Nonlinear Hemodynamic Responses of CBV, CBF and BOLD Signals during Visual Stimulation

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Introduction

In functional MRI, most experimental designs assume the cascaded neuronal and hemodynamic response system as a linear and time-invariant system, which greatly simplifies fMRI data analysis and interpretation. BOLD signal is explained as a phenomenon arising from complicated physiological processes involving CBV, CBF and $CMRO_2$ changes during neuronal activation. A number of studies have investigated whether the linear assumption (superposition and/or scaling property) of BOLD response is approximately valid in different brain regions (1-3). Fewer studies have examined the ASL perfusion signal (3,4) probably due to its lower sensitivity. The linearity of the CBV response in human brain is least understood due to a lack of noninvasive measuring methods. The recently proposed VASO technique provides a new fMRI contrast based on CBV change associated with brain activation (5). In this work, we investigate the additivity of VASO, ASL, and BOLD responses in human visual cortex by acquiring these signals concurrently (6) and by varying visual stimulus durations.

Methods

Experimental Design. A full-field black and white circular checkerboard with 8Hz reversal rate was delivered to subjects through a back-projection screen inside the bore of the scanner. Functional experiments were divided into two parts. First, a block-design experiment was performed to determine the region of interest (ROI) for evaluating the linearity of the signals. The block-design paradigm started with a 24s "rest" block, during which a small white fixation cross was placed at the center of the screen with black background, followed by five cycles of alternating 24s "task"/ "rest" blocks. Second, event-related tasks with varying stimulus durations were used to test linear additivity. A total of 7 scanning runs were acquired, consisting of two repeated runs each for the 0.5s (18 trials/run) and 1s (14 trials/run) stimuli, and one run each for the 2s (16 trials/run), 4s (8 trials/run) and 8s (6 trials/run) stimuli. Each run started with a 4s "rest" scan and the inter-stimulus interval (ISI) was 22s for the 0.5-4s stimuli and 26s for the 8s stimulus.

Data Acquisition. All data were acquired on six healthy volunteers on a 3T Siemens Allegra scanner with a head volume coil using a pulse sequence with an adiabatic inversion recovery and three EPI readouts (6). Three oblique axial slices (5mm thick/1mm gap) were prescribed to cover the primary visual cortex. Three sets of images sensitive to VASO (first echo: TE=6.6ms, blood nulling point TI_1 was chosen individually for each subject when the sagittal sinus area had minimal signal intensity), ASL perfusion (second echo: TE=7.6ms, TI_2=1200ms) and BOLD (third echo: TE=27ms), respectively, were collected within one inversion recovery cycle (TR=2000ms). Partial k-space acquisition (75%) capturing a field of view of $22\times22cm^2$ was used to minimize BOLD effects in VASO and ASL images. ASL perfusion information was encoded by alternating slab-selective inversion (control) and nonselective inversion (labeling). Inversion slab thickness of 150mm was selected to facilitate both VASO and ASL acquisitions. For each run with 0.5s, 1s, 2s, 4s, and 8s stimuli, 202, 158, 180, 136, 108 VASO, ASL and BOLD images were acquired, respectively.

Data Processing and Analysis. Image registration was carried out to reduce head motion artifacts using volume registration in AFNI. Linear trend was removed and a spatial Gaussian filter (FWHM = 4.8mm) was applied to all functional data sets before further processing. For the block-design data, VASO and BOLD time series were obtained by adding adjacent control and labeling images of the first and third echoes, while ASL time series was obtained by pair subtracting the second echo images. For the event-related data, adjacent trial addition/subtraction strategy was used to achieve an effective TR of 2s (6). Student's *t*-test was then used to compare the block-design data acquired during "task" and "rest" after accounting for hemodynamic delay. Activated voxels were identified by a *t*-threshold of 6.0 ($p<0.001$) and a clustering size of 4 for VASO and BOLD signal. For ASL signal, a *t*-threshold ranging from 2.0-3.0 ($p<0.05$) and a clustering size of 4 were chosen to confine the identified voxels to the primary visual cortex. For each activated voxel, time locked averages of the hemodynamic responses of different stimulus durations were performed. The data were then averaged over all activated voxels and across the six subjects and finally normalized to their respective baseline signals.

For a linear time-invariant system, the time integral of the system output is proportional to the time integral of the system input, which is proportional to the input duration, given a constant input amplitude. To assess the linearity of VASO, ASL, and BOLD signals, the ratio of the area under response curves to the stimulus duration was calculated.

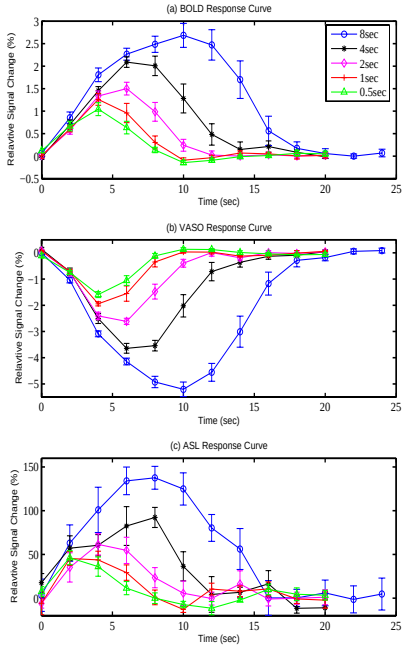

Fig.1 Average event-related (a) BOLD, (b) VASO, and (c) ASL response curves with varying stimulus durations, with SEM error bars calculated across the six subjects.

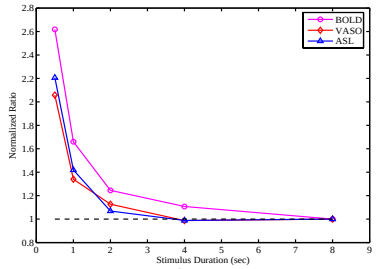

Fig.2 Normalized ratio of the area under the response curve to the stimulus duration for BOLD, VASO, and ASL signal. The dashed line indicates a linear system behavior.

Results and Discussion

Fig.1 shows the mean (±SEM) BOLD, VASO and ASL signal responses with 0.5-8s visual stimuli calculated from the six subjects. With increasing stimulus duration, the magnitude of the three response curves increased and the peak of the curves delayed. Note that the SEM error bars during rising slopes of BOLD and VASO signals were smaller than those during falling slopes, indicating larger time variations within subjects for these signals returning to baseline than their initial rise. Fig. 2 depicts the ratio of the response area to stimulus duration, with the ratio at the longest duration normalized to 1. All three responses showed nonlinear properties for stimulus durations less than 4s, and the degree of nonlinearity increased as the stimulus duration decreased. At 4s stimulus, VASO and ASL responses demonstrated an almost linear behavior while the BOLD response still deviated from linearity. In general, VASO and ASL signals showed similar nonlinearity, whereas BOLD signal demonstrated greater nonlinearity. This may be explained by the notion that VASO and ASL reflect similar hemodynamic processes with neuronal activation, while the BOLD signal is the end product of the interplay of CBV, CBF and $CMRO_2$.

In this work, a novel imaging technique that acquires VASO, ASL and BOLD images simultaneously was used to make it possible to investigate the linearity of these responses in a single scan. This technique substantially increases the efficiency of the measurements and would reduce errors caused by head motion between scans if the signals were acquired separately. Information on the nonlinear properties of the hemodynamic signals will be useful for better design of stimulation paradigms and for more accurate interpretation of fMRI data.

References

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