THE RELATIONSHIP BETWEEN M IN "CALIBRATED FMRI" AND THE PHYSIOLOGIC MODULATORS OF FMRI

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INTRODUCTION: Since the inception of fMRI, BOLD signal has been known to be an epiphenomenon of neural activation and much effort has been devoted to quantifying brain activity from the BOLD fMRI signal. At present, the most widely used quantitative technique is called "calibrated fMRI", in which experimental functional data are combined with biophysical models of the BOLD signal to estimate the brain's metabolic activity, cerebral metabolic rate of oxygen (CMRO2) (1,2). A methodological complication of this technique is that, in order to calculate CMRO2 from the experimental data, a calibration factor "M" is needed. M is typically estimated by performing an additional calibration experiment while having the subject breath 5% CO2 (3) or 100% O2 (4). It would be desirable to be able to obtain the M value without the need of a gas-challenge calibration, which would make the technique more feasible for neuroscientific and clinical studies. According to the analytical expression of M, it is a function of two baseline physiologic parameters, baseline CBF and baseline venous oxygenation (Y_v). Interestingly, both parameters have recently been shown to be significant modulators of fMRI signal and can explain a large fraction of intersubject variations in BOLD signal amplitude (5,6). Here we studied the relationship among M, baseline CBF and baseline venous oxygenation, and assessed the possibility of estimating M from the baseline physiologic parameters.

METHODS: *Theory:* Based on the calibrated fMRI model developed by Davis et al. (1) and Hoge et al. (2), the BOLD signal can be written as:

$$\frac{\Delta S}{S}|_{BOLD} = M \cdot [1-(1+\frac{\Delta CMRO2}{CMRO2_0})^{\beta} \cdot (1+\frac{\Delta CBF}{CBF_0})^{\alpha-\beta}] \quad [1]$$

in which the calibration factor

$$M = TE \cdot A \cdot CBF_0^{\alpha} \cdot [Hct \cdot (1-Y_{v,0})]^{\beta} \quad [2]$$

where TE and A are constants related to magnetic field strength and imaging parameters; CBF_0 is the baseline CBF, Hct is the hematocrit; $Y_{v,0}$ is the baseline venous oxygenation; α is the Grubb's coefficient between CBV and CBF; β is a coefficient related to vascular geometry. The physiologic meaning of the M factor is well known: it is the maximum BOLD signal one can get from the voxel when (hypothetically) displacing all the deoxyhemoglobin molecules. Therefore, the M factor is essentially an index of the baseline physiologic state, specifically related to baseline CBF and baseline venous oxygenation, and is not intrinsically linked to any vascular challenge. We therefore hypothesized that, if we could use experimental methods to measure baseline CBF and baseline venous oxygenation on a subject-specific basis, we could then estimate the M factor for each individual.

Experiments were performed on 17 healthy subjects on a 3T scanner (Philips). Global baseline venous oxygenation was measured using a novel TRUST MRI technique (7). Global baseline CBF was measured with the phase-contrast quantitative flow technique. These two parameters are used to calculate the M factor without the use of hypercapnic challenge. For comparison, the conventional hypercapnia-calibration experiments were performed. Simultaneous BOLD and ASL acquisitions were used to obtain BOLD and CBF changes concomitantly. The sequence was a pseudo-CASL method with two echo times (TE) at 11 and 30ms, respectively. The subjects breathed room air for 4 minutes and 5% CO2 (balanced with 21% O2 and 74% N2) for 6 minutes. The imaging parameters were: TRUST MRI: voxel size 3.44x3.44x5mm^3, TR=8000ms, TI=1200ms, four TEs: 0ms, 40ms, 80ms and 160ms. Phase contrast: voxel size 0.45x0.45x5 mm^3, maximum velocity 80cm/s, duration 30 sec. The phase-contrast slice was positioned at the level of sagittal sinus. Note that the blood flow in the sagittal sinus is about 50% of that of the whole brain. But this scaling factor can be combined with the constant *A* and should not affect the relationship between baseline CBF, baseline venous oxygenation and M.

