Revisit Nonlinearity in Blood-oxygenation-level-dependent Signal

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Introduction The majority of studies investigating the linearity of the BOLD signal suggested existence of significant nonlinearity[1,2]. In these studies, repeated stimuli led to successively smaller BOLD amplitudes and delayed BOLD onset latencies when the inter-stimulus interval (ISI) is shorter than a few seconds. The mechanism of nonlinearity in the BOLD signal remains unknown, partially because of its uncertain origin. Birn and Bandettini have suggested that the observed BOLD nonlinearity could come from neuronal and/or vascular origins[3]. By ensuring invariant neuronal activities in a paired-stimulus paradigm, we have selectively investigated vascular related (non)linear BOLD effects, excluding any neuronal refractory effects. Under these conditions, we demonstrated significant nonlinear BOLD effects including reduced BOLD amplitude and delayed BOLD onset latency in response to the second of paired stimuli when the ISI was shorter than ~4-6 seconds. More importantly, we found that the BOLD nonlinearity was significantly reduced when the contributions from large vessels to the BOLD signal were removed (a typical example can be seen in Fig. 2b)[4]. These findings raise the question of whether or not the BOLD nonlinearity originates primarily from hemodynamic changes in large vessels. The answer to this question is significant because it suggests the possibility that the BOLD response from the microvasculature, triggered by local neuronal activity, is a linear system, whereas the nonlinear effects observed in the BOLD signal in previous studies are only artifacts from down-stream vessels.

Nevertheless, our earlier study was not sufficient to provide a definite answer. This is because the criterion used to separate large vessel contributions to the BOLD signal was based on an index υ defined by the ratio between the standard deviation and the mean of the MRI signal intensity obtained from a series of fMRI images during the resting condition. Large vessel contribution to the BOLD signal was separated by eliminating activated pixels with large υ values. Although this criterion is sufficient to observe the effects of large vessels and the nonlinear characteristics of the BOLD signal, it does not guarantee a strict segregation between macro- and microvascular activities. Consequently, residual nonlinearity was still observed in the BOLD signal after removing all activated pixels with large υ values, even though it became much less significant (an example can be seen in Fig. 2b)[4]. On the other hand, spin-echo (SE) fMRI at high magnetic fields is known to be primarily sensitive to microvascular activity because the intravascular component of the BOLD signal is diminished at higher fields due to the dramatic shortening of blood T_2 relative to tissue T_2 and the removal of large vessel extravascular signals with the SE fMRI method, due to the refocusing of static dephasing effects induced by magnetic field inhomogeneities around large vessels. Given this feature, in the present study we investigated the (non)linear characteristics of the BOLD signal from the microvasculature using a combination of SE fMRI and a paired-stimulus paradigm. The ISIs selected were longer than 1 second to ensure invariant neuronal responses to all stimuli so that only the vascular effect was involved[4]. Under these experimental settings we examined and compared the BOLD amplitude in response to the second of paired stimuli to that of the single stimulus.

Method A paired-stimulus paradigm was composed of a pair of visual stimuli with a given ISI between them. Visual stimulation presented as 8 Hz flickering red/black light (100% contrast) was generated by a pair of red LED goggles (Grass Instruments, Quincy, MA). The duration of each stimulus was time locked to the repetition time (TR = 1.15 second) of SE echo-planar images (SE-EPI) acquisition. Full field visual stimuli were displayed either singly or in pairs separated by an ISI of 1, 2, 4 or 8 TRs. Successive trials of single or paired stimuli were separated by an inter-trial interval (ITI) of 30 s to allow the hemodynamic response to fully return to baseline. The control condition consisted of uniform darkness. All experiments were performed on a 4T/90 cm bore magnet (Oxford, UK) interfaced with the Varian INOVA console (Varian Inc., Palo Alto, CA). One coronal slice in the middle of the calcarine fissure was selected for acquiring fMRI data using SE-EPI with the parameters: field of view (FOV) = 12.8×12.8 cm^2, 64×64 in-plane matrix size, echo time (TE) = 67 ms, TR = 1150 ms, slice thickness = 5 mm, in-plane resolution = 2.0×2.0 mm^2.

