Influence of Spontaneous BOLD Fluctuation on Stimulus-Evoked BOLD in Human Visual Cortex using Event-related Paradigm

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Introduction The blood oxygen level dependent (BOLD) signals acquired at the resting state without any stimulation have been found to fluctuate coherently within many brain networks of many species[1], which were believed to reflect spontaneous neuronal activities and functional connectivity of the brain. Such coherent spontaneous activity has also been demonstrated to account for trial-to-trial variability of event-related BOLD responses in a functional study focusing on sensory motor areas[2]; therefore, it was hypothesized[1,2] that such spontaneous activity and stimulus-induced activity could be linearly superimposed in the human brain. In contrast, another study[3] employing continuous, sustained visual stimulations found that the BOLD signals from the activated brain regions fluctuate differently from those from inactivated regions and formed a new coherent network in the activated visual cortex. There are at least two possible reasons to explain this discrepancy. First, the instantaneous stimulus used for even-related fMRI studies would only induced a very brief change on the spontaneous brain activities, like a Dirac delta function in the time scale of BOLD responses; therefore, the BOLD responses provoked by short stimuli could be linearly superimposed on those induced by ongoing spontaneous activities if we assumed a linear system from neural activity to BOLD signal. However, when the spontaneous activity is constantly interrupted by continuous stimuli, the linear superimposition hypothesis can not be applied; because the "spontaneous" and "stimulus-induced" brain activities could not actually coexist at the same time due to significant suppression of spontaneous brain activities. The second and less likely reason is that these two studies focused on two different sensory systems: motor and visual systems, which might have different responses to external stimulations. The present study is to test if the linear superimposition hypothesis also works for the visual system when instantaneous stimuli are used and thus exclude the second possibility.

Method Four healthy subjects were scanned on a 4T/90 cm bore magnet (Oxford, UK) with the Varian INOVA console (Varian Inc., Palo Alto, CA) and a ^{1}H RF surface coil. For the fMRI experiments, GE-EPI (FOV = 20×20 cm^2; TR/TE = 1000/30 ms) was used to acquire 3 adjacent coronal image slices (64×64 image matrix size; 5 mm thickness) covering the calcarine fissure based on the anatomical MRI information. The radial red-black checkerboard flashing at 8 Hz with a white cross-mark in the center was presented in the right side of the subjects' visual field for activating the contralateral visual cortex. The BOLD signals were acquired under three conditions. For the block-design fMRI runs (150 GE-EPI volumes per run), the half-field visual stimulus was applied during two stimulated blocks (30 second each) which were sandwiched by three control blocks with only the cross mark. The data were first preprocessed and then cross-correlated with the experimental paradigm to generate functional activation maps. The preprocessing includes dropping the first 10 volumes, motion correction, and normalization. For the resting state runs (225 GE-EPI volumes per run), the subjects were instructed to close their eyes and refrain from cognitive, language, or motor tasks. After being preprocessed and bandpass filtered (0.005~0.1 Hz), the GE-EPI time courses of all the pixels were cross-correlated with the time course from the most activated region (based on functional activation map) to create a correlation map for each run. For the event-related fMRI runs (190 GE-EPI volumes per run), a single half-field visual stimulus was presented instantaneously every 30 second; and the GE-EPI data from those runs were normalized and cut into 30-second epochs. There are totally 132 trials (epochs) from four subjects.

Result Based on the functional activation maps and the resting-state correlation maps, three regions of interest (ROIs) were defined as the following: **L**eft **A**ctivated **V**isual **C**ortex (**LAVC**) is the primary visual cortex region showing strong activation to the half-field stimulus (according to the activation maps). **R**ight **C**oherence **V**isual **C**ortex (**RCVC**) is the visual cortex region in the right hemisphere showing strong coherent BOLD fluctuations with **LAVC** at the resting state (according to the resting-state correlation maps). **R**ight **N**on-coherence non-**V**isual **C**ortex (**RNVC**) is also in the right hemisphere and have the similar signal to noise ratio (SNR) as **RCVC,** but outside the primary visual cortex and had only weak correlations with **LAVC** at the resting state. The functional activation map, the resting-state correlation map, and three ROIs from Subject 1 are demonstrated in Fig. 1 as an example.