RESULTS and DISCUSSION: Baseline CBF (in sagittal sinus) and venous oxygenation were 289.6±80.5 ml/min (n=17, mean±STD) and 59.9±8.5%, respectively. The hypercapnia challenge increased the CBF and BOLD signals by 59.1±26.0% and 2.52±0.91%, respectively. Using the theoretical frameworks of Davis et al and Hoge et al, the M factor was found to be 0.074±0.017 (unitless), in good agreement with literature values at this field strength (4). A spatial map of hypercapnia-based M is shown in Fig. 1. Next, we studied the relationship among baseline CBF, baseline venous oxygenation and M. We found that baseline CBF and baseline venous oxygenation are highly correlated across subjects (Fig. 2, p<0.001). However, the M factor is not correlated with either baseline CBF or baseline venous oxygenation (p>0.05). Furthermore, when using Equation [2] to estimate the M values from baseline CBF and venous oxygenation, the estimated M and hypercapnia-based M were not correlated regardless the assumed values of α and β. Fitting the experimental data to Equation [2] did not yield a good correspondence either. Figure 3 shows the scatter plot between the hypercapnia-based M and CBF/Y_v-estimated M using typically coefficients of α=0.38, β=1.5 and Hct=0.4.

In summary, our data showed that baseline CBF and baseline venous oxygenation are positively correlated. On the other hand, the M factor as calculated from the hypercapnia-calibration experiments has no apparent relationship with baseline CBF or venous oxygenation. This was the case for the analysis of separate CBF or venous oxygenation or their combination according to the analytical expression. This discrepancy could be due to one or more of the following reasons: 1) the effect of hematocrit was not accounted for and may be a significant factor in determining M; 2) Equation [2] estimated total CBV but the more relevant blood compartment is venous CBV; 3) Hypercapnia-based calculation of M is based on the assumption that CMRO2 is not affected by CO2 inhalation but this assumption has recently come into question (8,9). Further study is needed to elucidate the true values of M and the method by which to most accurately estimate it.

REFERENCES: 1) Davis et al. PNAS, 95:1834,1998; 2) Hoge et al. MRM, 42:849, 1999; 3) Leontiev et al. NeuroImage 35:175, 2007; 4) Chiarelli et al NeuroImage, 37:808, 2007; 5) Lu et al. MRM, 60:364, 2008; 6) Liau et al. NeuroImage, 45:420, 2009; 7) Lu and Ge. MRM, 60:357, 2008; 8) Zappe et al. Cerebral Cortex, 18:2666, 2008; 9) Xu et al. ISMRM, p. 215, 2009.

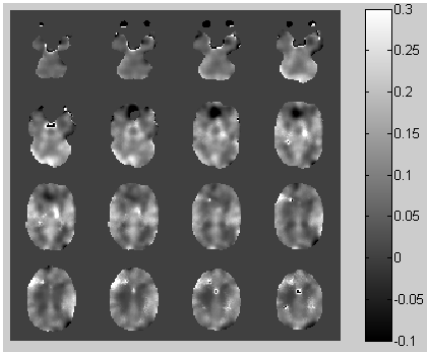

Fig. 1: Representative maps of the M factor obtained from the hypercapnia-calibration experiment.

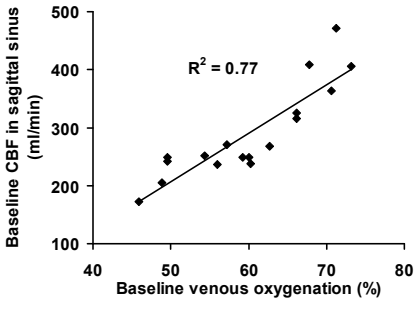

Fig. 2: Correlation between baseline venous oxygenation and baseline CBF across subjects (n=17, p<0.001).

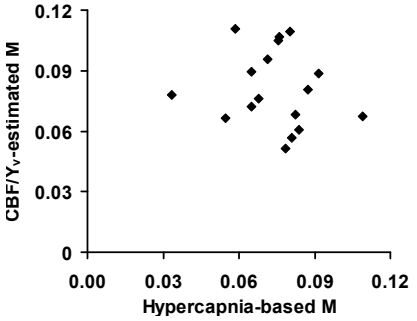

Fig. 3: Scatter plot between M obtained from the hypercapnia experiment and M estimated from the baseline CBF and venous oxygenation measures.