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Fast optical signal in visual cortex: Improving detection by General Linear Convolution Model

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ABSTRACT

In this study we applied the General Linear Convolution Model to fast optical signals (FOS). We modeled the Impulse Response Function (IRF) as a rectangular function lasting 30 ms, with variable time delay with respect to the stimulus onset. Simulated data confirmed the feasibility of this approach and its capability of detecting simulated activations in case of very unfavorable Signal to Noise Ratio (SNR), providing better results than the grand average method. The model was tested in a cohort of 10 healthy volunteers who underwent to hemi-field visual stimulation. Experimental data quantified the IRF time delay at 80–100 ms after the stimulus onset, in agreement with classical visual evoked potential literature and previous optical imaging studies based on grand average approach and a larger number of trails. FOS confirmed the expected contralateral activation in the occipital region. Correlational analysis between hemodynamic intensity signal, phase and intensity FOS supports diffusive rather than optical absorption changes associated with neuronal activity in the activated cortical volume. Our study provides a feasible method for detecting fast cortical activations by means of FOS.

Introduction

Non-invasive monitoring of brain activity is currently performed according to two approaches: i) by measuring the electrical activity of neurons, or ii) by evaluating local hemodynamic changes in response to the electrical activity itself. The first group of techniques includes ElectroEncephaloGraphy (EEG) and MagnetoEncephaloGraphy (MEG), which are capable of recording the electrical activity with a temporal resolution of few milliseconds. Unfortunately, the identification of the signal sources requires a series of approximated models and the solution of complex inverse problems, thus resulting in a low spatial resolution. The second group of techniques includes functional Magnetic Resonance Imaging (fMRI) which is based on metabolic and hemodynamic changes that occur in brain areas in response to functional stimuli (for review, see Van Horn and Poldrack, 2009). This is possible because the hemodynamic response associated with activation alters the $T2^*$ MR relaxation time. This has led to a comprehensive set of studies focusing on spatial and temporal relationships between neuronal activation and complex behaviors involving motor (Kansaku et al., 2005; Zang et al., 2003), sensory (Clos et al., in press), learning (Prakash et al., 2012; Van den Bos et al., 2012), memory (Mitchell and Johnson, 2009; Reber et al., 2002), and connectivity (Van Dijk et al., 2010) functionalities. However the MR method suffers from several disadvantages. For example, the requirement of immobility of subjects in the MR magnet prevents studies in natural settings or researches related to complex motor tasks. Moreover, the weak signal associated with the hemoglobin response limits the temporal resolution of the method to few seconds. An alternative technique to noninvasive study of brain function is the optical investigation of hemodynamic brain processes, also known as functional Near Infrared (NIR) Spectroscopy (fNIRS) or optical imaging (for review, see Cutini et al., 2012; Ferrari and Quaresima, 2012; Pereira et al., 2007; Taillefer and Denault, 2005; Wolf et al., 2007). fNIRS is particularly attractive thanks to the considerable flexibility, low cost, portability and fast temporal response. fNIRS topographic (Kato et al., 2002; Toronov et al., 2007; Wolf et al., 2007) and tomographic (Barbour et al., 2001) imaging studies have been performed as well. In the last years, optical imaging has been proposed to study fast changes of optical brain properties associated with neuronal activity. In fact, it was demonstrated *in vitro* that electrical activity of single neuron is accompanied by synchronous (within few tens millisecond scale) changes of NIR light scattering properties of activated neurons (Cohen et al., 1972; Frostig et al., 1990; Rector et al., 1997; Stepnoski et al., 1991). More recently, changes of optical transmitted intensity have been demonstrated on bulk rat brain tissue when supra-threshold electrical stimulation occurred (Lee and Kim, 2010). Gratton et al. (1995) proposed that fast optical signals (FOS), also called Event Related Optical Signals (EROS), could localize *in vivo* brain activity with a temporal resolution of 20 ms or less. During

