A Calibration Method for Quantitative BOLD fMRI Based on Hyperoxia

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Introduction

Changes in the cerebral metabolic rate of oxygen (CMR_{O2}) induced by neural activity can be estimated non-invasively using blood oxygenation level dependent (BOLD) fMRI and arterial spin-labelling measurements. The deoxyhaemoglobin-dilution model outlined by Davis *et al*[1] utilizes CO_2 breathing to calibrate the resting-state BOLD signal, by inducing an iso-metabolic global increase in cerebral blood flow (CBF). Hoge *et al*[2] extended this method with the use of graded hypercapnia to accurately estimate the resting-CMR_{O2} BOLD–CBF relationship. Although the use of CO_2 has multiple drawbacks - including a potential influence[3] on CMR_{O2}, a definite correlation with the onset of "air hunger", and potential intolerability in elderly or infirm subjects - CO_2 remains the dominant option for fMRI calibration studies, and the assumption is commonly made that CO_2 has a negligible impact on the baseline neural activity. The hypercapnia method also yields large potential variability in the calculated calibration parameter (M - the maximum theoretical BOLD signal change)[2], due to the use of arterial spin labelling for CBF measurement, which is a low-CNR technique. In this work, we introduce graded hyperoxia (breathing of O_2-enriched air) as a new technique for calibration of the baseline BOLD–CBF relationship. Whereas hypercapnia uses the CBF change as a means to increase oxygenation in the venous vasculature, O_2-breathing directly alters the oxygen saturation of arterial plasma and arterial Hb, inducing measurable changes in the concentration of oxygenated capillary and venous Hb[4]. Hyperoxia calibration requires measurement of the BOLD signal and end-tidal O_2 values, both of which are relatively low-variability measurements.

Theory & Methods

Analogous to the derivation of the hypercapnia-calibrated model[2], 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*[5], which was presented by Hoge *et al*[2] as:

$$\frac{\Delta BOLD}{BOLD_0} = TE \cdot A \cdot CBV_0 \cdot [dHb]_{v_0}^{\beta}\left(1-\left(\frac{CBV}{CBV_0}\right)\left(\frac{[dHb]_v}{[dHb]_{v_0}}\right)^{\beta}\right) \quad (1)$$

The full hyperoxia model, which takes changes in CBF caused by the increased PaO_2 into account, is given by:

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{[dHb]_v}{[dHb]_{v_0}}+\frac{CBF_0}{CBF}-1\right)^{\beta}\right) \quad (2)$$

where $M = TE \cdot A \cdot CBV_0 \cdot [dHb]_{v_0}^{\beta}$. In the case where there is no change in CBF or CBV then Eqn. 2 reduces to:

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1-\left(\frac{[dHb]_v}{[dHb]_{v_0}}\right)^{\beta}\right) \quad (3)$$

which is simply Eqn. 1 with no change in CBV. Importantly, M retains the same meaning in this approach as for the hypercapnia-calibrated approach. Therefore, calibration can be performed using hyperoxia to obtain M, and subsequent analysis of functional data can be performed by substitution of the hyperoxia-derived M value into the conventional deoxyhaemoglobin-dilution model described by Hoge *et al* and Davis *et al*[1, 2]. Changes in $[dHb]_v$ can be estimated by reformulating standard physiological relationships of oxygen transport in blood, and by assuming a value for the baseline oxygen extraction fraction (OEF). Although OEF is not measured here, it has been found to be remarkably consistent throughout the brain, in contrast to CMR_{O2} and CBF. Arterial oxygen tension (Pa_{O2}), and thus arterial oxygen content (CaO_2) can be inferred via the sampling of end-tidal O_2 partial pressure (Pet_{O2}).

6 healthy volunteers were scanned, 5 oblique slices were prescribed to cover the primary visual and motor cortices. Images were acquired on a Siemens Trio 3T MRI scanner using an 8-channel head-coil. An interlaced BOLD/pulsed arterial spin-labelling (ASL) sequence was used to collect T_2^*-weighted EPI images and Q2TIPS[6] cerebral perfusion images. Analysis was performed using the FMRIB Software Library (FSL) package[7]. Changes in the relaxation times caused by the oxygen were also taken into account[8]. The hyperoxia experiment lasted for 43 min, and involved alternating epochs of hyperoxia and normoxia, in a 5 min "on"/5 min "off" block design. Filtered air (21% O_2) and 100% O_2 were mixed to deliver FiO_2 values of 0.21, 0.4, 0.6, 0.8, and 1.0 in a pseudo-randomized order.

Results & Discussion

The BOLD changes with hyperoxia are shown in Fig. 1. A summary of the M values determined using the hyperoxia calibration method is given in Table 1. Data were obtained within the all-grey matter, visual cortex, and motor cortex ROI's (determined by BOLD/ASL activation overlap in a separate functional localiser), and are supplied as average values within the ROI ± CI_m. Data are shown both with and without the CBF correction. Estimated values of M appear in considerable agreement with those described earlier, calculated on the same MRI system using the hypercapnia approach.[9]

Table 1. Calculated vales of M with and without CBF correction.

Region	$M_{corrected}$±CI_m	$M_{uncorrected}$±CI_m	$M_{hypercapnia}$ (9)
Grey Matter	7.5±0.66	6.3±0.47	-
Visual	7.5±0.76	6.6±0.49	6.6±3.4
Motor	6.3±0.57	4.7±0.33	4.3±3.5

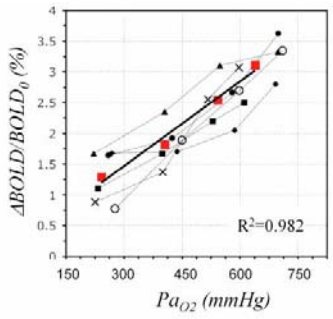

Figure 1. Relative change in BOLD signal with hyperoxia. Data from individual subjects (black) and averaged over the group (red) are shown, with individual values connected by lines, and a linear fit through the average values.

Hyperoxia calibration reveals substantially lower error margins for both individual and group data, compared to data obtained using the hypercapnia calibration. We estimate a ~2 - 4× reduction in errors when using the hyperoxia method as opposed to hypercapnia calibration methods. When using hyperoxia the BOLD change with [dHb], the SvO_2 needs to be extrapolated from ~60% up to 100%, whereas when using CBF change with hypercapnia, the flow needs to be extrapolated from ~50 ml/100g/min to infinity, thereby introducing significantly higher error estimates.

Conclusions

Hyperoxia calibration represents an alternative to the current technique of hypercapnia calibration. Rather than using changes in CBF to induce an oxygenation increase in the venous vasculature, a direct change in Hb oxygenation is implemented to induce the same effect. An alternative derivation of the dHb-dilution model has been developed, that accounts for a small reduction in CBF during hyperoxia, along with a correction for arterial T_1 in the ASL measurement. Results obtained using hyperoxia to estimate the calibration constant (M) are in good agreement with previous data acquired using a hypercapnia calibration. Hyperoxia calibration yields group estimates with lower apparent variability, and is potentially applicable to a wider range of subjects than the hypercapnia-based approach.

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