Appendix A

The arterial partial pressure of oxygen can be calculated from the end tidal fraction of oxygen using the equation

$$PaO_2 = F_{ETO_2} \cdot P_{atm} - P_{A-a}, \qquad \text{(A1)}$$

where F_{ETO2} is the end tidal fraction of oxygen, P_{atm} is the atmospheric pressure and P_{A-a} is the Alveolar-arterial gradient (A-a gradient). A normal A-a gradient for a young adult non-smoker breathing air, is between 5-10 mmHg. A value of 8 mmHg was assumed for all of the subjects in this study.

The arterial oxygen saturation can then be calculated using the Severinghaus equation (Severinghaus, 1979)

$$Sa_{O_2} = \frac{1}{\left(\frac{23400}{\left(Pa_{O_2}\right)^3 + 150\left(Pa_{O_2}\right)} + 1\right)} \qquad \text{(A2)}$$

The arterial oxygen content can be calculated by adding the oxygen bound to haemoglobin and the oxygen dissolved in the plasma

$$Ca_{O_2} = \left(\varphi \cdot [Hb] \cdot Sa_{O_2}\right) + \left(Pa_{O_2} \cdot \varepsilon\right) \qquad \text{(A3)}$$

φ represents the species-dependent O_2-carrying capacity of haemoglobin (1.34 ml O_2/g_{Hb} for humans), and ε is the solubility coefficient of oxygen in blood (0.0031 $ml_{O2}/(dl_{blood} \cdot mm\ Hg)$). We assume here a normal value for the concentration of haemoglobin ([*Hb*] =15 g $Hb \cdot dl^{-1}$ blood). The full version of Eq. 4 is

$$\frac{\Delta BOLD}{BOLD_0} = M\left(1 - \left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{[dHb]_v}{[dHb]_{v_0}} + \frac{CBF_0}{CBF} - 1\right)^{\beta}\right) \qquad \text{(A4)}$$

Rearranging this gives the fractional change in venous deoxyhaemoglobin concentration

$$\frac{[dHb]_v}{[dHb]_{v_0}} = 1 - \frac{CBF_0}{CBF} + \left\{\left(1 - \frac{\left(\frac{\Delta BOLD}{BOLD_0}\right)}{M}\right) \cdot \left(\frac{CBF}{CBF_0}\right)^{-\alpha}\right\}^{1/\beta} \qquad \text{(A5)}$$

The Fractional change in deoxyhaemoglobin concentration is equivalent to the fractional change in unsaturated venous haemoglobin

$$\frac{[dHb]_v}{[dHb]_{v_0}} = \frac{1 - Sv_{O_2}}{1 - Sv_{O_2}\big|_0} \qquad \text{(A6)}$$

the venous oxygen saturation is given by

$$Sv_{O_2} = \frac{Cv_{O_2} - \left(Pv_{O_2} \cdot \varepsilon\right)}{\varphi \cdot [Hb]} \qquad \text{(A7)}$$

If the small amount of oxygen dissolved in the venous plasma is ignored then the fractional change in haemoglobin is given by

$$\frac{[dHb]_v}{[dHb]_{v_0}} = \frac{1 - \frac{Cv}{\varphi \cdot [Hb]}}{1 - \frac{Cv_0}{\varphi \cdot [Hb]}} \tag{A8}$$

if we omit the O_2 subscript, and use a 0 to represent the normoxic condition, and no subscript for the hyperoxic condition.

It may seem obvious, but the venous oxygen content, Cv_{O2} under both normoxic and hyperoxic conditions is given by the arterial content, Ca_{O2} minus the net extracted oxygen (Ca_{O2} - Cv_{O2}), however what is critical is that the net extracted oxygen is constant between these two conditions (Mark et al., 2011). Thus

$$\frac{[dHb]_v}{[dHb]_{v_0}} = \frac{1 - \frac{Ca - (Ca - Cv)}{\varphi \cdot [Hb]}}{1 - \frac{Ca_0 - (Ca - Cv)}{\varphi \cdot [Hb]}} \tag{A9}$$

Rearranging this gives the net extracted oxygen in terms of the deoxyhaemoglobin, which is obtained from the hyperoxia calibration model, and the arterial content under both normoxia and hyperoxia, which can be obtained from the end-tidal measurements.

$$(Ca - Cv) = \left(\frac{[dHb]_v}{[dHb]_{v_0}} - 1 - \frac{\frac{[dHb]_v}{[dHb]_{v_0}} \cdot Ca_0 - Ca}{\varphi \cdot [Hb]} \right) \cdot \left(1 - \frac{[dHb]_v}{[dHb]_{v_0}} \right)^{-1} \tag{A10}$$

The oxygen extraction fraction is defined by

$$OEF = Sa_{O_2} - Sv_{O_2} \tag{A11}$$

which can be expressed as

$$OEF = Sa_0 - \left(\frac{Ca_0 - (Ca - Cv)}{\varphi \cdot [Hb]} \right) \tag{A12}$$

all of the variables of which can be measured or calculated using the above equations.

Appendix B

The models used in this study rely on a number of physiological parameters, some of which are quite constant across the population, and others which are known to have a significant degree of variation. It is essential to estimate the effect of assuming values for each of these on the final output values calculated. The parameters which have the greatest potential to influence the models, have the greatest variability across the population, or are the least well known are: the haemoglobin concentration [Hb]; the A-a gradient of the PO_2; the decrease in metabolic activity induced by hypercapnia; and the decrease in CBF induced by hyperoxia. The first two are known to vary significantly even in healthy subjects. The last two are still the subject of some debate, are not known with great accuracy, and may also vary between subjects.