Results Figure 1 shows the time courses of SE-EPI BOLD responses to the single and second of paired visual stimuli at different ISIs. There seems to be no significant difference between the time evolutions of BOLD responses to the single and second of paired stimuli even at very short ISIs. After normalizing to the single-stimulus condition, the relative integrals of the BOLD responses to the second stimuli as a function of ISI are shown in Fig. 2a. The dependency of the relative BOLD integral on ISI is in sharp contrast to gradient-echo EPI (GE-EPI) BOLD signals as shown in Fig. 2b[4]. Figure 3 compares the SE-EPI BOLD time course predicted by adding two replicated BOLD responses from the single-stimulus condition, shifted by a selected ISI, and the measured responses at the given ISIs, showing excellent agreement between the predicted and measured SE-EPI BOLD time courses based on the assumption of linear BOLD system.

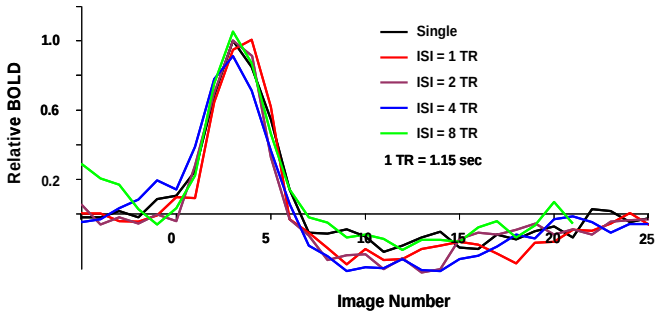

Fig. 1 SE BOLD responses to the single and second of paired stimuli. Each time course was aligned to the onset of the corresponding stimulus.

Conclusion Our results suggest that SE BOLD signals at high magnet fields, which is mainly sensitive to the microvasculature, is primarily a linear system. Therefore, the micro-vascular activity measured by SE BOLD signal should provide accurate estimate of the amplitude of neuronal activity change evoked by brain stimulation.

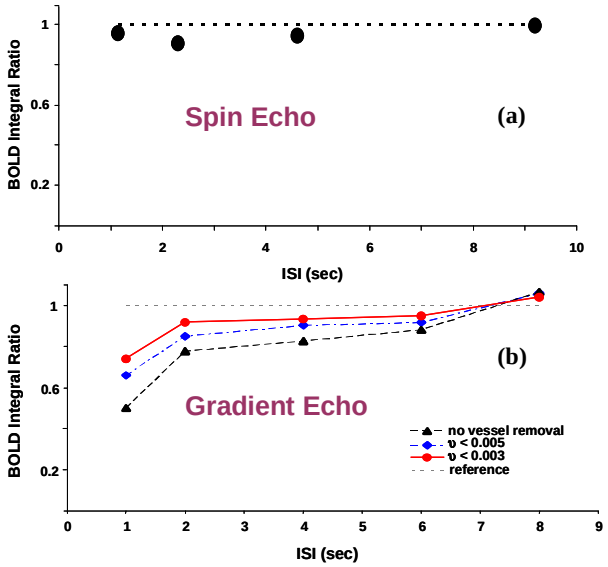

Fig 2. Dependency of relative integral spin-echo BOLD signal (a) and gradient-echo BOLD signal (b) on ISI.

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References: 1. *Boynton, G.M. et al. J Neurosci 1996*; 2. *Pfeuffer, J. et al. NeuroImage 2003*; 3. *Birn, R.M.. et al. NeuroImage 2005; 4. Zhang, N. et al. NeuroImage 2008*

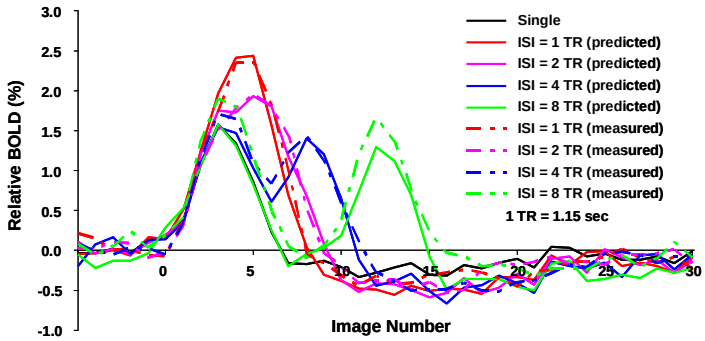

Fig. 3 Comparison of SE-EPI BOLD time course predicted by adding two replicated BOLD response at the single-stimulus condition shifted by a selected ISI and that measured at ISI.