Probing Fast Neuronal Interaction Based on Fundamental Hemodynamic Signals

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Introduction

BOLD based fMRI with the advantages of high spatial resolution and large coverage (whole brain) is most widely used as a mapping tool of brain function. The sluggish fMRI signal response on the scale of seconds, however, makes it very difficult to extract detailed temporal information of single neuronal events occurring in tens to hundreds of milliseconds. To overcome this obstacle, a novel fMRI approach that embeds fast temporal information of neuronal interaction into BOLD amplitude changes has been introduced recently[1]. The approach, when combined with a paired-stimuli paradigm (two short stimuli with a variable inter-stimulus interval (ISI) between them) which is used to elicit desired neuronal interaction, has been demonstrated to be capable of extracting temporal information of fast neuronal interaction.

Since the temporal information of neuronal interaction is reflected from the corresponding BOLD amplitude changes, one critical assumption of using this dynamic fMRI approach to probe fast neuronal interaction is that neuronal activity is linearly correlated with BOLD amplitude. However, BOLD signal depends on interplay among multiple physiologic parameters of CBF, CBV and $CMRO_2$, and the relationships among these fundamental vascular and metabolic changes induced by neuronal activity can be very complicated and remains a controversial topic of ongoing research. As a result, the interpretation of BOLD amplitude change, particularly when the conclusion virtually relies on this subtle change, can be ambiguous. To resolve this ambiguity and fundamentally establish the dynamic fMRI approach in exploring both temporal and spatial characteristics of neuronal interaction at various functional levels, it is necessary to study basic hemodynamic and/or metabolic changes including CBF, CBV and $CMRO_2$ during neuronal interaction. In this study, we have simultaneously measured BOLD and CBF responses to a paired-stimuli paradigm that can elicit different refractory responses of neurons in human primary visual cortex. Based on this measurement, we also estimated the corresponding $CMRO_2$ changes at various refractory levels. The corresponding neuronal activity has been quantified by the visual evoked potential (VEP) signal measured using the same paradigm.

Method

Visual stimulation was generated by a pair of LED goggles (Grass Instruments, Quincy, MA). All fMRI studies were performed on a 4T/90 cm bore magnet (Oxford, UK) system with the Varian INOVA console (Varian Inc., Palo Alto, CA). For the perfusion measurements: flow-sensitive alternating inversion recovery (FAIR) images[2] (FOV = 20×20 cm^2; 64×64 image matrix size; TI = 1.4 s, TE = 24 ms; TR = 4 s, 1 coronal slice, 5 mm slice thickness) located in the calcarine fissure were acquired. BOLD signal was obtained from non-selective inversion recovery images acquired during the acquisition of FAIR images. FMRI experiment was conducted in a block design manner. During the task period, a pair of short flashes (10 ms duration for each flash) with a selected ISIs (100 ms, 200 ms, 300 ms, 400 ms, 600 ms and 800 ms) was repeatedly presented with a relatively long inter-trial-interval (ITI = 2 s) to avoid refractory interference between consecutive pairs[1]. Each fMRI run was composed of three task periods (8 pairs of FAIR images each), sandwiched by four control periods (8 pairs of FAIR images each) when subject was in uniform darkness. The same ISI was used within each run and six fMRI runs corresponding to six different ISIs were acquired for each study. One additional run with the same experimental setting except that a single flash was repeatedly presented (ITI = 2 s) during the task period was acquired as a calibration control. VEP signal was acquired inside an electrically shielded room using a 64-channel EEG system (BrainAmp MR 64 Plus, BrainProducts, Germany). The paradigm was the same as that used in the fMRI experiment. The VEP signal for each task was averaged from 200 trials.

CBF and BOLD activation maps were generated using the cross correlation (CC) method. The voxels located at the proximity of calcarine fissure were included in the region of interest (ROI) and the time course for each task was averaged from the activated ROI voxels with CC > 0.45. BOLD contamination in CBF signals was corrected. $CMRO_2$ responses at different ISIs were estimated using Davis's model[3] based on CBF and BOLD signals. All data were normalized to the single flash task.

Results

Fig. 1 shows the event related potential (ERP) peak from the 'Oz' channel from the single-flash condition and the ERP peaks from the second flash of paired-flash conditions. The refractory inhibitory effect is clearly seen from ERP amplitudes. Compared with the single-flash condition, the ERP from the second flash in a paired-flash condition is significantly suppressed when ISI is short, whereas when ISI is long, the ERP signal recovers. The same pattern was also observed in CBF signals as shown in Fig. 2. At short ISIs, CBF responses to paired flashes are close to that in the single-flash condition (relative CBF amplitudes are close to 1) indicating the CBF signals from the second flashes are significantly suppressed, whereas the CBF signal gradually recovers as ISI gets longer.

Fig. 3 shows the correlation between relative CBF and relative BOLD at various refectory inhibition levels. Fig. 4 shows the correlation between relative CBF and relative $CMRO_2$ at various refectory inhibition levels. Both BOLD and $CMRO_2$ have good linear correlation with CBF.

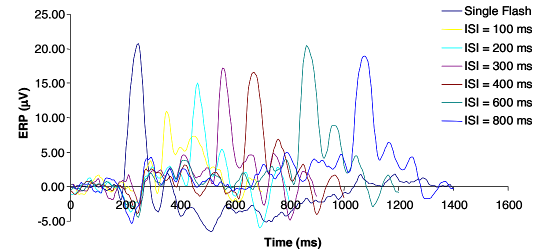

Fig. 1. Event related potential (ERP) peaks from single flash and the second flash of paired flashes at different ISIs from one subject.

Discussion and Conclusion

The experimental results suggest that the dynamic fMRI approach combined with a paired-stimuli paradigm can be used to extract fast temporal information of neuronal interaction with the signal sources of BOLD or basic hemodynamic and metabolic responses. This result is consistent with the finding that BOLD signal is linearly correlated with CBF signal as suggested by both biophysical models[4] and experimental measurement[5]. The data in this study can further validate the feasibility of using fMRI to provide both detailed temporal and spatial information of neuronal interaction.

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Reference

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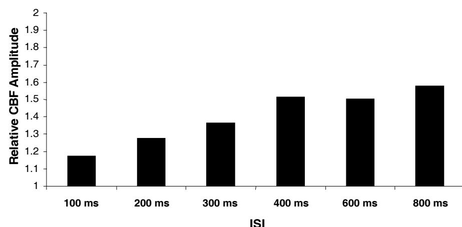

Fig.2. Relative CBF amplitudes at different ISIs (n = 6). All data were normalized to the single flash condition.

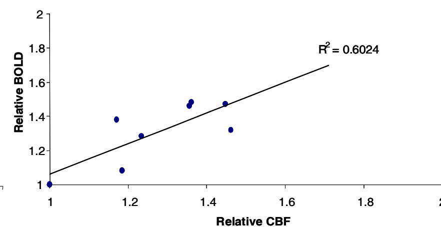

Fig.3. Correlation between relative CBF and relative BOLD at different ISIs (All data were normalized to the single flash condition).

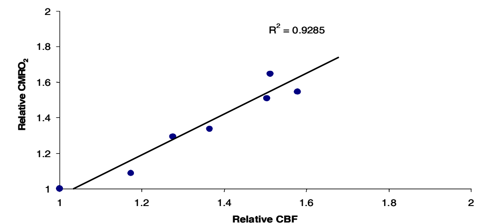

Fig.4. Correlation between relative CBF and relative $CMRO_2$ at different ISIs (All data were normalized to the single flash condition).