

Mapping the Dynamics of Oxidative Metabolism by Functional MRI

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INTRODUCTION

Neuronal activity causes increases in regional cerebral blood flow (CBF) out of proportion to increases in cerebral metabolic rate for oxygen (CMR_{O₂}) and glucose (CMR_{glu}), as measured by PET [1]. The current interpretation of blood oxygen dependent (BOLD) MRI signal changes relies on the assumption that this uncoupling occurs uniformly, and that there is little effect of oxidative metabolism on the BOLD signal. This assumption remains largely untested, and may be incorrect.

We provide evidence for BOLD modulation by CMR_{O₂}, by calibrating BOLD against CBF measured by flow-sensitive alternating inversion recovery (FAIR) [2, 3]. Calibration is accomplished through a quantitative model linking BOLD, FAIR, and CMR_{O₂}, and by an experimental step utilizing CO₂ breathing as a standard perturbation.

We also describe a new pulse sequence which measures FAIR and BOLD simultaneously, avoiding the necessity of a repeatable experimental paradigm or physiological stability.

The combination of mathematical model, physiological calibration, and pulse sequence design provide the necessary tools for noninvasive dynamic mapping of oxidative metabolism, essential to the application of fMRI brain mapping techniques to diseased tissues.

THEORY

Fick's equation describes conservation of oxygen delivery and oxygen uptake in the steady state: $CBF \times ([O_2]_a - [O_2]_v) = CMR_{O_2}$. This can be restated to relate deoxyhemoglobin production proportionally to metabolic uptake and blood flow: $dHb \propto CMR_{O_2}/CBF$.

Attenuation due to the BOLD effect is well described for a given range of echo times as $\Delta R_2^* \approx f_s(\Delta\chi)^{\beta}$ [4]. The susceptibility difference effect $\Delta\chi$, which is proportional to dHb , is supralinear ($1 < \beta < 2$) whereas the blood volume effect f_v is linear. The substitution of hemodynamic parameters from the modified Fick equation give

$$\Delta R_2^* \approx f_s(t) \left(\frac{CMR_{O_2}(t)}{CBF(t)} \right)^{\beta} - f_v(t) \left(\frac{CMR_{O_2}(t)}{CBF(t)} \right)^{\beta} \quad (1)$$

We define S_R and S_F as the BOLD-weighted and FAIR subtraction MRI signals normalized by ratio to a baseline period in the experimental paradigm. S_F is defined as proportional to venous CBF changes, and $S_{CMR_{O_2}}$ proportional to metabolic rate changes. For small change in relativity ($T_f \Delta R_2^* \ll 1$) the BOLD signal is $S_R \approx 1 - T_f \Delta R_2^*$. Substituting the above normalized variables into Eq (1) and extracting the baseline values at $t = 0$ from both terms, we have

$$1 - S_R \approx f_s(t) \left(\frac{CMR_{O_2}(t)}{CBF(t)} \right)^{\beta} \left[S_F^{\beta} / S_{CMR_{O_2}}^{\beta} - 1 \right] \quad (2)$$

The baseline values and other accumulated proportionality constants are aggregated into a proportionality constant, M .

$$M = (S_R - 1) / (1 - S_F^{\beta} / S_{CMR_{O_2}}^{\beta}) \quad (3)$$

Blood volume S_F is not measured directly. Rather, we utilize the results of Grubb [5] to express blood volume in terms of blood flow: $S_F = S_F^0$, $\alpha \approx 0.38$. We then apply Eq (3) to the calibration experiment, for which the metabolic rate ratio $S_{CMR_{O_2}}^0$ is unity, determining M based only on S_R and S_F measured for CO₂ breathing. With the fMRI experiment calibrated by determination of M , which is the maximum possible BOLD signal change, the normalized changes in task activation $S_F(t)$ and $S_R(t)$ can be used to compute dynamic CMR_{O₂} maps.

$$\frac{CMR_{O_2}(t)}{CMR_{O_2}(0)} = \left(1 - \frac{S_R(t) - 1}{M} \right)^{\frac{1-\alpha}{\beta}} S_F(t)^{\frac{1-\alpha}{\beta}} \quad (4)$$

Application of Eq (4) provides a dynamic noninvasive measurement of changes in the CMR_{O₂} not available by other means.

