Neuroscience 248 (2013) 529–540

BINOCULAR ACTIVATION ELICITS DIFFERENCES IN NEUROMETABOLIC COUPLING IN VISUAL CORTEX

B. LI AND R. D. FREEMAN *

Group in Vision Science, School of Optometry, Helen Wills Neuroscience Institute, University of California at Berkeley, Berkeley, CA 94720-2020, USA

Abstract—Non-invasive brain imaging requires comprehensive interpretation of hemodynamic signals. In functional magnetic resonance imaging, blood oxygen level dependent (BOLD) signals are used to infer neural processes. This necessitates a clear understanding of how BOLD signals and neural activity are related. One fundamental question concerns the relative importance of synaptic activity and spiking discharge. Although these two components are related, most previous work shows that synaptic activity is better reflected in the BOLD signal. However, the mechanisms of this relationship are not clear. The BOLD signal depends on relative changes in cerebral blood flow and cerebral metabolic rate of oxygen. Oxygen metabolism changes are difficult to measure with current imaging techniques, but it is possible to obtain direct quantitative simultaneous *in vivo* measurement of tissue oxygen and co-localized underlying neural activity. Here, we use this approach with a specific binocular stimulus protocol in order to activate inhibitory and excitatory neuronal pathways in the visual cortex. During excitatory binocular interaction, we find that metabolic, spiking, and local field potential responses are correlated. However, during suppressive binocular interaction, spiking activity and local field potentials (LFP) are dissociated while only the latter is coupled with metabolic response. These results suggest that inhibitory connections may be a key factor in the dissociation between LFP and spiking activity, which may contribute substantially to the close coupling between the BOLD signal and synchronized synaptic activity in the brain.
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Key words: neurometabolic coupling, binocular interaction; visual cortex.

INTRODUCTION

Noninvasive brain imaging has become a pervasive tool in both basic and clinical applications. Functional magnetic resonance imaging (fMRI) involves hemodynamic responses which are used to infer neural function. The blood oxygen level dependent (BOLD) signals that are measured depend on cerebral blood flow and volume and the cerebral metabolic rate of oxygen. However, the neurometabolic and neurovascular components of BOLD signals are not understood at a level sufficient for clear interpretation of fMRI signals. One obvious question concerns the nature of neural activity represented by the BOLD signal. The two relevant measures of electrophysiological measurement are action potentials that form the output spiking activity and local field potentials (LFP) that are considered to represent the input of synaptic processes. Although they are related, it is believed that synchronized synaptic activity is better reflected in the BOLD response than spiking output (Logothetis et al., 2001). However, the details of this association are not clear.

In previous studies on relationships between neural and metabolic factors, we made simultaneous co-localized measurements of neuronal activity and tissue oxygen concentration in the cerebral cortex (Thompson et al., 2003, 2004, 2005; Li and Freeman, 2007; Viswanathan and Freeman, 2007; Li and Freeman, 2010, 2011). Tissue oxygenation is directly related to the BOLD signal as follows. Activated neurons require oxygen which is provided by cerebral blood flow. The BOLD signal is a measure of deoxyhemoglobin change that occurs as tissue oxygen is increased. In a previous study, we used visual stimuli at high temporal frequencies which activate spiking activity of neurons in the thalamus but not the visual cortex. We found that the LFP signals were correlated with tissue oxygen even when spiking discharge was minimal (Viswanathan and Freeman, 2007). This implies that synaptic activity may contribute more to the BOLD signal than spiking discharge as found in previous work (Logothetis et al., 2001; Bartolo et al., 2011).

To examine underlying mechanisms of the dissociation between the two components of neural activity and their coupling with metabolic response, we use an approach here which clearly dissociates spiking response and synaptic activity in the visual cortex. The visual stream from left and right eyes is first physiologically combined in striate cortex. With dichoptic presentation of sinusoidal gratings at various relative interocular phases, neurons in striate cortex generally exhibit both facilitation and suppression in binocular interaction profiles (Freeman and Robson, 1982;

*Corresponding author. Address: 360 Minor Hall, University of California at Berkeley, Berkeley, CA 94720-2020, USA. Tel: +1-510-642-6341; fax: +1-510-666-2062.
E-mail address: rfreeman@berkeley.edu (R. D. Freeman).
Abbreviations: ANOVA, analysis of variance; BOLD, blood oxygen level dependent; fMRI, functional magnetic resonance imaging; LFP, local field potentials; LGN, lateral geniculate nucleus; MUA, multiple unit activity; RF, receptive field; s.e.m, standard error of the mean.

