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Fast optical signals in the sensorimotor cortex: General Linear Convolution Model applied to multiple source–detector distance-based data

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ABSTRACT

In this study, we applied the General Linear Convolution Model to detect fast optical signals (FOS) in the somatosensory cortex, and to study their dependence on the source–detector separation distance (2.0 to 3.5 cm) and irradiated light wavelength (690 and 830 nm). We modeled the impulse response function as a rectangular function that lasted 30 ms, with variable time delay with respect to the stimulus onset. The model was tested in a cohort of 20 healthy volunteers who underwent supra-motor threshold electrical stimulation of the median nerve. The impulse response function quantified the time delay for the maximal response at 70 ms to 110 ms after stimulus onset, in agreement with classical somatosensory-evoked potentials in the literature, previous optical imaging studies based on a grand-average approach, and grand-average based processing. Phase signals at longer wavelength were used to identify FOS for all the source–detector separation distances, but the shortest one. Intensity signals only detected FOS at the greatest distance; *i.e.*, for the largest channel depth. There was no activation for the shorter wavelength light. Correlational analysis between the phase and intensity of FOS further confirmed diffusive rather than optical absorption changes associated with neuronal activity in the activated cortical volume. Our study demonstrates the reliability of our method based on the General Linear Convolution Model for the detection of fast cortical activation through FOS.

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Introduction

Functional near-infrared spectroscopy (fNIRS) imaging is a promising technique for functional neuroimaging. fNIRS allows for non-invasive evaluation of the variations in the cortical concentrations of hemoglobin through optical investigation of the brain tissue (Baringa, 1997; for reviews, see Cutini et al., 2012; Ferrari and Quaresima, 2012; Pereira et al., 2007; Taillefer and Denault, 2005; Wolf et al., 2007). As for blood-oxygenation-level-dependent (BOLD) fMRI recordings, fNIRS relies on the cortical hemodynamic compensation processes that are associated with the neuronal activity of specific brain regions that respond to somatosensory or cognitive stimuli (Barbour et al., 2001; Kato et al., 2002; Toronov et al., 2007; Villringer et al., 1997; Wolf et al., 2007).

Moreover, near-infrared optical imaging has been used to study variations in the optical properties of the cortical tissue directly associated with neuronal activity, instead of the associated hemodynamic compensation processes (Gratton et al., 1995). The signals that are produced through this approach are referred to as fast optical signals (FOS), or event-related optical signals (Gratton and Fabiani, 2010).

It has been demonstrated *in vitro* that the electrical activity of a single neuron is accompanied by synchronous (within a few tens of milliseconds) changes in the 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 in the optical transmitted intensity have been demonstrated for bulk rat-brain tissue when supra-threshold electrical stimulation occurs (Lee and Kim, 2010).

Nevertheless, *in-vivo* detection of FOS remains difficult, and indeed, controversial (Franceschini and Boas, 2004; Gratton and Fabiani , 2001, 2003; Gratton et al., 1997, 1998, 2000, 2006; Medvedev et al., 2008, 2010; Morren et al., 2004; Parks et al., 2012; Radhakrishnan et al., 2009; Rinne et al., 1999; Steinbrink et al., 2000, 2005; Tse and Penney, 2006, 2007). The reasons for the greater difficulty in the *in-vivo* detection of FOS can be attributed to the low signal-to-noise ratio (SNR) (Chiarelli et al., 2012), the need for very accurate spatial localization of the signal sources (Gratton et al., 2006), and the time definition of neural activity (Gratton and Fabiani, 2010). To date, the processing methods for FOS detection that have been proposed have included the grand-average approach (Gratton et al., 1995), frequency analysis (Radhakrishnan et al., 2009), and independent-component-analysis-based methods (Medvedev et al., 2008, 2010). Grand-average

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approaches, however, need a large number of repeated trials to allow and compensate for the intrinsically low SNR.

In a recent study of FOS in the visual area, we proposed to process the signals by applying the Generalized Linear Model (GLM) (Friston et al., 1995), through the adopting of a multiple-delay simple-step impulse response function (IRF) (Chiarelli et al., 2012). Recording FOS using a frequency-domain system and 830-nm-wavelength light, we recorded significant phase and intensity FOS variations that were contralateral to hemi-field stimulation and had a temporal range that was compatible with neuronal electrical activity. Correlational analysis between the fNIRS hemodynamic signal and the FOS phase and intensity supported diffusive rather than optical absorption changes associated with neuronal activity in the activated cortical volume.

In the present study, we applied the GLM with a variable-delay IRF method that was previously developed and tested in the visual cortex, to study somatosensory FOS evoked by supra-motor-threshold electrical stimulation of the median nerve, and recorded by a multiple-distance source–detector pad. The design of this study relates to the controversial results in the literature about these kinds of signals and stimulation.

Maclin et al. (2004) recorded both phase and intensity FOS with very short latency (*ca.* 20 ms). Franceschini and Boas (2004) recorded FOS using intensity measurements during electrical median nerve stimulation, detecting FOS in 23% of the measurements.

