A Non-invasive Study of Neurovascular Coupling

N. Zhang[1], Z. Liu[2], B. He[2], and W. Chen[1,2]

[1]Radiology, University of Minnesota, Minneapolis, MN, United States, [2]Biomedical Engineering, University of Minnesota, Minneapolis, MN, United States

Introduction

Local neuronal activity is always spatially accompanied with local vascular and/or metabolic changes. These secondary physiologic changes, including CBF, CBV and $CMRO_2$, have been utilized as indirect signal sources for mapping brain function by a group of neuroimaging techniques such like functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). However, spatial coupling between local neuronal and vascular activities does not necessarily imply a strong correlation in amplitude changes between them. Therefore, quantitatively understanding the relationship of neurovascular coupling is pivotal in interpreting all perfusion-related neuroimaging signals.

The quantitative relationship of neurovascular coupling remains inconclusive and inconsistent results have been reported in the literature[1-3]. For example, Devor et al observed a power-law relationship between neuronal activity and hemodynamic response[1]. Martin et al reported a linear correlation between summed neuronal activity and peaked hemodynamic response in the awake rat whereas a strong nonlinear correlation in anesthetized animals[2]. Sheth et al suggested the neurovascular coupling relationship can be better described by a nonlinear power law or a threshold model compared to a linear model[3]. The factors that could cause the discrepancies mentioned above include anesthesia and difficulty in quantifying absolute neuronal activity, particularly when several types of neuronal interactions (e.g. refractory inhibition) are involved at the same time. Martin et al has demonstrated that anesthesia has a substantial effect on both the temporal and amplitude characteristics of neuronal and hemodynamic responses[2]. Therefore, an experimental design that can provide precise quantification of neuronal and hemodynamic activities without involving any anesthesia should be an ideal model in quantitatively addressing the issue of neurovascular coupling. In this study, in stead of attempting to quantify absolute neuronal activity, we calibrated all the neuronal and hemodynamic activities to a constant activation condition when no neuronal interaction was involved (a single short flash light repeatedly presented every 2 s). We utilized a paired-stimuli paradigm (two short flashes with a variable inter-stimulus interval (ISI) between them) that can elicit various levels of refractory response of neurons in human visual cortex to modulate neuronal and hemodynamic activities. We have simultaneously measured the BOLD and CBF responses to this paradigm. The corresponding neuronal activities have been quantified by the visual evoked potential (VEP) signals 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 (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 the 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) between them was repeatedly presented with a relatively long inter-trial-interval (ITI = 2 s) to avoid refractory interference between consecutive pairs[4]. 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 the 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 condition 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. All data were normalized to the single flash task.

Results

Fig. 1 shows the integrals of VEP peaks from the 'Oz' channel at different ISIs. The data indicate that neuronal activity is significantly suppressed when ISI is short. The suppression is entirely induced by inhibition of neuronal response to the second flash in the paired-flash conditions (data not shown). When ISI gets longer, refractory inhibition response disappears and the neuronal activity gradually recovers. Similar pattern is also observed in CBF and BOLD signals (CBF signals were shown in Fig. 2.). Fig. 3 shows the correlation between relative CBF and relative VEP. Strong correlation between VEP and CBF indicates a tight coupling between neuronal activity and hemodynamic response.

Discussion and Conclusion

Since all the activities are calibrated to a constant activated condition (i.e. single flash stimulation), this quantification method allows inter- and intra-subject comparison of neuronal, hemodynamic and metabolic responses at a variety of neuronal interaction conditions. More importantly, it allows a direct and quantitative comparison of activities from the signals of different imaging modalities (e.g. between VEP and CBF) at the same neuronal interaction condition regardless the absolute signal change. In this study, we modulate neuronal and hemodynamic activities by manipulating refractory level of the same neuronal group. We find a tight correlation between neuronal and hemodynamic activities. The results suggest that this approach should allow a precise determination of the neurovascular coupling relationship without being confounded by the factors such like anesthesia.

Acknowledgements

NIH RO1 grants of EB00329, NS41262, NS39043, EB00513, EB00178 and P41 RR08079, NSF BES-0411898, and the MIND institute.

Reference

1. *Devor A, et al. Neuron 2003;39(2):353-359.*
2. *Martin C, et al. Neuroimage 2006;32(1):33-48.*
3. *Sheth SA, et al. Neuron 2004;42(2):347-355.*
4. *Ogawa, S. et al. PNAS 2000; 97(20): 11026-31*

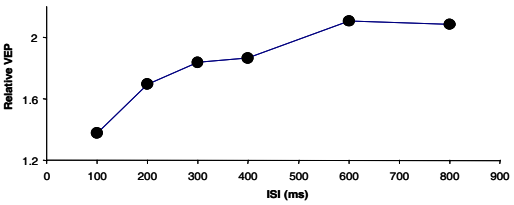

Fig. 1. Relative VEP integrals at different ISIs. The signal is normalized to the single-flash condition.

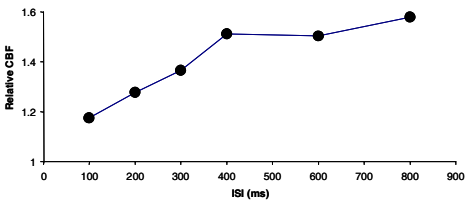

Fig. 2. Relative CBF amplitudes at different ISIs. The signal is normalized to the single-flash condition.

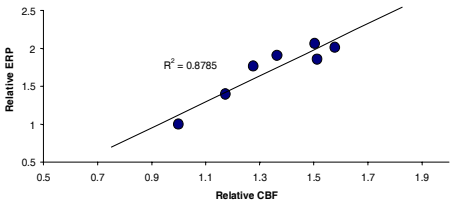

Fig. 3. Correlation between relative VEP and relative CBF signals.