A parametrized approach to BOLD calibration for the olfactory bulb

J. Schafer[1], F. Xu[1,2], D. L. Rothman[1], F. Hyder[1]

[1]Diagnostic Radiology, Yale Medical School, New Haven, CT, United States, [2]Neurobiology, Yale Medical School, New Haven, CT, United States

INTRODUCTION

Although the biophysical basis of BOLD signal change is quite complex, the availability of quantitative and multi-modal MR methods to disentangle the stimulation-induced hyperemic effect has become possible [1,2]. The stimulation-induced change in the BOLD signal (δs) depends on activity dependent change in oxidative metabolism (δm) which is coupled with changes in blood flow (δf) and volume (δv)

$$\delta s = A\left[\left(\delta f - \delta m\right)/\left(1+\delta f\right) - \delta v\right] \qquad \text{eq. 1}$$

where A is a measurable constant related to the basal transverse relaxation time (T_2) within a voxel or region of interest. Calibrating the BOLD signal for quantitative fMRI to represent activity in terms of oxidative energy change (i.e., δm) has become a popular technique [3]. This approach has been particularly successful in rat and human brain studies where quantitative MRI methods can be applied to measure δs, δf, and even δv in some cases. The possibility of using ^{13}C MRS methods to measure δm, in somewhat larger voxels, has been extremely valuable since that allows validation of the BOLD calibration [3]. However a limitation of this validation approach is associated with technological difficulties required to incorporate heteronuclear MRS and MRI studies in the same session. Another restriction of this validation approach is the concern about partial volume effects when the MRS voxels reside over highly heterogeneous spans of active tissue. However these factors were not of great concern for our BOLD calibration studies in the rat brain [1,2] where RF coils were constructed for concurrent ^{13}C MRS and quantitative MRI studies and all measurements were specifically focused on the cerebral cortex, which spans almost 2 mm and have small variations in activity across layers. Given the success in validating the BOLD calibration in the rat brain [3], we have taken on the task of calibrating the BOLD signal changes in the olfactory bulb. The olfactory bulb, in contrast to the cerebral cortex, is highly laminar with large gradients in BOLD signal change across olfactory nerve layer (ONL) and glomerular layer (GL) – the two most active layers residing adjacently over a span of ~500 μm [4]. To date, even at the highest magnetic fields, MRS studies in such small voxels are not feasible. How about using the hypercapnia approach to calibrate BOLD which has been used in human studies? The main assumption here is that δm in eq. 1 is zero with hypercapnia and therefore δs is only related to δf and δv allowing the calibration of A to be used for the functional studies. Since CO_2 from the air is inhaled repeatedly when smelling, the use of systemic hypercapnia may likely complicate the function and physiology of the bulb. In addition systemic hypercapnia is difficult in rats which are anesthetized but spontaneously breathing, as is the case for the olfactory experiments. Therefore a new approach to BOLD calibration is needed which exploits specific features of the bulbar response: (i) high and low concentrations of an odorant produce almost identical ONL and GL activity patterns [5]; there is high reproducibility in ONL and GL activity patterns to the same stimulation [6]. Since δs, δf, and δv can be measured in the bulb repeatedly with sufficient spatial resolution with MRI techniques, we sought to calibrate BOLD by parametrization of eq. 1.

MATERIALS and METHODS

Sprague-Dawley rats (~300 g; male; n = 6) were anesthetized with urethane (~1 g/kg). The procedures for basic fMRI scans for olfactory studies have been described [5,6]. All MRI experiments were performed on a 9.4T Bruker horizontal-bore system with custom-made RF coils for homogenous transmit and local receive experiments [1,2]. Single shot EPI experiments were performed (TR/TE = 2000/15; matrix = 64×64; FOV = 20×20 mm; slice thickness = 1 mm; inversion thickness = 5 mm) on three slices preferentially shimmed to minimize macroscopic field inhomogeneities. Baseline f images were obtained with inversion recovery times (TIR) ranging from 200 to 1600 ms, with slice and global inversion adiabatic pulses [1,2]. Relative δf images were obtained by using a slow version of a dynamic perfusion imaging technique [7]. Relative δs and δv images were images were obtained with EPI images in the absence and presence, respectively, of a long-lived superparamagnetic contrast agent (AMI-227; 10 mg/kg). The high and low concentrations of amyl acetate (400 and 4 μM) were achieved by dilution in mineral oil. By applying reasonable constraints (i.e., voxels with $\delta s > 0$; measure baseline T_2, etc), it is possible to calibrate BOLD by parameterization of eq. 1 as shown below

