Neural and Vascular Response Nonlinearity in Human Visual Cortex

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Introduction

The fMRI technique typically assumes that the BOLD signal at an activated voxel results from the convolution of external stimuli with a linear time-invariant system. However, a number of previous studies have demonstrated a nonlinear stimuli-to-BOLD relationship[1,2] (i.e. the BOLD nonlinearity), which may reflect a nonlinear neural response to stimuli and/or a nonlinear vascular response to neural activity. To pinpoint the origin of the BOLD nonlinearity, we investigated the nonlinear effects of neural and vascular responses to sustained visual stimuli with variable temporal frequency ranging from 1/6 to 25 Hz, with the aid of a mathematical model (see Fig. 1) describing the cascaded interactions between stimuli, neural and hemodynamic responses[3].

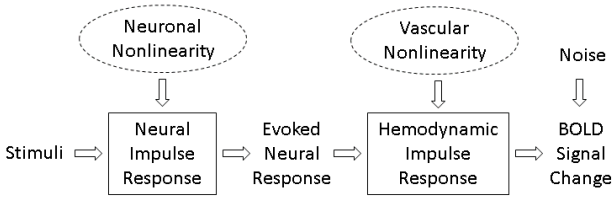

Fig. 1 A system model describing the cascaded processes from brain stimuli to BOLD fMRI signals.

Methods

To investigate the *neural response nonlinearity*, we recorded EEG signals (SynAmp[2], Neuroscan, USA) from 5 subjects presented with sustained (>1 min) full-screen reversal black-and-white checkerboard visual stimuli. When the stimuli were presented with a 2-sec inter-stimulus interval (ISI), we obtained the visual evoked potential (VEP) at the Oz channel through averaging over >1000 trials. When the stimuli were presented with short ISIs ranging from 40 to 533 ms, we obtained the sustained steady-state VEP (SSVEP) oscillating at the stimulus frequency. The frequency spectra of the measured SSVEP were compared with those of the predicted SSVEP resulting from the convolution of the stimuli (i.e. a train of delta functions spaced by the ISI) with the VEP. The recovery coefficient (RCC), defined as the ratio between the discrete integral of the measured and predicted SSVEP spectra, was computed for each individual ISI. To investigate the *vascular response nonlinearity*, we recorded BOLD-fMRI signals (3T Siemens Trio scanner, Germany) from 10 subjects presented with quarter-circular grating visual stimuli with either 100% or 10% contrast. Each fMRI experiment involved several 30-sec blocks with sustained stimuli interleaved with 30-sec resting blocks. Different ISI values from 0.25 to 6 sec were applied to different stimulus blocks. The BOLD signals measured at the primary visual cortex (V1) were compared with the predicted responses obtained through convolving the stimuli (a train of delta functions) with a canonical hemodynamic response function (HRF). The BOLD effect size, defined as the ratio between the measured and predicted BOLD signals, was computed for each ISI through the linear regression with a general linear model. When the linearity holds true for both neural and vascular responses, the BOLD effect size should reflect the integrated neural impulse response[3] and remain constant for different ISIs.

Results

The SSVEP spectra peaked at the stimulus frequency and its harmonics up to 40 Hz. As shown in Fig. 2, small RCC values (<1) indicating the neural refractory effect were found mainly at short ISIs (<200 ms), whereas the RCC remained around 1 for longer ISIs. This refractory effect can be well represented by an exponential function of ISI with the time constant of 69 ms and the limit value of 1.01, suggesting that the linearity holds true for the steady-state visual evoked neural response when ISI>200 ms. In contrast, the fMRI experiment revealed a nonlinear BOLD response to sustained visual stimuli even with ISI>250 ms. When ISI<4 sec, the measured BOLD signals were significantly smaller than what a linear neurovascular coupling system would predict based on the external stimuli, as shown in Fig. 3. The observed BOLD nonlinearity had an exclusively vascular origin, since the neural response nonlinearity was effectively ruled out for ISI>250 ms (see Fig. 2). As shown in Fig. 4, when ISI>4 sec the stimuli-to-BOLD relationship appeared to be linear, and the BOLD effect size remained virtually unchanged for ISIs from 4 to 6 sec. Figure 4 also shows that the nonlinear BOLD effect did not differ between 100% and 10% contrasts. In both cases, the nonlinear effect disappeared when ISI>4 sec. Since the 100% contrast elicited a significantly larger BOLD response at V1 than 10%, this result indicates that the vascular nonlinearity is independent of the absolute level of the BOLD response.

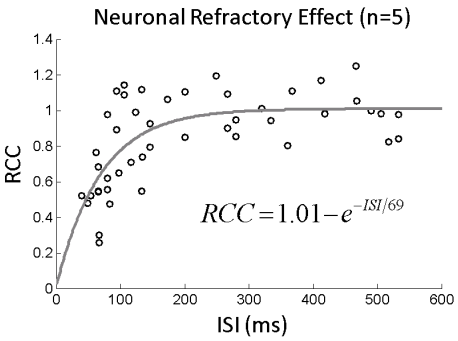

Fig. 2 Ratio between the measured and predicted SSVEP spectral integrals at different ISIs.

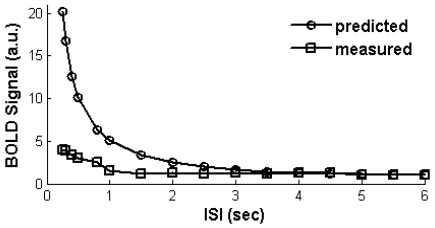

Fig. 3 Comparison between the measured and predicted BOLD heights after normalizing them to the BOLD heights for ISI=6 sec.

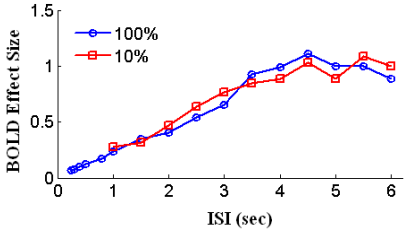

Fig. 4 BOLD effect sizes vs. ISI for stimuli with 100% (blue) and 10% (red) visual contrast.

Conclusion & Discussion

The present study has quantitatively evaluated the neural and vascular response nonlinearity in the human visual cortex. The neural nonlinearity exists only at very short ISI (<200 ms); at longer ISI, the evoked neural response can be regarded as the output of a linear system with sustained stimulus inputs. The vascular nonlinearity is exclusively responsible for the BOLD nonlinearity for 0.25<ISI<4 sec, and the nonlinear effect is dependent only upon the ISI value, rather than the absolute BOLD response level. Therefore, we can further attribute the vascular nonlinearity to the vascular refractory effect instead of the vascular saturation (or ceiling) effect, because the latter also implies that a smaller response should reach saturation for shorter ISIs.

The present study successfully distinguishes the neural and vascular origins of the BOLD nonlinearity, and provides important insights to further advance our current understanding of BOLD-fMRI signals in relation to neural activity as well as external stimuli or tasks.

References: 1. *Zhang et al. NeuroImage, 2008*; 2. *Birn et al. NeuroImage, 2005*; 3. *Liu & He. NeuroImage, 2008.*

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