*Neuroscience* 213 (2012) 112–121

# SPATIAL SUMMATION OF NEUROMETABOLIC COUPLING IN THE CENTRAL VISUAL PATHWAY

**B. LI AND R. D. FREEMAN** *

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

**Abstract—Noninvasive neural imaging has become an important tool in both applied and theoretical applications. The hemodynamic properties that are measured in functional magnetic resonance imaging (fMRI), for example, are generally used to infer neuronal characteristics. In an attempt to provide empirical data to connect the hemodynamic measurements with neural function, we have conducted previous studies in which neural activity and tissue oxygen metabolic functions are determined together in co-localized regions of the central visual pathway. A basic question in this procedure is whether oxygen responses are coupled linearly in space and time with neural activity. We have previously examined temporal factors, and in the current study, spatial characteristics are addressed. We have recorded from neurons in the lateral geniculate nucleus (LGN) and striate cortex in anesthetized cats. In both structures, there is a classical receptive field (CRF) within which a neuron can be activated. There is also a region outside the CRF from which stimulation cannot activate the cell directly but can influence the response elicited from the CRF. In this investigation we have used several specific spatial stimulus patterns presented to either the CRF or the surrounding region or to both areas together in order to determine spatial response patterns. Within the CRF, we find that neural and metabolic responses sum in a nonlinear fashion but changes in these two measurements are closely coupled. For stimuli that extend beyond the CRF, neural activity is generally reduced while oxygen response exhibits uncoupled changes. Published by Elsevier Ltd. on behalf of IBRO.**

**Key words: tissue oxygen, neural activity, spatial summation, visual stimulus.**

## INTRODUCTION

The rapidly increasing use of noninvasive neural imaging techniques as a central procedure in a wide range of basic and applied applications requires appropriate interpretation of the measurements that are made. The main current technique, functional magnetic resonance imaging (fMRI) involves estimates of changes in hemodynamic activity from which neural function is implied. The changes in hemodynamic events involve various metabolic processes that underlie neural activity. We have conducted studies intended to elucidate some of the basic relationships between the neural and metabolic functions that are involved. For this purpose we have recorded from single and multiple cells and have used a co-localized sensor to determine changes in tissue oxygen levels during visual stimulation. The measured changes in oxygen concentration are presumed to follow energy demands from activated neural activity. We assume that the rules of the neurometabolic coupling that we determine are directly applicable to interpretation of noninvasive imaging procedures.

As cortical neurons are activated by a stimulus, a hemodynamic response is produced. This process includes local increases in oxygen metabolism, cerebral blood flow and cerebral blood volume, which in combination, determines the blood oxygenation level-dependent (BOLD) response function in fMRI. The BOLD signal is complex, with a brief initial dip that presumably reflects an increase in deoxyhemoglobin concentration from oxygen consumption by activated neurons, followed by a prolonged positive peak that results from an influx of oxygenated hemoglobin with increased blood flow. This is generally followed by an undershoot that may be accounted for by a reduced cerebral blood flow and a slow return of steady-state cerebral oxygen consumption and cerebral blood volume (see reviews, (Brown et al., 2007; Kim and Ogawa, 2012)). The positive BOLD signal has been widely used to probe brain function. The initial dip, however, is relatively small and unreliable, and is often not readily measurable (Buxton, 2001). However, it has been observed in both optical imaging and fMRI studies (Malonek and Grinvald, 1996; Kim et al., 2000). We have obtained analogous data in previous work by use of a dual sensor housed in a double micro-capillary tube by which simultaneous measurements of neural and tissue oxygen responses may be made in co-localized regions in the central visual pathway. Similar to the BOLD signal, tissue oxygen response generally exhibits a small initial dip followed by a large positive peak. The initial dip presumably reflects an increase in oxygen consumption by activated neurons, and the positive peak reflects a rise of oxygen concentration from an activity-dependent increase in blood flow (Thompson et al., 2003, 2004, 2005; Li and Freeman, 2007, 2010, 2011). We have found that the

*Corresponding author. Address: 360 Minor Hall, University of California at Berkeley, Berkeley, CA 94720-2020, USA. Tel: +1-510-6426341; fax: +1-510-6423323.
E-mail address: freeman@neurovision.berkeley.edu (R. D. Freeman).
*Abbreviations:* BOLD, blood oxygen level dependent; CRF, classical receptive field; ECG, electrocardiogram; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; LGN, lateral geniculate nucleus; MUA, multiple unit activity.

0306-4522/12 $36.00 Published by Elsevier Ltd. on behalf of IBRO.
http://dx.doi.org/10.1016/j.neuroscience.2012.04.007

initial dip of tissue oxygen response is approximately linear with stimulus duration in the lateral geniculate nucleus (LGN). However, the positive peak exhibits a nonlinear property in temporal integration (Li and Freeman, 2007). The positive peak is the measurement of choice in the BOLD signals that are used in fMRI. Our previous results are consistent with other observations of nonlinear temporal summation in noninvasive neural imaging studies (Boynton et al., 1996; Robson et al., 1998; Vazquez and Noll, 1998; Liu and Gao, 2000; Birn et al., 2001; Miller et al., 2001; Soltysik et al., 2004; Gu et al., 2005).

In the current study, to evaluate spatial rules of neural and metabolic responses, we have made measurements of local changes in tissue oxygen and neural activity that follow activation with visual stimuli. We have made use of the fact that there are both a classical receptive field (CRF) and a region outside the CRF, which have influence on the neural response to a visual stimulus within the CRF but cannot activate a neuron directly (Freeman et al., 2001). We have differentially activated these two regions using specifically tailored visual stimuli. In both LGN and primary visual cortex, our results show that for visual stimuli within the CRF, neural and oxygen responses sum nonlinearly, but their coupling is largely linear. For large stimuli which exceed the boundaries of the CRF, however, this linear relationship breaks down, i.e., tissue oxygen signals are not coupled with neural activity.

