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Non-Contact Time-Domain Imaging of Functional Brain Activation and Heterogeneity of Superficial Signals

H. Wabnitz[1,*], M. Mazurenka[1], L. Di Sieno[2], D. Contini[2], A. Dalla Mora[2], A. Farina[3], Y. Hoshi[4], E. Kirilina[5,6], R. Macdonald[1] and A. Pifferi[2]

[1]Physikalisch-Technische Bundesanstalt (PTB), Berlin, Germany; [2]Dipartimento di Fisica, Politecnico di Milano, Milano, Italy; [3]Consiglio Nazionale delle Ricerche, Istituto di Fotonica e Nanotecnologie, Milano, Italy; [4]Hamamatsu University School of Medicine, Hamamatsu, Japan; [5]Free University Berlin, Berlin, Germany, [6]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
heidrun.wabnitz@ptb.de

Abstract: Non-contact scanning at small source-detector separation enables imaging of cerebral and extracranial signals at high spatial resolution and their separation based on early and late photons accounting for the related spatio-temporal characteristics.
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1. Introduction

Two major methodological challenges of functional near-infrared spectroscopy (fNIRS) of the brain are low lateral spatial resolution and contamination of cerebral fNIRS signals with hemodynamic artefacts from superficial skin layers [1]. These challenges are difficult to address with conventional fNIRS acquisition schemes where a limited number of optode-based channels are available. Non-contact scanning imaging combined with time-gated detection promises to overcome these limitations [2]. It provides superior lateral spatial resolution on the one hand and enables the separation of deep and superficial signals based on the analysis of late and early photons on the other hand. Further, following impressive achievements in integrated photonics devices, it could lead to compact and cost-effective devices [3] with extreme depth sensitivity [4].

Our recently presented non-contact time-domain system scans a tissue area with dimensions of several cm, with a fixed, small (few mm) separation between the illumination and detection spots, a 32×32 pixel resolution and a frame time of 1 s. After proof-of-concept tests on phantoms [5] and first successful *in-vivo* tests [6] we designed and characterized an upgraded system with two detection channels [7,8].

In the present contribution we demonstrate the potential of this system for studies of functional activation of the human frontal lobe. In particular, we characterize task-evoked artifacts in the forehead skin and explore their separation from functional brain signals. We illustrate the substantial spatial heterogeneity of superficial signals localized in skin draining veins which can be hardly captured with conventional fNIRS techniques.

2. Methods

2.1 Instrumentation

Picosecond pulses with rapidly switchable wavelength were provided by a supercontinuum laser in combination with an acousto-optical tuneable filter. A second generation compact fast-gated single-photon avalanche diode (SPAD) module with embedded gating and signal conditioning circuitry [9] was employed for selective detection of late photons that carry information on deep absorption changes. A second parallel detection channel was equipped with a non-gated SPAD detector, to separately record purely superficial absorption changes. We obtained two-dimensional arrays of photon time-of-flight distributions by means of a 2-axis galvanometer scanner operated in conjunction with imaging time-correlated single photon counting [10]. The wavelength was switched line by line between 760 nm and 860 nm. For details of the upgraded system and its performance characterization by phantom measurements see Ref. 8. Data processing was based on a time-window analysis for both detection channels.

2.2 Functional activation study

In-vivo tests of the two-channel system included motor and cognitive stimulation experiments, in particular a self-referential task with an expected localized response in the frontopolar region [11]. The cognitive stimulation was performed on 8 subjects with 10 trials consisting of two different task periods of 33 s (8 sentences), with rest periods of 33 s in between. Informed written consent was obtained from all subjects prior to the study.

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3. Results and Discussion

The motor stimulation experiments had revealed localized cerebral responses, with lateral extensions differing for finger tapping and hand grip experiments [7]. Here we focus on the cognitive stimulation for which no significant cerebral activation was detected. However, in several subjects task-evoked superficial responses were found that exhibited a distinct spatio-temporal pattern. An example for one of the subjects is presented in Fig. 1. The intensity in the time windows representing early and late photons, integrated over the recording time for the whole session, is plotted in Figs. 1a and b for the original spatial resolution of 32×16 pixels. Figs. 1c and d show the block-averaged responses to brain activation, binned to 8×8 pixels whose effective separation is 5 mm.

The signals for early photons were clearly confined to the location of superficial veins (cf. Figs. 1a and 1c) the pattern of which was also visible by eye on the forehead of this subject. The nearly "triangular" response observed, with parallel increase of intensity at both wavelengths during stimulation and decrease during rest, is another indication of the systemic origin of the signal. These results confirm the findings of Kirilina et al. showing task-evoked vasoconstriction on forehead skin based on fMRI [12]. Recognition of the potential heterogeneity of superficial systemic responses to functional brain activation is of high relevance for the analysis of standard fNIRS measurements that often assume a global nature of superficial hemodynamic responses. Based on this novel physiological information dedicated methods for separating the task-evoked venous contribution from the cerebral signal can be developed.

The different intensity distributions for early and late photons (Figs. 1a and b) indicate that different tissue types are probed. When comparing the pattern of the responses (Figs. 1c and d) it is obvious that the response for late photons is more extended spatially. This does not contradict the presence of a sharply localized absorption change at a depth of a few mm. Phantom measurements with small black inclusions also showed similar spatial broadening for late photons [7].

In the cases discussed so far, either cerebral activation or superficial contributions dominated the observed signals. In general, both signal contributions are expected to be present in the gated signal (late photons). The non-gated signal (early photons) should allow the superficial contribution to the late-photon signal to be eliminated.

