Determination of maximum BOLD calibration constant using hyperoxia.

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Introduction

An essential step in measuring the CMRO2 in brain using FMRI is the determination of the theoretical maximum BOLD signal change in a region of interest. This value is typically denoted by *M* and has usually been calculated from flow and BOLD changes measured during hypercapnia[1]. It has been shown that hyperoxia may also be employed to cause signal changes during BOLD scans to calculate this value[2]. Previous hyperoxia measurements of *M* have used long duration blocks of up to 5 minutes, adding up to 20 minutes on the end of the functional scan. It was hypothesised that shorter duration blocks would suffice to provide accurate and robust determination of *M*. In the majority of subjects breathing a FiO2 of approximately 0.5, it takes on the order of 2 minutes to reach a steady state in their end-tidal oxygen levels, which have been shown to correlate to the BOLD signal time course. To test this, subjects were scanned while breathing hyperoxic gas mixtures during blocks for 1, 2 and 3 minutes in length, and the measured BOLD signal and end-tidal oxygen changes were used to calculate *M* in structurally defined brain regions.

Theory & Methods

Analogous to the derivation of the hypercapnia-calibrated model[1], hyperoxia calibration makes use of the expression for BOLD signal change, as well as the expression for $R_2^*|_{dHb}$ derived by Boxerman *et al*[3]. The full hyperoxia model, which takes changes in CBF caused by the increased PaO_2 into account, is given by[2]:

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{[dHb]_v}{[dHb]_{v_0}}+\frac{CBF_0}{CBF}-1\right)^{\beta}\right) \qquad (1)$$

where $M = TE \cdot A \cdot CBV_0 \cdot [dHb]_{v_0}^{\beta}$.

Subjects were all healthy, non-smoking volunteers, and were scanned on a 3T Siemens TIM Trio, using a 12-channel receive head-coil. The sequence was a gradient echo EPI, TR=3s with 3mm isotropic voxels and 40 slices to give whole-brain coverage. The protocol lasted 24 minutes and 30 seconds, and consisted of 2x1 minute, 2x2 minute and 2x3 minute oxygen blocks, each block being followed by the same duration breathing room air. The order of the blocks was randomised during the scan and for each subject. Oxygen was delivered via a 2-tube nasal cannula, which could deliver the pure oxygen at a rate of 7 litres per minute while simultaneously sampling the inspired and expired gases. The delivery rate produced end-tidal values between 25 and 45% depending on subject breathing rate and the clearance rate of oxygen from the magnet bore. Respiratory gas composition was measured using a Biopac MP150 with oxygen and carbon dioxide gas analyser units, at a rate of 25 Hz. The maximum end-tidal oxygen value at the end of each block was subsequently used to calculate *M*, along with the measured BOLD signal change during that length of block.

Analysis was performed using the FMRIB Software Library (FSL) package[4]. Activation was defined as the parameter estimate fitting with a Z statistic of greater than 2.3. All subjects were registered first to a T1-weighted 1mm isotropic structural image, and then to a MNI standard brain. Structurally defined ROI's were then produced from the standard brain, and the *M* value was calculated in the occipital and parietal lobes.

Results

All subjects showed similar responses to the hyperoxia challenges, with the maximum end-tidal values reached during the 1 minute blocks being significantly lower than those attained during the longer blocks, there was no significant difference between the 2 and 3 minute blocks, indicating that the subjects had reached a steady state by 2 minutes. The BOLD responses were also similar across subjects, with very few voxels passing the threshold during the 1 minute blocks, most grey matter voxels reaching the threshold during the 2 minute blocks, and almost complete brain activation during the 3 minute blocks (see Figure 1). The measured values were used in equation (1) to calculate *M* in each of the two brain regions, and the results are presented in Table 1.

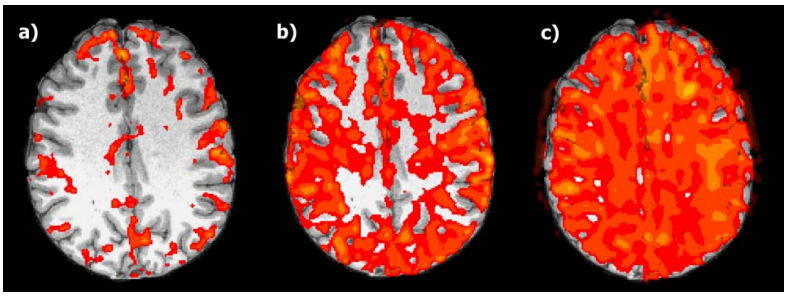

Figure 1: Regions of BOLD activation above the Z-stat threshold of 2.3 during each of the 3 block lengths: a) 1 min. b) 2 min. c) 3 min. for a single slice from a single subject, overlaid onto a high-resolution structural image.

Table 1: Mean *M* values (±SD) calculated from data during the 3 hyperoxia block lengths in the structurally defined ROI's.

Region	1 min	2 min	3 min
Occipital Lobe	6.11±3.05	5.92±0.81	4.06±0.90
Parietal Lobe	4.63±0.21	6.03±0.55	4.26±1.99

Discussion and Conclusions

Previous studies have reported *M*-values in these regions in the range of 4 to 7[5], providing strong support for the hypothesis. The values calculated during the 1-minute blocks are close to the expected values, however the occipital lobe showed a much greater variance than the other blocks, this may be due to the lower signal changes and Z-stats (Figure 1a). The 2-minute blocks showed very good activation across grey matter regions, and produced very good fits to the time course, and the *M*-values have a much lower variance than the 1-minute blocks. Surprisingly, the *M*-values calculated for the 3-minute blocks were substantially lower than those for the 2-minute blocks. Although some voxels during the 3-minute blocks had a higher maximum Z-statistic than any during the 2-minute blocks, the fits were in general, not quite as good. This is possibly due to the smeared temporal shape of the 3-minute blocks in comparison to the relatively sharply define peak of the 2-minute blocks, but further study will be required to confirm this.

We have shown that 2 periods of mild hyperoxia, 2 minutes in length and separated by 2 minutes of normal air is sufficient to reliably produce estimates within the expected range for the maximum theoretical BOLD value.

References

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