## EXPERIMENTAL PROCEDURES

### Physiological preparation

Our general physiological procedures have been described in previous publications (Thompson et al., 2003, 2004, 2005; Li and Freeman, 2007, 2010, 2011). All procedures were conducted in accordance with guidelines by NIH and by the Animal Care and Use Committee at the University of California, Berkeley. We obtained data from 21 mature cats (2.5–4.2 kg) used for different experimental protocols. Animals were monitored by veterinary staff. At the start of each experiment, an animal was anesthetized with 3% isoflurane. After a few minutes, anesthesia level was reduced to 2–2.5% as adjusted individually for each animal. Following catheter placement in all four legs, isoflurane was stopped and anesthesia was maintained with intravenous infusion of pentothal sodium, starting at an infusion rate of about 6.0 mg/(kg h) and fentanyl at a rate of 10.0 μg/(kg h). During surgery, bolus injections of pentothal (10 mg/ml) were given as required. A tracheal cannula was positioned and the animal was artificially ventilated with a mixture of 25% $O_2$ and 75% $N_2O$. Expired $CO_2$ was maintained at 32–38 mm Hg and body temperature was kept at around 38 °C. A craniotomy was performed over area 17 at H–C P4 L2 or over LGN at A6L9. Relevant dura was then resected, and agar, then wax, was used to cover the aperture which formed a closed chamber. Following surgery, infusion of fentanyl was discontinued and pentothal was gradually reduced to a level required for steady-state anesthesia, as determined individually for each animal (generally 1–2 mg/(kg h)). General muscle relaxation was then induced to prevent eye movements with pancuronium bromide (0.2 mg/(kg h)). Lactated ringer with 5% dextrose was intravenously infused at a rate of 4 ml/(kg h). EEG, ECG, expired $CO_2$, and intra-tracheal pressure, were monitored throughout each experiment, which typically lasted for 4 days. An overdose of pentobarbital sodium was given to the animal at the end of each experiment.

### Visual stimulus

Visual stimuli consisted of drifting sinusoidal gratings of varying parameters. Prior to detailed measurements at a recording site, preliminary estimations were made to determine approximately preferred orientation, spatial frequency, and temporal frequency, as well as the size and position of the CRF for each eye. We then obtained tuning functions to quantitatively determine the parameters that were later used in experimental protocols. Visual stimuli were presented simultaneously on two CRT monitors. Refresh rate of the monitors was 85 Hz. We used a 100% contrast level for recordings from LGN. Neurons in visual cortex are more susceptible to contrast adaptation, so we used a 50% contrast level for measurements in area 17. In all cases, mean screen luminance was 45 cd/m$^2$. Each grating stimulus was presented for 4 s. In general, visual stimuli were presented monoptically to the dominant eye while the other eye viewed a blank screen with the same mean luminance. Visual stimulus interval values were randomly varied from 30 to 44 s to avoid synchrony with spontaneous oscillations in the baseline oxygen signal which are believed to be relevant to regional cerebral microcirculation (Mayhew et al., 1996). Stimulus conditions were interleaved randomly and sequences were repeated in multiple trials (16–64).

### Recording and analysis procedures

Tissue oxygen responses were measured with a Clark style (Fatt, 1976) polarographic oxygen sensor (Unisense, Aarhus, Denmark). Neural activity was recorded simultaneously with a platinum microelectrode enclosed in a double-barreled glass micropipette along with the oxygen sensor. The tip of the combined sensing system is around 30 μm. The spherical sensitivity region of the oxygen sensor is roughly 60 μm in diameter (Thompson et al., 2003). The sensing unit was controlled and advanced via a micro-manipulator. For recordings from the LGN, electrode penetrations were made vertically from H-C coordinates A6L9. For visual cortex, 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. The oxygen sensor was connected to a high-impedance picoammeter. Sampling rate for tissue oxygen signals was 10 Hz. Impedance of the neural electrode was 0.2–1.0 MΩ at 1 kHz in 0.9% saline at 38 °C. Neural signals were amplified and filtered to generate extracellular multiple unit activity (MUA, 0.25–8 kHz), which was sampled at rates of 25 kHz. Local field potential signals are not included in the analysis because they are generally weak and noisy in the LGN (Rasch et al., 2009; Li and Freeman, 2010).

Oxygen signals were averaged across multiple trials. Baseline levels 10 s prior to stimulus onset were subtracted from average oxygen signals. Oxygen responses were normalized by the mean oxygen levels in order to obtain percentages of change (Thompson et al., 2003). Spike rates 10 s prior to stimulus onset are defined as spontaneous activity which was subtracted from MUA.

Recording sites with significant tissue oxygen and neural responses to at least one stimulus condition were included for data analysis. Oxygen responses were evaluated to determine if there was a statistically significant change in the initial dip or subsequent positive peak compared with that of the baseline activity ($p < 0.05$, $t$-test). Similarly, MUA was considered significant if it was different from spontaneous activity ($p < 0.05$, $t$-test). The Wilcoxon signed rank test (signrank.m, Matlab function) was used to compare responses to paired stimuli with those of individual components that were summed together. Error estimates are in the form of standard errors of the mean (SEM), unless otherwise noted.

Download English Version:

https://daneshyari.com/en/article/4338459

Download Persian Version:

https://daneshyari.com/article/4338459

Daneshyari.com