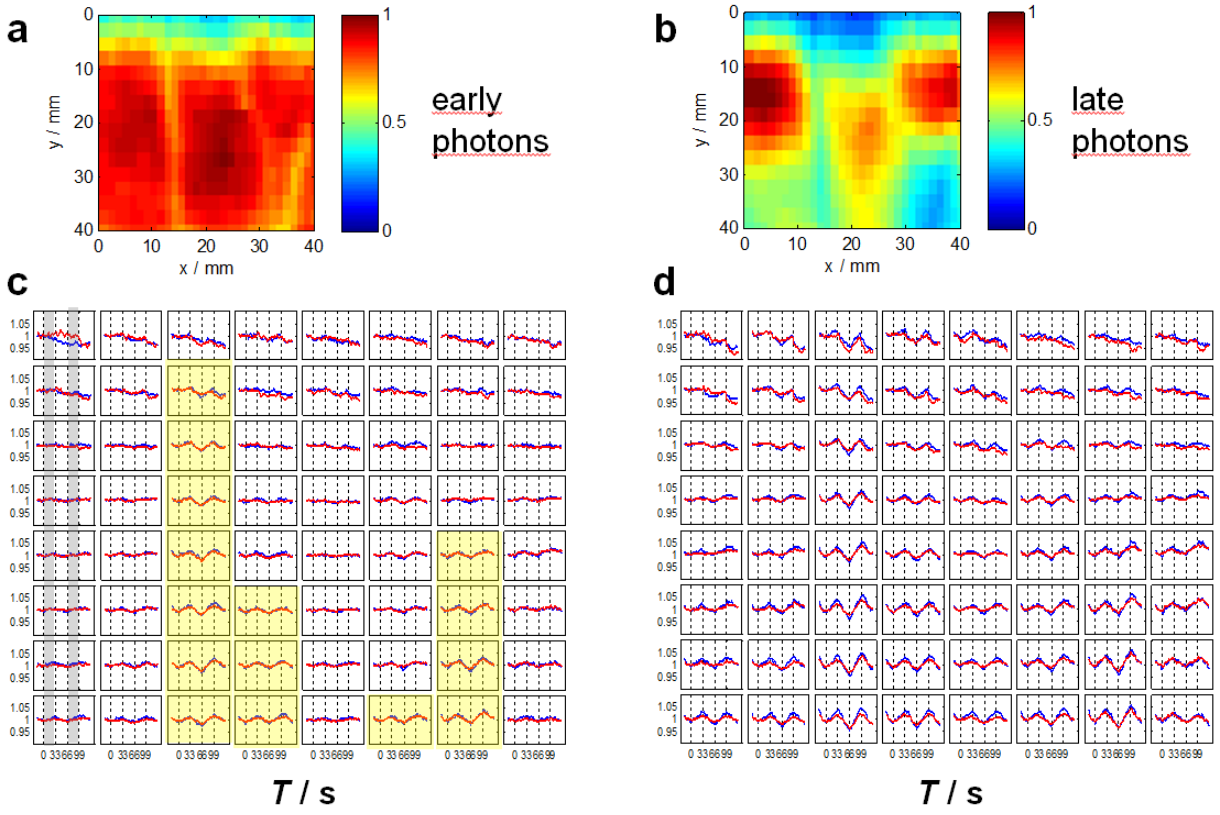

Fig. 1. Results of cognitive activation for one subject: Intensity images at 760 nm for early (a) and late (b) photons and time traces of the responses for the wavelengths 760 nm (blue) and 860 nm (red), for early (c) and late (d) photons (normalized photon counts). The scan area was 4 cm x 4 cm. In (c) the task periods (*T* from 0 to 33 s and from 66 s to 99 s) are indicated by gray bars in the leftmost column, and pixels with substantial response are highlighted in yellow.

However, straightforward pixel-wise ratio formation based on the activation responses pertaining to a late and an early time window as described earlier [13] for measurements at large source-detector separation is not sufficient here. The different lateral spatial extension and magnitude of the sensitivity of early and late photons to near-surface absorption changes have to be taken into account. With increasing photon propagation time, the sensitivity regions expand into depth, but also along the lateral directions [14]. We performed simulations with narrow rod-like absorbers to mimic blood vessels located at different depths, employing TOAST++ [15]. For late times (> 1 ns) a substantial contrast was observed even at locations far (10 mm) from a shallow (3 mm depth) rod. A tomographic reconstruction approach employing an analytical perturbation model [4] based on the time-domain diffusion equation was tested on these simulations and applied to the measured data. It was based on the total photon count in two specific time windows selected from the time-of flight distribution recorded with the non-gated and gated detectors (early and late photons, respectively). For the case reported in Fig. 1, an activation was found at a shallow depth only, with a pattern resembling the pattern of the superficial veins. These results are promising regarding the feasibility of 3D reconstruction based on time-gated scanning at fixed small source-detector separation and selected time windows.

4. Conclusions

Non-contact scanning with a dense, flexible grid of measurement positions has the potential to become a useful tool to image and separate brain activation and accompanying superficial responses. The details of their lateral spatial profile can be investigated with high spatial resolution. In our study we found another piece of evidence for the occurrence of a non-global superficial, systemic response in the prefrontal area. This finding is relevant for the design of methods to eliminate superficial contamination in fNIRS in general, but also to study the superficial hemodynamic response and its coupling to systemic physiology. We demonstrated that our time-domain non-contact imaging approach can provide unique neurophysiologic information that is not accessible to conventional optode-based methods. Advanced analysis of images based on early and late photons aiming at the separation of cerebral and extracranial signal contributions needs to take into account the time dependence of the related spatial sensitivity profiles. Empowered with 3D reconstruction, the non-contact time-domain functional optical imager could provide well resolved images with high sensitivity, from superficial systemic hemodynamics down to brain activation, thus filling a gap in existing fNIRS instrumentation.

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