Modeling the Effect of Changes in Arterial Blood Volume on the BOLD Signal

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Purpose: The BOLD effect is modeled as primarily due to a mismatch of cerebral blood flow (CBF) and cerebral metabolic rate of O_2 ($CMRO_2$), but it is still not clear how we should include the effects of changes in cerebral blood volume (CBV) in the model. Having an accurate model is important because it serves as the framework for interpreting combined CBF and BOLD measurements in the calibrated-BOLD approach, providing quantitative assessments of *n*, an index of $CBF/CMRO_2$ coupling defined as the ratio of the two fractional changes. The original Davis model [1] only took into account CBV changes on the venous side, and yet a number of recent studies have found significant CBV changes on the arterial side [2]. While CBV increases on the venous side increase the local deoxyhemoglobin content and reduce the BOLD signal, arterial CBV changes can increase the BOLD signal by exchanging blood water, with an intrinsically higher MR signal, for tissue water. Here the BOLD signal model is extended to include arterial CBV effects, and the new model was used to test the range of error that occurs when data is analyzed with the simpler Davis model to estimate *n*.

BOLD signal model: The original Davis model (Eq 1) expresses the BOLD signal in terms of the baseline-normalized CBF (*f*) and $CMRO_2$ (*r*) with venous CBV changes described as a power law relation with *f* with exponent α. Additional parameters are β, an exponent originally derived from Monte Carlo simulations of diffusion effects around vessels, and a scaling parameter *M*. A more recent model described by Obata et al [3] (Eq 2) explicitly considered intravascular signal changes as well as extravascular changes, and expressed the BOLD signal as two terms describing the effects of total baseline-normalized deoxyhemoglobin (*q*) and venous CBV (*v*), with parameters k_1, k_2, and k_3, and a scaling factor of venous CBV (V_0). The connection with $CBF/CMRO_2$ is the relation $q=vr/f$. This model was modified to include effects of changes in arterial CBV (Eq 3), with *v* now representing total CBV (and assumed relation to *f* with exponent α) and a separate exponent α_v describing the venous CBV change. Additional parameters are a scaling parameter *A*, and a parameter κ that describes the relative magnitudes of total deoxyhemoglobin and other volume effects. The parameters κ and α_v (Eqs 4 and 5) depend on three parameters related to arterial CBV: w_A, the arterial CBV fraction at rest; δ_A, the fraction of the CBV increase with activation that is on the arterial side; and ε_A the intrinsic signal ratio of arterial blood to tissue. This more general model reduces to the Obata model if $\delta_A=0$, and, although not as obviously, closely approximates the Davis model when $A=M\beta$, $\kappa=(\beta-1)/\beta$, and $\alpha_v=\alpha$.

(1) $\delta S = M\left[1 - f^{\alpha}\left(\frac{r}{f}\right)^{\beta}\right]$ (Davis model, [1])

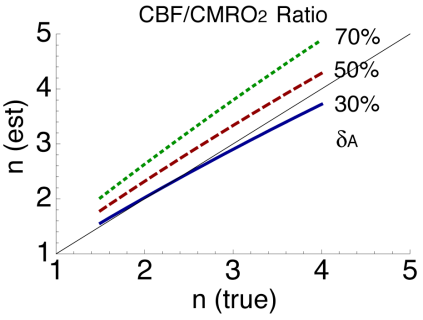
(2) $\delta S = V_0[(k_1+k_2)(1-q)-(k_2+k_3)(1-v)]$ (Obata model [3])

(3) $\delta S = A\left[\left(1 - f^{\alpha_v}\frac{r}{f}\right) - \kappa\left(1 - f^{\alpha}\right)\right]$ (new model)

(4) $\alpha_v = \alpha\,\frac{1-\delta_a}{1-w_a}$

(5) $\kappa = \frac{(1-\delta_A)(k_2+k_3)+(\varepsilon_A-1)\delta_A}{(1-w_A)(k_1+k_2)}$

Simulations: In the calibrated BOLD approach, CBF and BOLD responses are measured to both brain activation and to hypercapnia. The hypercapnia experiment is used to measure *M* from Eq 1 with the assumption that there is no change in $CMRO_2$ ($r=1$). The activation data is then analyzed to calculate *r* with the measured value of *M*. To test the importance of arterial CBV effects in this analysis, activation and hypercapnia data were simulated for different true values with Eq 3 and then analyzed with Eq 1 to derive an estimated *n*. This calculation was done for three values of the arterial fraction of the change in CBV (δ_A), with assumed values of $w_A=0.3$, $\alpha=0.4$, a 30% CBF change with activation, and a 40% CBF change with hypercapnia. For proportional changes across arterial and venous vessels ($\delta_A=w_A=30\%$), the Davis model gives an accurate estimate of *n*. As the arterial fraction increases the estimated *n* is larger than the true *n*.



Conclusions: The new model provides a way to assess the effects of CBV change in different compartments. For the calibrated BOLD experiment, the simulations suggest that use of the simpler Davis model may lead to an *overestimate* of *n* when arterial CBV changes are large, and so these effects cannot account for differences with some PET measurements that find larger values of *n* than those typically found with calibrated BOLD.

[1] Davis, PNAS 95:1834,1998; [2] Kim, JCBF+M 27:1235, 2006; [3] Obata, Neuroimage 21:144, 2004