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Intrinsic signal optical imaging of visual brain activity: Tracking of fast cortical dynamics

Haidong D. Lu[b,c,*], Gang Chen[a,c], Junjie Cai[d], Anna W. Roe[a,c,e]

[a] Interdisciplinary Institute of Neuroscience and Technology, Qiushi Academy for Advanced Studies, Zhejiang University, Hangzhou, China
[b] State Key Laboratory of Cognitive Neuroscience and Learning, Collaborative Innovation Center for Brain Science, Beijing Normal University, Beijing, China
[c] Department of Psychology, Vanderbilt University, Nashville, TN, USA
[d] Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, China
[e] Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, OR, USA

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ABSTRACT

Hemodynamic-based brain imaging techniques are typically incapable of monitoring brain activity with both high spatial and high temporal resolutions. In this study, we have used intrinsic signal optical imaging (ISOI), a relatively high spatial resolution imaging technique, to examine the temporal resolution of the hemodynamic signal. We imaged V1 responses in anesthetized monkey to a moving light spot. Movies of cortical responses clearly revealed a focus of hemodynamic response traveling across the cortical surface. Importantly, at different locations along the cortical trajectory, response timecourses maintained a similar tri-phasic shape and shifted sequentially across cortex with a predictable delay. We calculated the time between distinguishable timecourses and found that the temporal resolution of the signal at which two events can be reliably distinguished is about 80 milliseconds. These results suggest that hemodynamic-based imaging is suitable for detecting ongoing cortical events at high spatial resolution and with temporal resolution relevant for behavioral studies.

1. Introduction

Monitoring cortical events with both high spatial and high temporal resolution is crucially important for studying brain function. Most recording and imaging techniques, however, cannot meet both requirements simultaneously. The intrinsic signal optical imaging (ISOI) technique, which measures cortical reflectance change due to hemodynamic response (Grinvald et al. 1986), has high spatial resolution (on the order of 100 μm). Its temporal resolution, however, is believed to be very slow, taking 1–2 s to peak, followed by a long (up to 10 s) return to baseline. Because of this, ISOI is not considered useful for studying fast cortical events.

Our premise in this study is that extended signal timecourses and long delays to peak do not necessarily imply low temporal precision. In fact, we argue that if used properly, significant temporal information can be inferred from the response. Simply put, if two events occur at two different cortical locations with a small onset-time difference, and if the induced response timecourses are similar at the two sites, then the two responses should reach their peak with a similarly small time difference. This would happen regardless of a long delay to peak. Thus the temporal relationship between the two events, even if it is quite small, is faithfully relayed, thereby resulting in a high temporal resolution of event onsets. The limits of detecting such differences can also be determined. Recent fMRI studies have used this rationale to demonstrate that cortical responses can be tracked with high temporal precision using hemodynamic signals. Thus, event-related fMRI has been used not only for brain mapping, but also for tracing the sequence of cortical activation across brain regions during task performance (see review Formisano and Goebel, 2003). However, because the fMRI scanning rate is normally low and the spatial resolution of fMRI signal is on the order of 1 mm, both pose serious limitations on its application for high-spatial, high-temporal resolution brain imaging. In contrast, ISOI has a much higher spatial resolution, with almost unlimited scanning rate, making this approach potentially more suitable for such goals.

Similarly, precise temporal resolution can also be achieved in another hemodynamic-based optical technique, fNIRS (Ferrari and Quaresima, 2012; Scholkmann et al., 2014; Gratton and Fabiani, 2001). fNIRS is a non-invasive optical measurement of brain activity. It uses longer wavelength (650–1000 nm) for better penetration. Due

* Corresponding author at: State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Collaborative Innovation Center for Brain Science, Beijing, China.
E-mail address: haidong@bnu.edu.cn (H.D. Lu).

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to the influence of skull and scalp, the signal noise ratio and spatial resolution of fNIRS (in the order of 1 cm) is poorer than ISOI. However, the temporal aspects of the origin of these two signals are similar and thus the rational of the precise temporal measurement discussed above still holds. The most important advantage of fNIRS is that it is non-invasive, and thus can be used in human subjects.

Reliability of signal timecourse across different cortical locations is important for this approach. Similar to the signal sources in fMRI and fNIRS, the signal measured in ISOI mainly reflects the overall changes in blood due to neural activation. There are three main sources (blood volume, blood oxygenation, light scattering) that contribute to the overall light reflectance change in ISOI. The amplitude and temporal dynamics of this signal depends on the wavelength of the illumination light and specific stimulus parameters. A large set of studies have shown that, for red light illumination (e.g. 605 nm or 630 nm) the intrinsic signal has a stereotypical response timecourse characterized by an early phase (the initial dip) followed by a large rebound (late positive signal, known as the BOLD in fMRI). Such signals have been observed in both anesthetized (e.g. Frostig et al., 1990; Chen-Bee et al., 2007) and awake preparations (e.g. Vanzetta et al., 2004; Sirotin et al., 2009; Tanigawa et al., 2010).