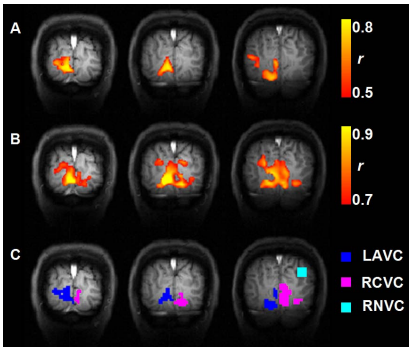

Fig. 1 (A) Functional activation map; (B) resting-state correlation map; (C) three ROIs from Subject 1.

The event-related fMRI data (132 trials) were spatially averaged within three ROIs to obtain BOLD response curves in each ROI and for each trial (Fig. 2A). When the BOLD fluctuations in **RCVC** were subtracted from the corresponding BOLD responses in **LAVC**, the trial-to-trial variation was significantly reduced. By comparing across-trial standard deviations of the data before and after subtraction (Fig. 2B, upper panel), we estimate that the trial-to-trial variation was reduced by 42%. In contrast, if the BOLD fluctuations in **RNVC** were used for subtraction, the trial-to-trial variation was not reduced but increased roughly by 28% (Fig. 2B, lower panel), presumably, owing to the incoherent BOLD signal fluctuations between **LAVC** and **RNVC.** These results suggest that the reduction of trial-to-trial variation is not due to the subtraction of global brain fluctuations but owe to the removal of "spontaneous" BOLD fluctuations intrinsic to the resting-state visual networks.

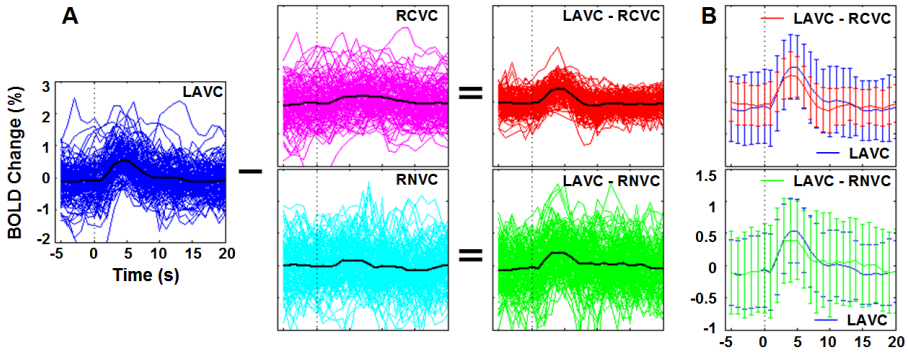

Fig. 2 BOLD response curves of different trials (132 trials in total). (A) The BOLD response curves of all trials and their averaged time courses from three ROIs, and their corresponding differences. (B) The mean and standard deviation of BOLD responses (across trials).

Discussion and Conclusion Our results clearly show that the trial-to-trial variation of event-related BOLD responses in the activated visual cortex is largely due to the underlying spontaneous and coherent BOLD fluctuations. This finding is consistent with the former observation in human somatomotor system[2]. Moreover, we also demonstrated that the trial-to-trial variation is specifically affected by the spontaneous BOLD fluctuations within the same resting-state network of visual system rather than the global brain BOLD fluctuations. In future studies, such effect should be taken into account when interpreting the event-related BOLD responses.

After ruling out the second possibility that the difference of motor and visual systems accounts for the discrepancy of previous studies, we should grant more credits to the first explanation. The instantaneous stimuli used by event-related studies would only perturb the spontaneous brain activity briefly and slightly and thus result in the linear superimposition of BOLD signals; while the continuous stimuli could change the brain activity to an entirely new state and therefore the linear superimposition hypothesis may not hold. However, to further verify this explanation, more studies, especially those involving the electrophysiological signal measurement, are needed.

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References 1. *Fox, MD. et al. Nat Rev Neurosci 2007;* 2. *Fox, MD. et al. Nat. Neurosci. 2002;* 3. *Liu X. et al. ISMRM 2008 p.*2412.