METHODS

Volunteers breathed gases delivered through a nonbreathing face mask at 15 l/min and attended to a projected image. Periods of baseline visual stimulus were interleaved with images of a radial pinwheel alternating at 12 Hz. After 3 one-minute periods of flashing visual stimulation alternating with baseline stimulus, inhalation was changed from air to a mixture of 3.21% percent CO₂:O₂:N₂ for 3 minutes. During the final 3 minutes, the subjects again breathed air and repeated the same pattern of visual stimulation as during the first 3 minutes. Physiological monitors recorded heart rate, respiratory rate, oxygen saturation, and

end-tidal CO₂ whenever possible.

fMRI images (Advanced NMR/GI; Signa 1.5 T) were collected through calcarine cortex with the following three pulse sequences: (A) BOLD, asymmetric spin echo, 7 mm slice, TR=2 s, TI=70 ms, and refocusing pulse advanced 23 ms from TI/2. (B) FAIR inversion recovery spin echo, 7 mm slice, TR=5 s, TI=1 s, TI=45 ms, and slice-selective inversion pulse thickness 14 mm alternating with a nonselective inversion pulse. Subtraction of nonselective from selective echoes in the FAIR signal. (C) A hybrid sequence designed to measure both attributes simultaneously: the FAIR sequence above was modified by using an asymmetric spin echo, TI=70, refocusing pulse advanced 25 ms for BOLD sensitization, after selective and nonselective inversion. The difference between selective and nonselective echoes then provides CBF-weighting, whereas the nonselective echo provides BOLD weighting. The order of experiments A and B was randomized between subjects.

RESULTS



Figure 1. Maps from a representative subject showing task activation for (A) BOLD and (B) FAIR, and (C) the M parameter. (D) shows oxidative metabolism task activation of 15% in visual cortex.

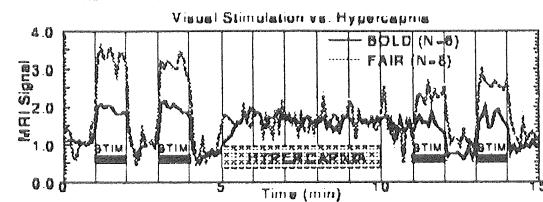


Figure 2. BOLD and FAIR time courses, here shown normalized to the hypercapnia signal change. These are averaged data from 14 experimental runs (6 BOLD, 8 FAIR), on 4 subjects. When the data are normalized in this way, it is apparent that FAIR during photic stimulation is relatively more responsive than BOLD.

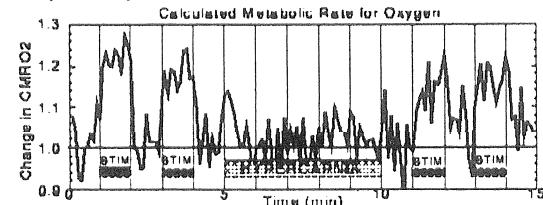


Figure 3. Calculated CMRO₂ time course, increasing by at least 15% within seconds of photic stimulation onset. These results are consistent across subjects, experiment order, and for longer activation periods.

CONCLUSIONS

We present a model, calibration method, and pulse sequence which produce dynamic maps of changes in oxidative metabolism. Preliminary results show a significant, immediate increase in oxygen demand in activating visual cortex, which reduces the BOLD effect by as much as 30% from the level expected from FAIR.

Although oxygen demand does not increase as much as blood flow, its effect on BOLD signal is significant, and should be considered in comparing relative activation by BOLD. Further work is needed to determine the constancy of the ratio of CMRO₂ to CBF change.

Of note, our maps of the coupling constant M show increased sensitivity to BOLD in primary visual cortex. This finding may contribute to the robustness of BOLD activation seen in this region.

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