 min off and 1 min on. Contrast agent Combidex® (ferumoxtran-10, Advanced Magnetics, Cambridge, MA) was administrated (I.V.) at an iron dose of 0 (BOLD), 5, 15 and 23 mg/kg. Activated pixels were identified using cross correlation (CC >0.5, $p<10^{-5}$). ΔR_2 during the plateau period was quantified on a pixel-wise basis. For each iron dosage, a grand average of ΔR_2 among all activated pixels from each animal is calculated. Data from each animal were averaged, and are presented as mean ± standard error.

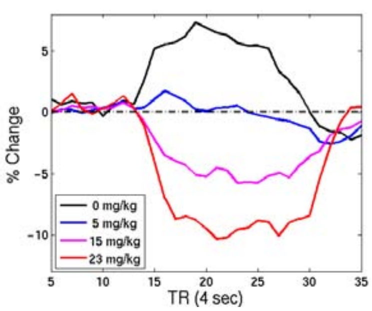

Fig. 1. Fractional change of spin echo fMRI signal at different iron doses from one animal. A strong post-undershoot is apparent in the response at 5 mg/kg iron.

Table 1. Transverse relaxation rate change and BOLD contribution at different iron dosage.

Dosage (mg/kg)	Spin Echo		Gradient Echo	
	ΔR_2 (1/s)	BC[1] (%)	ΔR_2* (1/s)	BC[1] (%)
0	-1.1 ± 0.3		-2.1 ± 1.2	
5	0.1 ± 0.3	46 ± 4.9	2.4 ± 1.3	34.5 ± 4.5
15	1.3 ± 0.7	31.5 ± 6.8	6.4 ± 1.2	18.3 ± 2.9
23	3.4 ± 0.8	19.9 ± 3.5	8.9 ± 0.6	14.7 ± 3.1

[1] BC, BOLD contribution.

RESULTS AND DISCUSSION: Figure 1 illustrates fractional fMRI signal change at different contrast dosage from one animal. At an iron dose of 5 mg/kg, there was a slight increase in fMRI signal after stimulus onset, followed by a negative response with a strong "post-undershoot", indicating BOLD effect and iron effect are comparable at this dosage. Table 1 lists ΔR_2 values at each iron dose and corresponding BOLD contribution calculated based on Eq. 8. At an iron dose of 15 mg/kg, there was about 18% BOLD contribution in the gradient echo data, and $\Delta R2^* = 6.4 \pm 1.2$. Increasing iron dose to 23 mg/kg reduced BOLD contribution to about 15%, while image signal-to-noise ratio was dramatically reduced. In the spin echo data, at an iron dose of 15 mg/kg, there was about 30% BOLD contribution, and $\Delta R_2 = 1.3 \pm 0.7$. Increasing iron dose to 23 mg/kg reduced BOLD contribution to about 20%, while $\Delta R_2 = 3.4 \pm 0.8$. These data suggest that 15 and 23 mg/kg iron may be realistic dosages for gradient echo and spin echo CBV-weighted fMRI at 9.4T.

At a TE of 30 ms, we measured $\Delta R_{2\ BOLD}$ in separate BOLD experiments, and estimated extra BOLD effect in spin echo BOLD experiments to be 84 ± 3.5%. A diffusion-weighted fMRI study by Lee et al. (5) suggested that extra-vascular BOLD effect dominates spin echo fMRI signal at 9.4T. Our quantitative results are consistent with the previous finding.

REFERENCES: 1. Lu H et al. MRM 2004; 52:1060-8. 2. Mandeville JB et al. MRM 2004; 52:1272-81. 3. Zhao F. et al. Neuroimage 2005; 27:416-24. 4. Mandeville JB et al. MRM 1998; 39:615-24. 5. Lee SP et al. MRM 1999; 42:919-28.

AKNOWLEDGEMENT: We thank Advanced Magnetics, Inc. for providing ferumoxtran-10.