Calibrated-BOLD fMRI: the effect of the BOLD post-stimulus undershoot on the calculation of the flow/metabolism coupling ratio

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Introduction

Functional MRI is now in widespread use, but the physiological basis of the method (the coupling of neural activity to cerebral blood flow (CBF) and energy metabolism ($CMRO_2$)) is still poorly understood. Recent work has shown that a calibrated-BOLD methodology, measuring local CBF and BOLD responses to mild hypercapnia in addition to neural activation, can provide a reproducible measurement of flow/metabolism coupling defined as *n*, the ratio of the fractional CBF change to the fractional $CMRO_2$ change (typically, *n*~2-3) (1,2). However, the Davis model of the BOLD effect (1) that is commonly used to calculate $CMRO_2$ changes is quite simple, and neglects some phenomena thought to be involved in the BOLD response, such as intravascular signal changes and the post-stimulus undershoot. The undershoot may be explained by a slow return of venous cerebral blood volume (CBV) to baseline (the balloon model (3)), or alternatively by $CMRO_2$ returning to baseline more slowly than CBF (4). These differing hypotheses leave us with the question of how the undershoot should be treated in the analysis of CBF/$CMRO_2$ coupling. If it is due to slow CBV recovery, then during the undershoot period the BOLD response is not reflecting CBF/$CMRO_2$ coupling, and this period should be excluded from the analysis. However, if the undershoot *does* reflect a slow recovery of $CMRO_2$, then it is important to include the undershoot period in the calculations for a full accounting of the $CMRO_2$ change. In this study, simulations and *in vivo* data were used to test the magnitude of potential errors introduced by including the post-stimulus undershoot in the calibrated-BOLD calculations.

Methods

Simulations. CBF and $CMRO_2$ responses were modeled as linear but independent convolutions of an impulse response function (IRF) with an arbitrary neural stimulus time course. All IRF's were modeled as gamma-variate functions, and the $CMRO_2$ response as a variable sum of a fast and a slow response. The model for the BOLD signal included both intravascular and extravascular signal changes (5). The coupling factor *n* is defined as the ratio of the areas under the respective IRF's for CBF and $CMRO_2$. The CBF and BOLD curves were analyzed using the Davis model (1) and the estimated $CMRO_2$ and *n* values compared to the simulated values.

Experiments. Simultaneous BOLD and CBF data were acquired on 6 healthy subjects on a 3T system, using a dual echo PICORE QUIPSS II arterial spin labeling sequence with spiral readout (TR=2.5s, TE=2.9, 24ms). For each subject, two hypercapnia scans (each 7min long: 2min air/3min 5% CO2/2min air), three block design visual stimulus runs (flashing checkboard at 8Hz, 4 cycles of 20s 'on'/60s 'off') and high resolution structural scans were acquired. Data were averaged over pixels in the visual cortex satisfying R>0.3, minimum cluster size 15, and the Davis model was used to estimate a dynamic $CMRO_2$ response curve. *n* was estimated as the ratio of the area under the CBF curve to the area under the $CMRO_2$ curve. To test the influence of the post-stimulus undershoot, the area under the two curves was calculated both for the entire curve and only up to the end of the stimulus block.

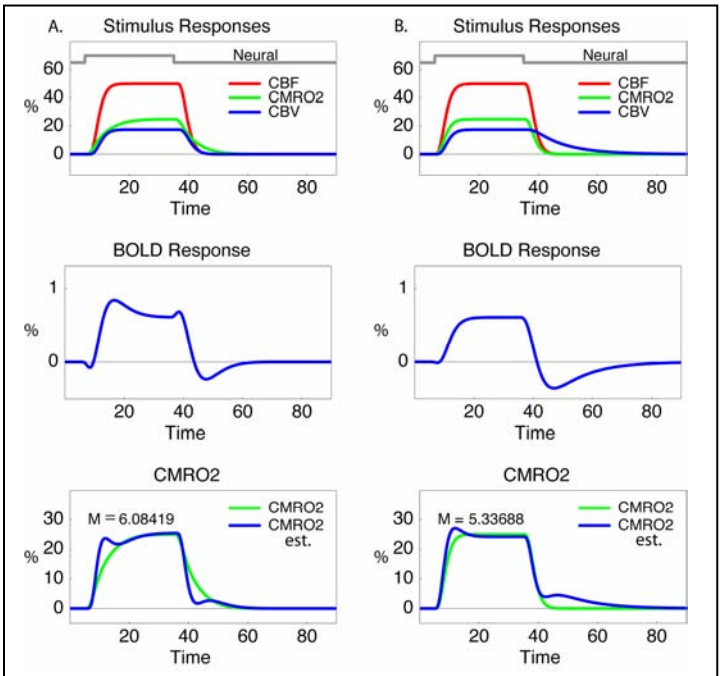

Figure 1. Simulations of the post-stimulus undershoot arising from a slow return of CMRO2 to baseline (A) or a slow return of CBV to baseline (B). Below are the simulated and calculated CMRO2 curves.

Results

Figure 1A shows simulated curves for a model in which CBF and CBV *are* tightly coupled, but $CMRO_2$ contains a slowly recovering response with an overall coupling index of *n*=2. The estimated $CMRO_2$ time course using the Davis model shows some deviation from the true curve, most likely due to the interplay of intra- and extra-vascular effects that are not considered in the Davis model. Nevertheless, the estimate of *n* is within 2% of the true value. Figure 1B shows the balloon model case, where $CMRO_2$ closely follows CBF, but a slow recovery of CBV produces a BOLD undershoot unrelated to metabolism. Inclusion of this undershoot in the data analysis—effectively assuming that it is due to slow-$CMRO_2$ rather than slow-CBV—creates an expected artifactual bump in the estimated $CMRO_2$ curve during the BOLD undershoot period. However, this leads to an error of only 11% in the estimate of *n*. Simulations for *n*=3 produced an error of <10%. Figure 2 shows the measured BOLD and CBF responses to visual stimulation, and the calculated $CMRO_2$ response for one subject, normalized for clarity. A small post stimulus bump in $CMRO_2$ can be seen, due to the BOLD undershoot. The mean decrease in *n* over all subjects was 7.4% (range 0-12%) when the undershoot was included, similar to the simulations.

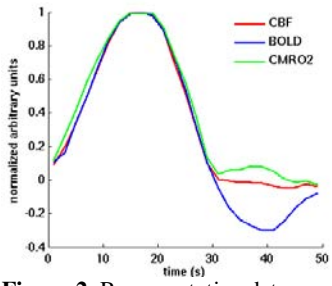

Figure 2. Representative data from one subject, showing normalized CBF, BOLD and calculated CMRO2 responses to visual stimulation.

Discussion

The simulations and *in vivo* data suggest that the errors induced by ignoring the potential confounds of slow CBV dynamics in the analysis of calibrated-BOLD data using the Davis model are quite modest, i.e. this model is robust to BOLD post-stimulus undershoot effects for the calculation of $CMRO_2$ changes.

References

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