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http://dx.doi.org/10.1016/j.neuroscience.2013.06.036

Ohzawa and Freeman, 1986; Freeman and Ohzawa, 1990; Ohzawa et al., 1990; Chino et al., 1994; Truchard et al., 2000). During facilitation, there is an increase in spiking activity, and in suppressive states there is a reduction in action potential events. Because inputs from the lateral geniculate nucleus (LGN) to striate cortex are exclusively excitatory (Ferster et al., 1996), the suppression of spiking activity may derive from intracortical inhibitory drives, which are reported to enhance synchronized gamma oscillation synaptic activity while reducing spiking activity (Traub et al., 1996; Tamas et al., 1998; Whittington and Traub, 2003). Therefore, spiking output and synaptic activity may be dissociated when binocular suppression is activated by visual stimuli at certain interocular phases. We utilize this type of binocular interaction during simultaneous recordings of neural activity and oxygen concentration. We have analyzed spiking multiple unit activity (MUA) and LFP along with both components (initial dip and positive peak) of the biphasic tissue oxygen concentration responses. Our results show that LFP and spiking activity are both coupled to oxygen metabolism during excitatory binocular interaction. In marked contrast, during suppressive binocular interaction, there is a dissociation of the two forms of neural activity, such that LFP signals are coupled with oxygen metabolism but spiking activity is not.

EXPERIMENTAL PROCEDURES

Surgical procedure and preparation

Mature cats (2.9–4.0 kg, 5–10 months old) were prepared for physiological experiments as described previously (Thompson et al., 2003; Li and Freeman, 2007). All procedures were conducted in accordance with guidelines by NIH and by the Animal Care and Use Committee at the University of California, Berkeley. For every experiment, the animal was initially anesthetized with isoflurane (2–3%, adjusted individually for each animal). A catheter was inserted into a femoral vein in each leg for intravenous infusion. A tracheal cannula was positioned and the animal was then secured in a stereotaxic apparatus. Isoflurance was stopped and anesthesia was maintained with intravenous infusion of propofol (15–20 mg/(kg h)) and fentanyl (10.0 μg/(kg h)). The animal was artificially ventilated with a mixture of 25% O_2 and 75% N_2O. Expired CO_2 was maintained at 32–38 mmHg and body temperature was kept at around 38 °C. A craniotomy was performed above the central representation of the visual field in the striate cortex (Horsley-Clark coordinates P4 L2). The dura was dissected away to allow insertion of a microelectrode. Agar and wax were applied to create a closed chamber. Following surgery, the infusion rate of fentanyl was reduced to 4 μg/(kg h) and the rate of propofol was gradually reduced to 6–10 mg/(kg h) as determined individually for each animal. After the anesthesia was stabilized, paralysis was then induced to prevent eye movements with pancuronium bromide (0.2 mg/(kg h)). Pupils were dilated with 1% atropine sulfate and nictitating membranes were retracted with 5% phenylephrine HCl. Contact lenses with 4-mm artificial pupils were applied to protect the corneas. Lactated Ringer with 5% dextrose was intravenously infused at a rate of 4 ml/(kg h). Electroencephalography (EEG), electrocardiography (ECG), expired CO_2, and intra-tracheal pressure were monitored throughout the experiment, which typically lasted 3–4 days. An overdose of pentobarbital sodium was given to the animal at the end of each experiment.

Visual stimulation

Drifting sinusoidal gratings were presented simultaneously on two CRT monitors. Refresh rate of the monitors was 85 Hz. For each recording site, preliminary subjective estimations were made to determine approximate preferred orientation, spatial and temporal frequency, and size and position of the receptive field (RF) for each eye. We then obtained quantitative tuning functions to be used in experimental protocols. In all cases, contrast level, mean screen luminance, and stimulus duration were 50%, 45 cd/m^2, and 4 s, respectively. Visual stimulus interval values were randomly varied from 30 to 44 s to avoid synchrony with spontaneous oscillations in the baseline oxygen signal. We fixed the initial phase of the grating presented to the dominant eye and varied that to the non-dominant eye in 60° steps over a full range of 360°. This results in six different relative phases in the binocular mode. Since gratings for both eyes drift at the same rate, relative phase of the gratings between the two eyes remains constant during stimulus presentation. In addition to dichoptic presentation, a monocular stimulus presented to the dominant eye is included as a control condition in the stimulus protocol. All stimulus conditions were interleaved randomly and sequences were repeated in multiple trials (16–80).

Data recording

We used a double barrel APOX microelectrode (Unisense, Aarhus, Denmark) in the experiment. A Clark style (Fatt, 1976) polarographic oxygen sensor and a platinum microelectrode were enclosed in the APOX (30 μm in tip size) for simultaneous measurements of co-localized tissue oxygen and neural responses. The spherical sensitivity region of the oxygen sensor is roughly 60 μm in diameter (Thompson et al., 2003). The APOX microelectrode was advanced into the striate cortex via a micro-manipulator until visually driven spiking activity was identified. Penetrations were made along the medial bank of the postlateral gyrus from H-C coordinates P4L2 at an approximate angle of 10° medial and 20° anterior. A high impedance picoammeter was used for sensing the small currents generated by the oxygen sensor. Sampling rate for tissue oxygen signals was 10 Hz. Impedance of the tungsten electrode for neural signal recording was 0.3–0.8 MΩ at 1 kHz in 0.9% saline at 38 °C. Neural signals were amplified and filtered to generate extracellular MUA (0.25–8 kHz) and LFP signals (0.7–170 Hz). Sampling rates were 25 kHz and 500 Hz for MUA and LFP signals, respectively.

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