Investigating the source of BOLD Nonlinearity

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Introduction The fMRI technique relies on the measure of hemodynamic and metabolic changes spatially accompanied with local neuronal activity. These changes result from several cascaded processes including neuronal processing to external input, neurovascular coupling and vascular response. Quantitative relationships among these neurophysiologic processes are extremely important to the interpretation of fMRI signal and brain function. Among these relationships, the linearity of vascular response is of particular interest. This is because not only the vascular response dominates the BOLD signal, but also a great number of fMRI studies employ the rapid event-related (ER) design. The advantage of rapid ER design includes time efficiency and the ability of randomizing trial types and sorting data based on behavioral responses. At the same time, the rapid ER fMRI design needs to assume a linear BOLD signal, that is, vascular response to two identical events shifted in a time delay is the same as the superposition of two replicated responses shifted in the same delay, and every of the two replicated responses should be identical in shape and amplitude to the response to the single event. If BOLD linearity holds, the inference from the BOLD signal to neuronal activity can simply be characterized by a hemodynamic impulse-response function.

Unfortunately, several studies have demonstrated that significant nonlinearity exists in the BOLD signal[1,2]. These nonlinear effects in BOLD signal have posed a serious problem in rapid ER fMRI designs. In attempt to solve this problem and improve the detection reliability using rapid ER fMRI designs, several models have been developed to account for the nonlinearity in fMRI data. Validation of these models, however, needs to answer a very important question with the goal of understanding the source of BOLD nonlinearity: does BOLD nonlinearity result from vascular refractoriness caused by viscoelastic properties of blood vessel or refractoriness at the neuronal level? To answer this question, we have employed a paired-stimulus paradigm composed of two ultra-short (10 ms in duration) visual stimuli with a variable inter-stimulus interval (ISI) between them. We have demonstrated that, when visual stimulation duration is as short as tens of milliseconds, the neuronal activities elicited in the primary visual cortex in response to the first and second visual stimuli are identical at ISI longer than 600~800ms[3]. Based on this fact, we chose five different ISIs (1, 2, 4, 6 and 8 seconds) to ensure no neuronal refractoriness is involved and measured the corresponding BOLD responses to the single stimulus and paired stimuli. This design allows us to individuate the BOLD response to the second stimulus by subtracting the BOLD response to single stimulus from that to paired stimuli at each ISI. If there is a refractory period, the BOLD response to the second stimulus should be a function of ISI. Alternatively, if BOLD nonlinearity reported in the literatures is neuronal origin, the BOLD response to the second stimulus should be independent of ISI.

Method Visual stimulation presented as brief flashing red light was generated by a pair of LED goggles (Grass Instruments, Quincy, MA). Visual stimuli were displayed in the full visual field either singly or in pair separated by an ISI. Successive trials of single or paired stimuli were separated by a long inter-trial interval (ITI) of 25 seconds to allow the hemodynamic response to return to the baseline. During the baseline condition, subjects were in uniform darkness. The fMRI experiment was conducted using an ER design. All experiments were performed on a 4T/90 cm bore magnet (Oxford, UK) system interfaced with the Varian INOVA console (Varian Inc., Palo Alto, CA). Six coronal images covering most of the calcarine fissure were selected for acquiring fMRI data using the gradient-echo planar images (GE EPIs) with the parameters of FOV = 18×18 cm^2, 64×64 in plane matrix size, TR/TE = 415/31 ms, slice thickness= 5 mm.

