Feasibility of Using Simultaneous BOLD-ASL to Estimate the Magnitude of the CBF Response to an Unknown Stimulus

Aaron Benjamin Simon[1], and Richard Buxton[2]
[1]*Department of Bioengineering, University of California San Diego, La Jolla, CA, United States,* [2]*Department of Radiology, University of California San Diego, La Jolla, CA, United States*

Purpose: To develop a methodology for quantitative measurement of cerebral blood flow (CBF) fluctuations during complex behavior.

Background: Current BOLD-fMRI studies primarily use one of two basic analysis paradigms to investigate brain activation: 1) correlation of measured time series with a reference function related to the stimulus applied; or 2) correlation of measured time series with a seed-voxel time series to identify correlated "networks". We are investigating an alternative approach based on the simultaneous measurement of BOLD and ASL time series that exploits the idea that underlying fluctuations in neural activity are driving both signals. Our goal is to develop tools for quantifying brain activity during complex behavior that overcome three challenges: 1) the driving stimulus function for a particular brain region is unknown; 2) interpreting the magnitude of BOLD fluctuations in a quantitative physiological sense is difficult because of the complexity of the BOLD signal; and 3) quantification of CBF fluctuations from an ASL time series alone is difficult because of low SNR. Previously we found that the correlation of the ASL and BOLD signals for a voxel could be used to identify activation without knowing the dynamics of the stimulus driving that activity[1]. As a first step toward quantifying the level of activity, we investigated here whether the simple projection of the ASL time series onto the BOLD time series for a voxel can be used to accurately estimate the magnitude of CBF fluctuations despite the intrinsic noise in the ASL measurements.

Methods: We hypothesized that, after mean subtraction and the removal of known sources of physiological noise, BOLD and ASL time courses could be represented as two scaled versions of the same time series with different levels of added noise, with higher SNR in the BOLD series but more meaningful magnitude information in the CBF series. The variance of CBF fluctuations, σ_f^2, can then estimated from the magnitude of the projection of the CBF series onto the BOLD series, and its square root, σ_f, provides an estimate of the characteristic scale of CBF fluctuations. However, σ_f will be underestimated if the shape of the BOLD series differs from that of the underlying true CBF fluctuations, either due to noise in the BOLD series or BOLD signal transients arising from dynamic coupling of flow and oxygen metabolism that are not present in the CBF signal. To test the significance of these effects, we applied this method of analysis to data from a previous study investigating the hemodynamic and metabolic response to a visual stimulus[2]. To avoid confusing issues of detection with the determination of measurement bias, voxels were selected for analysis using a standard general linear model approach. Before further analysis, known sources of physiological noise and linear scanner drifts were removed from the BOLD and ASL time courses through RETROICOR[3] and RVT[4] based regression. To estimate the bias attributable to intrinsically uncorrelated BOLD/CBF fluctuations, BOLD and ASL responses to a 4-cycle block visual stimulus were averaged across stimuli and the ROIs defined for each subject, and the correlation of the average time courses was determined. To estimate the bias attributable to noise, σ_f was estimated four ways: 1) by calculating the standard deviation of the average time courses described above; 2) by calculating the standard deviation of the ASL signal on a per-voxel basis, then averaging the calculated values across the ROI; 3) by projecting the ASL signal onto the BOLD signal on a per-voxel basis, then averaging the calculated values across the ROI; and 4) by spatially averaging locally clustered active voxels before proceeding as in method 3.

Results: ROI-averaged ASL and BOLD time courses were highly correlated ($R^2 = 0.946 \pm 0.01$), suggesting that intrinsic periods of uncorrelated BOLD/CBF fluctuations should introduce only an approximately 3% underestimate into estimates of σ_f in this experiment. However, noise was found to significantly bias σ_f (fig. 1). For the ROI-averaged ASL time course, σ_f, expressed here as a fraction of the mean ASL signal, was 0.19 ± 0.06 across subjects. This was taken to be the best-possible estimate of σ_f under the experimental conditions. σ_f for the ASL signal without BOLD-projection or averaging was found to be 0.31 ± 0.09 across subjects, suggesting that the ASL signal contains significant noise. Per-voxel projection of the ASL signal onto the BOLD vector space reduced the estimate of σ_f to 0.16 ± 0.06, a 15.7% underestimate of the accepted value. Spatially averaging across locally clustered active voxels significantly improved the estimate of σ_f to 0.18 ± 0.06 across subjects, reducing the underestimate to 5.3%.

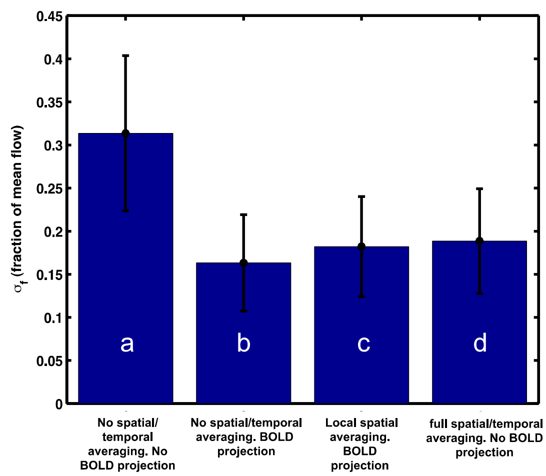

Figure 1: Bar chart comparing estimates of characteristic magnitude of CBF fluctuations (σ_f) as a fraction of mean flow. Without benefit of averaging (a), CBF fluctuations are overestimated compared to (d) due to ASL noise. Per-voxel BOLD projection (b) eliminates CBF noise but underestimates σ_f due to BOLD noise. Local averaging of active voxels (c) before projection reduces BOLD noise and improves estimate of σ_f.

Conclusions: Projection of the ASL signal onto the BOLD vector space is a novel method of obtaining quantitative information about CBF fluctuations if the temporal pattern of the hemodynamic response cannot be assumed. Both intrinsically uncorrelated fluctuations in BOLD and CBF and noise in the BOLD signal may contribute to biasing estimates of CBF fluctuations based on this technique, with BOLD noise the most significant of the two in this study. However, before this method may be used to study dynamic neural activity with an unknown stimulus, it will be critical to examine how BOLD transients affect BOLD/CBF correlation under different physiological and experimental conditions.

References

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