Less reliable results were provided by Steinbrink et al. (2000, 2005), who measured FOS intensities during electrical stimulation of the median nerve. They did not exclude that the variations seen for the signal intensity might be attributed to synchronous-to-stimulation motion artifacts.

The aims of our study were four-fold: (i) to verify the reliability of our previously proposed GLM method for detecting somatosensory FOS; (ii) to investigate the dependence of the performance of the method on the sampling depth using multi-distance measurements; (iii) to compare the GLM and grand-average methods; and (iv) to demonstrate with certainty that the results obtained in this way are not attributable to physiological or mechanical artifacts.

Materials and methods

Participants

Twenty healthy, right-handed volunteers were enrolled for this study (mean age, 30 years; age range, 25–40 years; 8 females). After being informed about the methodologies and outcomes of the study, all of the subjects provided written informed consent for their participation. All of the procedures used throughout the study were performed in agreement with the ethical standards of the Helsinki Declaration, 1964, and were approved by the local Human Board Review and Ethical Committee.

Somatosensory stimulation

Each subject underwent two measurement sessions, as the control and experimental sessions, the sequence of which was randomly assigned to each participant. Thus, half of the subjects underwent the control session first, and the other half underwent the experimental session first.

During the experimental and control sessions, the right median nerve was stimulated electrically at the wrist, using a DC current. Intensities of stimulation were settled at a level producing a painless, clearly visible thumb opposition (Del Gratta et al., 2002). The electrical stimulation was delivered through a PowerLab ADInstruments system. Stimuli were delivered by means of a pair of 3-cm-spaced Ag–AgCl disk electrodes filled with conductive paste (skin-electrode resistance < 10 kΩ), *via* a twisted pair of wires. The stimulation timing was controlled by a MATLAB suite (The MathWorks, Inc.), and it comprised 20 blocks, each of which lasted 20 s. Each block administered 40 supra-threshold stimuli (stimulation frequency, 2 Hz; time duration: 0.2 ms). The inter-block rest was for 10 s, and therefore the whole stimulation procedure lasted for 10 min. The stimuli delivery and signal recordings were triggered through transistor–transistor logic (TTL) serial communication. Jittering effects accounted for much less than the sampling time (*i.e.*, the reciprocal of the sampling frequency: 104 Hz; see the Optical imaging recording and instrumentation section). During the experimental session the optical pad was positioned over the primary sensory–motor cortex (Identification of the left primary motor area and Optical imaging recording and instrumentation sections).

The control session was designed to define any potential systematic errors and artifacts in the procedure. Thus, the control session exactly replicated the experimental session, but the optical pad was positioned over Cz, according to the 10–20 reference system.

Identification of the left primary motor area

Detecting FOS requires the exact localization of the signal source (Gratton et al., 2006). Therefore, for each participant, we first identified the cranial projection of the left primary motor area through transcranial magnetic stimulation (Ruohonen and Karhu, 2010). For this, an 8-shaped coil, connected to a Magstim Rapid2 stimulator (Magstim, Whitland, UK), was used and placed approximately over the left primary motor cortex, with the handle pointing backwards at 45° from the midline (Fig. 1). With this configuration, the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus, which is optimal for trans-synaptic activation of the corticospinal pathways (Brasil-Neto et al., 1992). Using a slightly supra-threshold stimulus intensity, the coil was moved over the left hemisphere to determine the optimal position from which the maximal amplitude motor-evoked potentials were recorded for the first dorsal interosseous muscle.

Optical imaging recording and instrumentation

We used a commercial frequency-domain system (Imagent, ISS Inc.) to investigate the cortical activation. The Imagent system is equipped with 32 sources (32 laser diodes, 16 at 690 nm, 16 at 830 nm) that are modulated at 110 MHz, and four photomultiplier tube (PMT) detectors. The sources were time-multiplexed during the measurements. The light power emitted by the diodes at the fiber end was <4 mW/cm^2, which was thus within the limits of the American National Standards Institute. The light emitted by the diodes was directed through the scalp using low NIR attenuation glass optic fibers.

FOS recordings were carried out using a four-channel, multi-distance pad. Each channel comprised a single detector and coupled 690 nm and 830 nm light sources. The detector comprised four 3-mm-diameter fiber optic bundles that were connected to the PMT. The four coupled sources were aligned and placed at 2.0 cm, 2.5 cm, 3.0 cm and 3.5 cm from the detector (Fig. 2).

This multi-distance channel configuration allowed the investigation of variations in the optical properties at different depths from the scalp. During the experimental session, the pad was placed on the head of the participant, with the detector lying over the left primary motor area (as previously identified with the transcranial magnetic stimulation; Identification of the left primary motor area section) and the light sources were oriented towards the occipital area, over the axial plane that contains the primary sensory–motor area (Fig. 1). During the control session, the pad was placed on the head of the participant, with the detector placed over Cz (in the 10–20 reference system) and the light sources oriented towards the occipital area, as for the experimental session. The current feeding into the PMTs was modulated at 110 MHz + 5 kHz, which generated 5 kHz heterodyne detection. The output current of the PMTs, which was sampled at 40 kHz, was subjected to fast Fourier

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