ISOI signal can also be broken down into global and local response components. The global signal is stimulus-non-specific; the local signal is feature-specific and is confined to functionally specific cortical columns. Many studies have characterized the global signal in response to a point stimulus, including its tri-phasic nature, its point-spread function and the possible underlying hemodynamic components (Chen-Bee et. al., 2007; Sirotin et al., 2009). Temporal features for the local (mapping) signal, however, are less well-understood. In this study we imaged cortical response to moving spot stimuli presented to one eye. We analyzed eye-specific activation (mapping signal) in a 10 s long period after stimulus onset. We found the presence of functionally specific ocular-dominance (OD) signals in all three phases of the hemodynamic responses. This signal appears independent of the global signal, as it does not change its sign with the global signal and lasts longer than the global signal. The timecourses of cortical activation are also similar at different locations. By calculating the timecourse shift along the cortical activation trace, we estimate the temporal resolution limit of ISOI is about 80 ms.

2. Materials and methods

All surgical and experimental procedures conformed to the guidelines of the National Institutes of Health and were approved by the Institutional Animal Care and Use Committees (Institute of Neuroscience, Chinese Academy of Sciences; Vanderbilt University, USA).

2.1. Intrinsic optical imaging

Two Macaque monkeys (*Macaca mulatta*) were used in this study. Monkeys were anesthetized (thiopental sodium, 1–2 mg/kg/hr intravenously [i.v.] and/or isoflurane, 0.2%–1.5%), paralyzed with vecuronium bromide (0.05 mg/kg/hr i.v.), and artificially ventilated. Anesthetic depth was assessed continuously via implanted wire electroencephalographic electrodes, end-tidal CO_2, oximetry, and heart rate, and by regular testing for response to toe pinch while monitoring heart rate changes. A craniotomy and durotomy were performed to expose visual areas V1 and V2 (near the lunate sulcus at an eccentricity of 1–6 degrees from the fovea). Eyes were dilated (atropine sulfate) and fit with contact lenses of appropriate curvature to focus on a computer screen 57 or 76 cm from the eyes. Risley prisms were placed over each eye and eyes were aligned using a rapid retinotopic imaging method (Lu et al., 2009). Alignment was checked before and after each imaging block. The brain was stabilized with agar and images were obtained through a cover glass.

Images of reflectance change (intrinsic hemodynamic signals) corresponding to local cortical activity were acquired with 632 nm illumination (for details, see Roe and Ts'o, 1995; Lu and Roe, 2007). Signal-to-noise ratio was enhanced by trial averaging (usually 20–50 trials per stimulus condition). Frame size was 504×504 pixels and represented 20 mmx20 mm of cortical area. Stimuli were presented in blocks. Each block contained four to nine stimulus conditions presented in a randomly interleaved fashion.

2.2. Visual stimulus

Visual stimuli were created using VSG 2/5 or ViSaGe (Cambridge Research Systems Ltd., Rochester, UK) and presented on a CRT monitor (SONY GDM F500R or CPD-G520). The stimulus screen was gamma corrected. Full screen drifting squarewave gratings were used to obtain basic functional maps including those for ocular dominance, orientation, and color. Spatial and temporal frequencies were optimized for these maps (see Lu and Roe, 2007, 2008).

2.3. Retinotopic grid stimulus

Stationary bar stimuli containing orthogonal squarewave gratings were used for mapping the retinotopy of the imaged V1. Full screen stationary squarewave gratings (SF=1 cycle/deg, duty cycle 0.1) were presented monocularly at two different locations (phase shifted 90 degrees) for 3.5 s each after a 0.5 s delay. Subtraction of these two phase-shifted gratings resulted in a retinotopic map of horizontal or vertical grids (See Fig. 1E & F).

2.4. Moving spot stimulus

A white spot (luminance 60 cd/m^2) was displayed on a black background traveling vertically downward for 4.5 degrees parallel to the vertical meridian. Two traveling speeds (1.5 and 4.5 deg/s) were tested. Spot size was 0.23 degrees and was viewed monocularly. Optical signal was collected for 10 s at 8 Hz, resulting in a total of 80 frames. During the imaging, the first 0.5 s of imaging was collected with no stimulus on the screen for background activity. A spot appeared at time 0.5 second and started to move immediately. The spot disappeared at time 3.5 s (for 1.5 deg/s speed) or 1.5 second (for 4.5 deg/s speed), with a traveling duration of 3 or 1 s, respectively. Each condition was imaged 20 times and results shown are the average of these 20 trials.

2.5. Data analysis

To visualize the cortical response to moving spot, we constructed "single-frame maps". For each frame, the gray value of each pixel was calculated using the following function: $dR/R=(F_x-F_0)/F_0$, in which dR/R represents percent change, F_0 is the average raw reflectance value of the first four frames (taken before stimulus onset and thus representative of the baseline activity), and F_x is the raw reflectance values of the frame under study. Single-frame maps obtained in this way represent the percent intrinsic signal change relative to the initial (pre-stimulus) baseline. Multiple repeated trials were averaged to improve signal-noise ratio.

Cortical functional maps (e.g. Fig. 1D, E, F) were calculated with a standard subtraction method (i.e. difference map, Lu and Roe 2007). Unless otherwise specified, difference maps were clipped at two standard deviations on each side of the median pixel values for display.