In order to investigate the sensitivity of the model to these parameters, a fixed value of flow change was assumed to be caused by a 4% hypercapnic stimulus in an example grey matter voxel. The BOLD response that would be expected from such a stimulus (~3%) was calculated as a constant (0.001) multiplied by [Hb] raised to the power of β. From this, a value of M was calculated. Similarly a BOLD response was calculated that would be expected from a 50% hyperoxic stimulus (~1.5%) as a constant (1/3000) multiplied by [Hb] raised to the power of β. The default values used as the starting point in the sensitivity analysis were: [Hb] = 15 g/dl (Mark et al., 2011), A-a = 8 mmHg, $\Delta CMRO_2(CO_2)$ = -10% (Xu et al., 2011b), and $\Delta CBF(O_2)$ = -4% (Bulte et al., 2007b). As a rough estimate, the oxygen A-a gradient is given by (Age + 10)/4 mmHg (Kingsnorth and Bowley, 2011). The OEF was then calculated from these input values.

These values were each varied in turn while holding the others constant at their default values, and the range of OEF values calculated. The ranges over which each was allowed to vary was chosen so as to represent that which was most appropriate. Thus, the [Hb] was varied from 12 to 18 g/dl, which is the range from a typical low value for a healthy female to typical high value for a healthy male. The A-a gradient was varied from 0 (as most studies do not include this effect at all) to 15 mmHg (estimate for a healthy 50 year old subject). The decrease in metabolism induced by a 4% hypercapnia stimulus was varied from 0 (as most studies have not considered this) to 15%, which is greater than 1 standard deviation above that expected. The reduction in CBF induced by a hyperoxia stimulus of 50% was varied from 0 (as some studies do not consider this effect) to 10% (the approximate effect expected due to a 100% oxygen stimulus).

The results of these calculations are shown in Figure B1. As can be seen, none of the parameters have a dramatic effect on the OEF calculation. The A-a gradient has almost no effect despite the significant range of variation, and thus is most likely justified in being ignored. The decrease in metabolism due to hypercapnia is the next largest effect and yet still causes a change in the calculated OEF of less than ±0.04. Most encouragingly, the variation in [Hb] causes a change in OEF of less than ±0.05. Thus using an assumed value of 15 g/dl should introduce very little error into the calculation. Moreover, this is a parameter that is easily measured for every subject, but would require a blood sample to be taken and analysed, thus being more invasive and delaying the creation of the final images. This means that if speed is required, a value can be assumed with little error, or if greater accuracy is required a value can be measured.

Surprisingly, the reduction in blood flow caused by the hyperoxia causes the largest variation in the calculation of the OEF. This demonstrates why it is important to consider this effect and include a CBF term in the hyperoxia calibration model. Fortunately, any CBF change should be measured by the sequence itself and thus can be accurately included for every subject.

The sensitivity of the model to the parameters α and β was also investigated. As default, a value for α of 0.2 results in an OEF of 0.37, if α is changed to the commonly used value of 0.38 the calculated OEF only changes to 0.41. Similarly if the value of β is changed from 1 to 2, the calculated OEF ranges from 0.36 to 0.38. As these changes were so small, the plots were not included in the figure.

Bulte 2009 (Bulte et al., 2009)
Ances 2008 (Ances et al., 2008)
Ances 2009 (Ances et al., 2009)
Chen and Parrish 2009 (Chen and Parrish, 2009)
Chiarelli 2007 (Chiarelli et al., 2007b)
Ances 2009 (Ances et al., 2009)
Gauthier 2011 (Gauthier et al., 2011)
Lin 2008 (Lin et al., 2008)
Leontiev and Buxton 2007 (Leontiev and Buxton, 2007)
Perthen 2008 (Perthen et al., 2008)

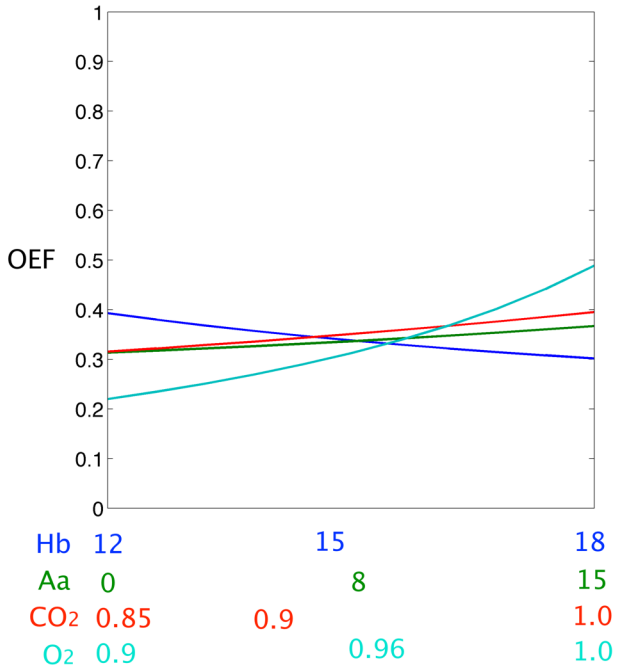

Fig. B1. Sensitivity analysis of the model for calculating the OEF. Each of the values depicted was varied across the given range, while all of the others remained at their default values (the value marked in the centre region). The x-axis values are: The haemoglobin concentration (g/dL), A-a gradient (mm Hg), fractional change in $CMRO_2$ due to CO_2, and fractional change in $CMRO_2$ due to O_2.