Mapping BOLD-coupled CBF changes with improved sensitivity

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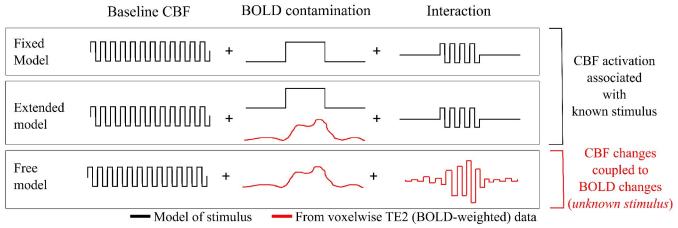
Target audience: This framework for identifying CBF changes coupled to BOLD signal changes in the presence of a known or unknown stimulus will interest researchers investigating functional changes in cerebral blood flow.

Purpose: Resting state functional BOLD MRI has emerged as a powerful technique for probing brain function in health and disease. However, it is difficult to characterize these intrinsic fluctuations using arterial spin labelling (ASL), primarily due to the relatively low SNR. Here, we present a new technique that maps changes in CBF that are coupled to BOLD fluctuations, rather than linked to a modelled stimulus, performed within the framework of a general linear model and utilizing a dual-echo sequence to capture ASL and BOLD data simultaneously. We hypothesize that this is a more sensitive method for mapping coupled CBF and BOLD changes throughout the brain than conventional correlation approaches. In addition, we apply this method to improve the robustness of CBF statistical maps during a known visual stimulus.

Methods: A dual-echo gradient-echo spiral PICORE QUIPSS II pulsed ASL sequence was used to collect data at 3 Tesla in 10 subjects during a block design visual stimulus (90 s blocks, full-contrast flashing checkerboard, 8 TR/TE1/TE2=2200/3.3/29 ms, 10 slices, 3.4x3.4x7.9 mm^3 voxel resolution, 10.5 min scan duration). Three subjects were removed from analysis due to tagging artifacts. Data were preprocessed to correct for physiological (RETROICOR, RVT, HR, end-tidal CO_2 and O_2 [1]; AFNI) and motion artifacts (FSL). A subject-specific mask of the visual cortex was defined using a clustered BOLD activation map determined by the TE2 data ($p<0.05$, Bonferroni corrected). The TE1 data were modelled as the sum of a baseline CBF term, BOLD contamination term, and an interaction term (Fig. 1), plus nuisance regressors (6 head motion time-series and their derivatives). The baseline CBF regressor modelled the alternating tag/control volumes. In the Fixed Model, the known visual stimulus was represented as a boxcar function convolved with an HRF, and incorporated into the BOLD contamination and interaction regressors. The TE2 dataset offers simultaneously acquired BOLD-weighted data, and was implemented as voxelwise BOLD contamination regressors following low-pass temporal filtering to remove residual ASL tagging ($f<0.227$ Hz). The Extended Model adds TE2 data to the Fixed Model to determine if significant additional variance can be explained. The Free Model uses the TE2 data to determine both the BOLD contamination *and* the interaction regressors. The baseline CBF (uncalibrated beta weight) and CBF interaction (t-statistic) were averaged within the visual cortex mask and compared across models.

Fig. 1. Schematic of general linear models to measure functional CBF changes.



Results: The addition of voxelwise TE2 data (Extended Model) explained significant additional variance compared to the Fixed Model in the visual cortex ROI (48.3±7.4% of voxels) and throughout the brain (52.7± 5.1% of voxels, F-test, $p<0.05$, Bonferroni corrected). Within the visual cortex, the Extended Model did not significantly affect the baseline CBF or interaction statistics. These results suggests that the addition of TE2 data to the GLM is not detrimental to mapping CBF activation and may mitigate the sources of noise that are common to both echo datasets [1]. In contrast, the Free Model resulted in significantly higher t-statistics associated with the interaction term, and a corresponding decrease in the baseline CBF term (Fig. 2). The median %CBF/%BOLD within the visual cortex was 29.4±12.5 (averaged across subjects), in agreement with the literature assuming a linear model [2]. The Free Model mapped significant CBF-BOLD interactions throughout the cortex, not only in the activated visual cortex where % changes were higher, identifying a greater number of significantly coupled voxels than a conventional correlation method (Fig. 3). This indicates the Free Model is more sensitive for investigating CBF-BOLD coupling throughout the brain during an unknown stimulus.

Discussion: The Free Model maps CBF changes that are specifically coupled to simultaneous BOLD changes, without providing a specific experimental paradigm: this creates a framework for studying coupled fluctuations in CBF and BOLD signals in the absence of stimuli, such as in resting state studies. Fig. 3b shows disparity between the extent of coupling measured in the activated region versus all gray matter, indicating contrast-to-noise may limit the sensitivity of this method in other, unactivated areas of cortex. Although the linear Free Model could be improved with non-linear terms [3], the quantitative coupling between CBF and BOLD can be approximated, probing the metabolic status of resting fluctuations. It can also be applied to measure CBF activation in traditional paradigms if the spatial extent of activation is established via BOLD data.

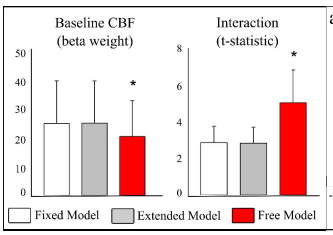


Fig. 2. The Free Model significantly increases significance of interaction and reduces baseline CBF estimation (*$p<0.05$, paired t-test).

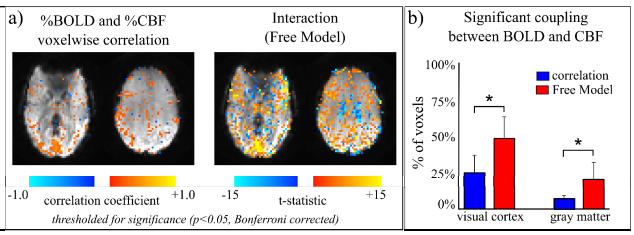


Fig. 3. The Free Model identifies significant CBF-BOLD coupling throughout the brain (a), in significantly more voxels (b) than a simple correlation approach (paired t-test, *$p<0.05$).

Conclusions: The Extended Model addresses residual BOLD contamination and noise in ASL data. The Free Model provides a robust method for disentangling baseline CBF, functional CBF changes, BOLD contamination and other noise sources during a known or an unknown stimulus.

References: [1] Bright MG, Murphy KM (2013) NeuroImage 64:526-537; [2] Lin et al. (2009) NeuroImage 44(1):16-22. [3] Simon et al. (2012) Proceedings ISMRM, Melbourne, Poster #2044.

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