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the last 15 years, there have been several attempts to record FOS noninvasively through the scalp and skull in human subjects (Franceschini and Boas, 2004; Gratton and Fabiani, 2001, 2003, 2010; Gratton et al., 1998, 2000, 2006; Morren et al., 2004; Parks et al., 2012; Rinne et al., 1999; Steinbrink et al., 2000, 2005; Syré et al., 2003; Tse and Penney, 2006, 2007, 2008; Wolf et al., 2002, 2003). However, the results of these studies have been largely controversial. Gratton and colleagues, by means of a frequency-domain NIRS system, recorded FOS phase and intensity (for definition, see Fast optical signals section) associated with a variety of event-related tasks involving the primary sensory and motor cortex (Gratton and Fabiani, 2010; Gratton et al., 1995, 1998), and visual evoked potential (Gratton et al., 1997). Penney's group recorded FOS from auditory and prefrontal cortex using methods identical to Gratton's group (hardware, software and procedures). They adopted dense montages for the data collection and performed the data analysis taking into account the individual anatomy of the subjects. Reports by Steinbrink and colleagues were less reliable (Steinbrink et al., 2000, 2005; Syré et al., 2003). Steinbrink et al. (2000) measured intensity FOS during electrical median nerve stimulation using a continuous-wave NIRS system rather than a frequency-domain one. The reported signal changes were smaller (~0.05%) than those reported by Gratton. In another study, the same group failed to reproduce the results obtained by Gratton using an almost identical instrumentation (phase measurement with a frequency-domain system) and experimental protocol (Syré et al., 2003). This negative result has been told to be caused by the poor spatial sampling used by the authors compared to the one used in Gratton's works (Gratton et al., 2006). In fact, spatial sampling could play a crucial role in detecting FOS, which are highly localized both in space and time. A further study by the same group yielded limited results. The authors detected a significant change in activity only in one subject during finger tapping task. No significant activation was found during visual stimulation (Steinbrink et al., 2005). Franceschini and Boas (2004) recorded FOS using intensity measurements in 10 healthy volunteers during finger tapping, tactile stimulation, and electrical median nerve stimulation. FOS were detected in 43% of finger tapping measurements, 60% of tactile stimulation measurements, and 23% of electrical median nerve stimulation measurements. The relative intensity changes associated with brain activation were around 0.07%, with about 100 ms latency. Additional concerns about the replicability of FOS detection were raised by Radhakrishnan et al. (2009), because of the very low signal-to-noise ratio (SNR). A large number of trials (*i.e.*, long and uncomfortable experimental time) is required to overcome the poor SNR when evaluating grand average responses. Even applying a frequency-domain analysis does not improve the reliability of FOS detection (Radhakrishnan et al., 2009). Morren et al. (2004) shifted the attention on the method used for FOS analysis. They employed an adaptive filter and Independent Component Analysis (ICA) for better separation of a signal component containing the fast signal. In 9 out of 14 subjects, a significant fast neuronal signal related to the finger tapping was found in the intensity signals. In the phase signals, however, indications of the fast signal were found in only two subjects. To improve detection of FOS in rapid recognition tasks, Medvedev et al. (2008) used ICA to reduce interference from heartbeat and contribution of superficial layers. They recorded optical signals from the left prefrontal cortex in 10 right-handed participants with a continuous-wave instrument. Data were band-pass filtered (2–30 Hz) and artifacts were identified either visually (mostly artifacts due to heartbeats) and using the ICA weight matrix. Optical signals were restored from the ICA components removing the artifact ones. FOS were obtained by averaging over target and non-target epochs. After ICA processing, the event-related response was detected in more than 70% of the subjects. The processed signal showed a temporal course fitting the profile of a differential ERP response found in similar object-detection tasks. In another study (Go–NoGo task), Medvedev et al. (2010) applied ICA method to a simultaneous EEG and continuous-wave optical measurement. They identified FOS components similar to event-related potential (ERP) components. The correlation between FOS and EEG provided evidence that at least some FOS components directly "reflect" electrical brain processes. The detection of FOS by using continuous-wave instruments could be therefore improved through ICA processing. ICA has been proved to be capable of removing noise, global interference and superficial layer activity. In addition, the study by Medvedev and colleagues showed that FOS may provide further information on brain processing during higher order cognitive tasks, such as rapid categorization of objects.

To summarize, FOS feasibility remains controversial, especially when the signals are measured by using photon delay measurement methods.

In this paper, we propose to apply General Linear Convolution Model (GLM, Friston et al., 1995) to FOS analysis. GLM was proposed and well validated for BOLD and fNIRS signals (Ye et al., 2009). In these cases it relies on the modeling of a Hemodynamic Response Function (HRF) which is supposed to be the Impulse Response Function (IRF) of the system (as reflected by the BOLD and fNIRS signal) to a brief, intense period of neural stimulation (Hu et al., 2005). Since there are no previously defined IRFs for FOS, we tested the reliability of the method by adopting a square IRF, with a variable onset delay after the stimulus administration. First we ran simulated experiments to evaluate the reliability of applying GLM to FOS (Comparison between grand average and GLM performances to simulated FOS section). Then, we applied GLM to both FOS and standard hemoglobin signals (HS) obtained during a hemi-field visual stimulation. Both signals were recorded by means of a frequency-domain optical system (Baringa, 1997; Gratton et al., 1998; Villringer, 1997; Villringer et al., 1997). Slow changes of the light continuous component (DC) reflect the hemodynamic process, whereas fast variations of DC optical signal and modulated component (AC) phase permit to evaluate FOS as changes in intensity attenuation and time of flight of photons within the activated brain tissue, respectively. So, we could study both HS and FOS and investigate their functional relationships in the activated regions.

Materials and methods

Participants

Ten healthy volunteers (age: 25–40 years, mean: 26 years) were enrolled for the *in vivo* experiment. All the subjects, after having been informed about finalities and methodologies of the study, provided written informed consent for attending the study, which was performed in agreement with the ethical standards of the Helsinki Declaration, 1964, and approved by the local Human Board Review and Ethical Committee.

Visual stimulation

The stimulus was a reversing black and white checkerboard (visual angle: 22°, spatial frequency: 0.22 cycles/°, time frequency: 2 cycles/s, and duration: 0.500 s). Blocks of 20 stimuli were presented either on the right or on the left of a fixation cross, positioned at the center of the screen. Each block lasted 10 s. A total of 56 blocks (28 right and 28 left hemi-field stimulations) were presented in a pseudo-random order. Inter-block interval of 1 s served as rest period, during which a static fixation cross was displayed on a black screen. A total of 560 checkerboard inversions were acquired for each condition, *i.e.* hemi-field stimulations. Participants comfortably sat in front of a computer screen, which was positioned approximately 50 cm in front of them. Experiments took place in a dimly illuminated and acoustically isolated room.