$$\delta s = X\left[\delta f/\left(1+\delta f\right)\right] \qquad \delta s = Y\left[\delta v/\left(1+\delta f\right)\right] \qquad \text{eq. 2}$$

where X and Y are parametrized constants in lieu of eq. 1 and they can be experimentally determined because δs, δf, and δv were all measured. Since all parameters in eq. 2 can be reproducibly measured for either odor concentration and for a given voxel all parameters in eq. 2 can also be measured for two odor concentrations, there is redundancy within the experimental design of this system. By choosing a value of A, values of δm can be iterated to calculate $\langle X\rangle$and $\langle Y\rangle$. The goal of the iteration process was to minimize $(X - \langle X\rangle)^2$ and $(Y - \langle Y\rangle)^2$ so that best estimates of A and δm can be realized for all experimental results.

RESULTS and DISCUSSION

Figure 1A shows typical multi-modal MRI data collected from the olfactory bulb, for anterior and posterior slices, in two given subjects. Specifically the f maps in the bulb shows great heterogeneity in absolute flow units, ranging from ~2 mL/g/min in the ONL to about ~0.7 mL/g/min in the GL. The inner layers of the bulb had flow values which were less than 0.4 mL/g/min, similar to values in the cerebral cortex (data not shown). The main difference between the s and v maps (i.e., BOLD and volume) were the loss of signal due to the presence of the superparamagnetic contrast agent was more prominent in the ONL and GL, rather than the inner layers. Figures 1B and 1C show multi-modal MRI data during odor stimulation, where the comparison of high (black symbols) and low (gray symbols) concentration data from all rats (shown for δs vs. δf and δs vs. δv, respectively) provided the experimentally determination of X and Y (0.24±0.07 and 3.49±0.60). Figure 1D shows the final result of the parametrized BOLD calibration process where the relationship between δs vs. δm is shown for the estimated A value of 0.75±0.10. Plots of δm vs. δf from the bulb (data not shown) show a linearity like in the brain [2] but the slope of these metabolism-flow curves are closer to ~0.5.

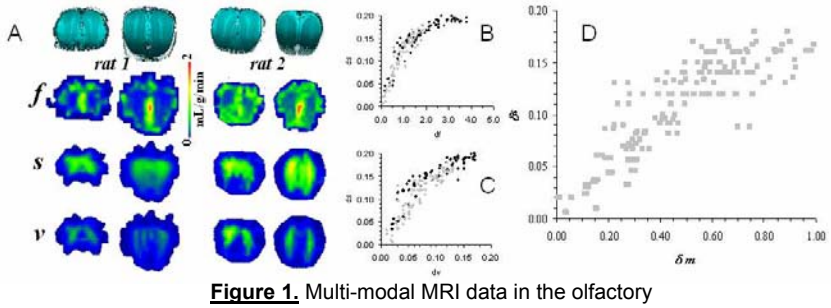

Figure 1. Multi-modal MRI data in the olfactory

REFERENCES and ACKNOWLEDGEMENTS

1. Kida I et al (2000) *J Cereb Blood Flow Metab* 20:847-860
2. Hyder F et al (2001) *NMR Biomed* 14:413-431
3. Hyder F (2004) *Stroke* 35 Suppl 1:2635-2641
4. Yang X et al (1998) *Proc Natl Acad Sci USA* 95:7715-7720
5. Xu F et al (2000) *Proc Natl Acad Sci USA* 97:10601-10606
6. Schafer JR et al (2005) *NeuroImage* (in press)
7. Kida I et al (2004) *J Cereb Blood Flow Metab* 24:1369-1281

The research was supported by grants from NIH (MH-067528, DK-59635, DC-0003710 and DC-04732) and a gift from Pfizer Incorporated.