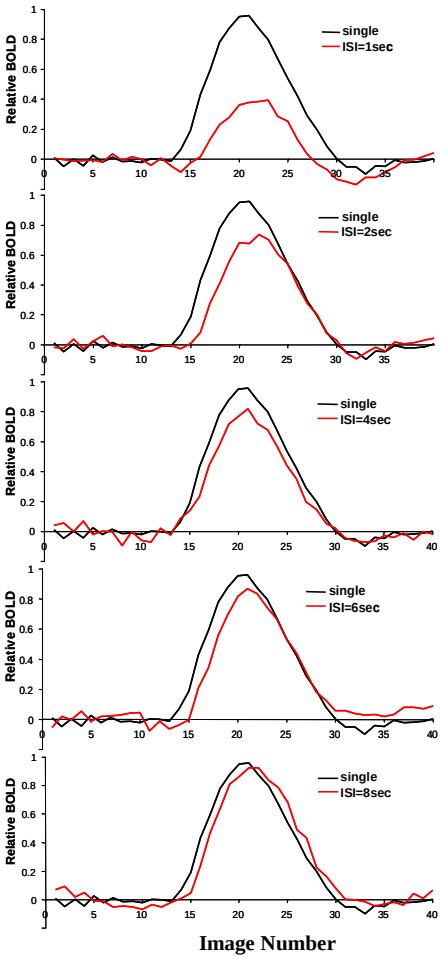

Figure 1. The time courses of BOLD responses to the single and second of the paired-stimulus, respectively.

Results BOLD nonlinearity at each paired-flash condition was quantified by the ratio of BOLD integrals between the BOLD response to the second stimulus and the response to the single stimulus. Figure 1 compares, for each ISI, the averaged BOLD time course from the single stimulus (black curves) to that from the second stimulus (red curves) shifted by the amount of ISI to align the stimulus onset. Clearly, the BOLD response to the second stimulus at short ISI is significantly reduced presumably due to vascular refractoriness. This BOLD reduction gradually becomes smaller, eventually disappearing, when ISIs get longer. Figure 2 demonstrates the relationship of BOLD integral ratio between the response to the second stimulus and the response to the single stimulus as a function of ISI.

In addition to BOLD amplitude variation as ISI changes, the onset latency of BOLD response to the second stimulus always delays compared to the response to the single stimulus. The delay appears to be longer when BOLD reduction is more significant. To further validate this view, all BOLD time courses in Figure 1 are fitted by two Gamma functions accounting for the positive BOLD signal and undershoot, respectively. The onset time is calculated at the time when the BOLD response is larger than one standard deviation of pre-stimulus baseline at the single-stimulus condition. Figure 3 plots the onset latency against BOLD integral ratio obtained from fitting results. A strong correlation ($R^2 = 0.86$) is observed between them.

Conclusion Taken together, our results verify significant nonlinearity in BOLD signal and suggest that this nonlinear behavior entirely result from the nonlinearity in the vascular response when ISI ≥ 1 second. Given the observed relationship between BOLD refractoriness and ISI, we postulate that onset latency also provides a measure of BOLD nonlinearity originated from vascular response. This information should be crucial for quantifying the neurovascular coupling relationship based on the BOLD measurement.

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References: 1. *Boynton, G.M. et al. J Neurosci 1996*; 2. *Pfeuffer, J. et al. NeuroImage 2003*; 3. *Zhang, N. et al. JCBFM 2007*

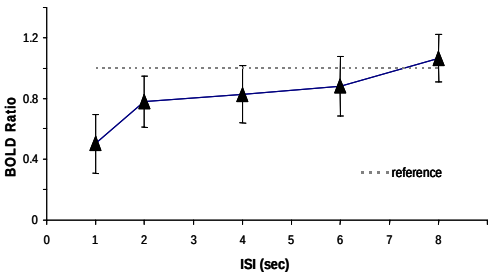

Figure 2. Dependency of BOLD refractoriness on ISI

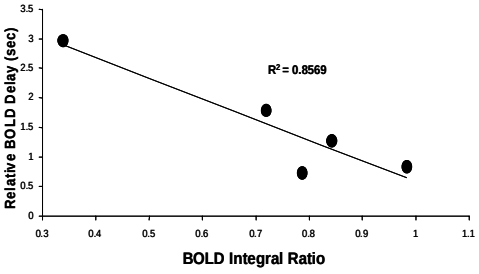

Figure 3. Correlation between BOLD refractoriness and BOLD onset latency.