BOLD and CBF Sensitivites to Variable Intensity Neuronal Stimulation

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Introduction

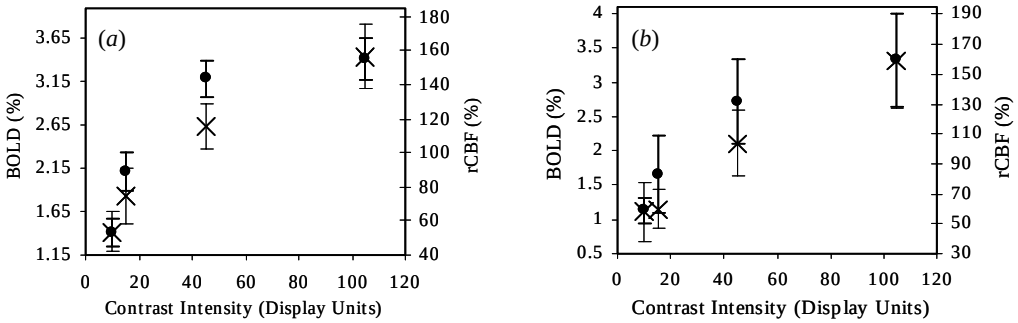
Recent advances in the investigation of cerebrovascular coupling have embraced graded functional activation as a means to disentangle the biophysical and physiological factors complicating the typical interpretation of fMRI data [1,2]. Previous studies have investigated the relationship between BOLD and perfusion in the human visual cortex [3,4], although little attention has been given to the changing relationship that exists between BOLD and perfusion when delivering stimuli of varying intensity. In this study, we simultaneously acquired graded-stimulation BOLD and CBF data over multiple subjects, and also studied a large number of repeat sessions in a single individual. A series of visual stimuli were designed to probe the complete range of fMRI activation. We identified trends in BOLD measurement that show superior contrast between low-intensity visual stimuli. Perfusion measurements, conversely, appear to provide improved discrimination between high-intensity stimuli.

Experimental

Interlaced BOLD and pulsed arterial spin-labelling images were acquired on a Varian 3 Tesla MRI scanner, coupled to a Magnex head-dedicated gradient insert coil in conjunction with a birdcage head radio-frequency coil tuned to 127.4 MHz. BOLD experiments had TR/TE=3.5s/32ms, and perfusion experiments (QUIPSS2) had TR/TE=3.5s/22ms and TI=1.4s. Each fMRI study consisted of a randomized block design visual stimulus, with a non-isoluminant square checkerboard stimulus of variable white/black contrast intensity oscillating at 8 Hz (48 sec on, 28 sec off per epoch). Sixteen epochs of randomized contrast intensity were used per study, with four visual stimulus levels each repeated four times. Eight subjects were studied once (5 male, 3 female), and 8 repeat-trials were performed for a single individual (male). BOLD and perfusion data were analyzed using the FSL analysis package [5], incorporating motion correction (MCFLIRT), brain extraction (BET), and a GLM-based estimation of activation intensity. Temporal sinc-interpolation was applied to perfusion images prior to pair-wise subtraction of control and tag. For all studies, BOLD and perfusion were interrogated within a single common brain area, defined by the overlap of BOLD and perfusion activation, statistically valid across all co-registered studies (using FLAME, a Metropolis-Hastings Markov-Chain Monte Carlo sampling approach to estimate the mixed-effects component of random effects variance across sessions [6]), further masked by the anatomical boundary of V1.

Results

Data comparing BOLD and perfusion measurements are displayed below for an array of visual stimulation intensities, designed to cover a wide range of the fMRI response spectrum. Averages were obtained for (*a*) 8 repeat trials on a single individual and for (*b*) 8 individuals, with one trial each. Each trial represents an average of the four 48s stimulation epochs, embedded within the randomized study design. Data are displayed with the lowest and highest matching BOLD and perfusion data points coincident, for ease of comparison.



Simultaneously acquired BOLD (•) and perfusion (×) data for four visual stimuli of variable contrast intensity, shown for (*a*) 8 repeat studies on a single individual, and (*b*) 8 individuals, one study each. Perfusion is expressed as relative CBF increase divided by baseline (rCBF (%)). Data are shown as (mean)± (confidence interval of the mean over all 8 sessions).

Discussion and Conclusions

Observed trends between BOLD and perfusion activation intensities in (*a*) and (*b*) correspond well to the underlying physiological and biophysical mechanisms supplying each contrast. Estimates of BOLD activation in (*a*) for the two stimulus conditions of highest amplitude are not statistically different from one another (95% confidence, based on pooled-variance *t*-test), while they are well distinguished based on the perfusion estimates. BOLD contrast, supplied by CBF-and CBV-related fluctuations in deoxyhemoglobin (dHb), is minimal at this point, and neuronal stimulation may be incorrectly determined to be *saturated* if gauged by BOLD alone. The converse effect is observed when comparing between the two stimulus conditions of lowest amplitude, where BOLD is able to statistically differentiate the activation levels in comparison to the perfusion estimates which do not (95% confidence). The data suggest that "windows" exist within the spectrum of stimulation intensity, where either contrast may act as a preferable option for quantitative discrimination between stimuli of different but similar amplitude.

BOLD and perfusion data from the single subject (*a*) agree well with the data from multiple subjects (*b*), both falling within the error boundaries of the multi-subject averages, and displaying a similar qualitative trend. Data from multiple subjects display a more pronounced difference between BOLD and perfusion measurement, with roughly equivalent rCBF (%) values at the two lowest stimulation intensities.

These observations may be of importance both from a fundamental neuroscientific perspective, and from a clinically relevant standpoint—offering the potential for using combined imaging to better assess cerebral response to disease or exogenous agents, in cases where a single imaging modality alone shows minimal effect. Our results are presented with the future goal of better characterizing CBF, CBV, and CMR_{O2} within the brain, during periods of varied stimulation.

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