

## Short Communication

# Human Visual Cortical Function During Photic Stimulation Monitoring by Means of Near-Infrared Spectroscopy

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**Summary:** Near-infrared spectroscopy (NIRS) was used to monitor human visual cortical function during and after photic stimulation (PS) in five adult volunteers. Cerebral blood volume (CBV) increased on the occipital surface during PS, but NIRS parameters did not change on the frontal surface. The increase in CBV was caused by a rapid increase in oxyhemoglobin with but a small increase in deoxyhemoglobin, suggesting cerebral vascular dilatation with decreased oxygen consumption. After PS

stopped, CBV promptly decreased and then slightly increased again. Cytochrome  $aa_3$  did not show any change during and after PS. These phenomena reappeared following repeated PS in all five subjects. These results may represent the first step in the development of NIRS imaging. **Key Words:** Visual cortical function—Photic stimulation—Cerebral blood volume—Near infrared spectroscopy.

A study of human subjects using positron emission tomography (PET) indicated that photic stimulation (PS) raises blood flow and glucose consumption in the visual cortex by about 50%, whereas oxygen consumption increases only 5% (Fox et al., 1988). Using proton magnetic resonance spectroscopy, Prichard et al. (1991) demonstrated that PS causes an increase in brain lactate in the human visual cortex. However, the mechanism of PS action on human visual cortical function is still not clear. Near-infrared spectroscopy (NIRS) is a non-invasive tool for the continuous monitoring of changes in cerebral blood volume (CBV), oxyhemoglobin (HbO<sub>2</sub>), deoxyhemoglobin (HbR) and redox state of cytochrome  $aa_3$  (Cyt). Voluntary hyperven-

tilation, which decreases cerebral circulation through hypocapnia (Jobsis, 1977), was used as a functional test. Recently, we used NIRS to investigate human visual cortical function during and after PS. We also tested the hypothesis that CBV remains constant during PS.

## SUBJECTS AND METHODS

Five normal subjects (ages 27, 28, 30, 31, and 38 years) were examined with NIRS. The subjects lay quietly on beds in a dark room with their eyes open throughout the PS. Care was taken to allow for adaptation to the darkness before the examination. NIR probes were vertically attached on the occiput just beside the occipital process or on the frontal surface at the center of the forehead. The distance from the photon source probe to the photon detector probe was 2.5 cm. The differential path length factor (DPF) was determined by time-of-flight measurement of an ultrashort optical pulse through the tissues. The DPF (mean  $\pm$  SD  $5.93 \pm 0.42$ ) of adult heads was used. The DPF of the adult head was almost constant beyond an interoptode spacing of 2.5 cm (van der Zee et al., 1991). The sensitive volume of the detector, using the 2.5-cm probe separations, includes the calcarine fissure and visual cortex which are situated ~2.0–6.0 cm from the occipital surface.

The sampling time for each photon count (PC) was 5 s. In order to suppress possible background noise from the PS light, dark clothing was worn around the head and

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**Abbreviations used:** CBV, cerebral blood volume; Cyt, cytochrome  $aa_3$ ; DPF, differential path length factor; HbR, deoxyhemoglobin; HbO<sub>2</sub>, oxyhemoglobin; HbT, total hemoglobin (HbO<sub>2</sub> + HbR); MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; PET, positron emission tomography; PC, photon count; PS, photic stimulation.

background noise of extraneous light was monitored as photon counting darkness (PC darkness) in the NIRS. PC darkness is defined as the contamination signal of light (e.g., sunlight or other illumination) excluding the photon light source probe.

The total cerebral blood hemoglobin concentration ( $HbT = HbO_2 + HbR$ ), oxyhemoglobin ( $HbO_2$ ), deoxyhemoglobin ( $HbR$ ) and the redox state of cytochrome  $aa_3$  (Cyt) in situ were estimated using an NIRS instrument (NIR-1000, Hamamatsu Photonics K. K.). Light for the NIRS from six laser diodes (wavelengths 780, 808, 828, 850, 870, and 904 nm) was directed into the head through a fiberoptic bundle. Using an algorithm developed by Wray et al. (1988), the variation in NIRS absorption was continuously analyzed by means of a computer incorporated into the apparatus. The change in CBV was considered to be that of total hemoglobin ( $\Delta HbT = \Delta HbO_2 + \Delta HbR$ ) (Wyatt et al., 1986).

PS was produced by flashing light (laser emitting diode) at 8 Hz (Fox and Raichle, 1984) using a NIPPON KODEN photosonic stimulator. NIRS-data were obtained for 10 min before, during, and after PS.

All estimated values were averaged and described as mean  $\pm$  SD.

## RESULTS

In all subjects, CBV increased on the occipital surface during PS, but the NIRS parameters did not change on the frontal surface.

Figure 1 shows NIRS observations on the frontal and occipital surfaces in a healthy 38-year-old man taken before, during, and after PS. Immediately after the start of PS, the concentration of  $HbO_2$  rap-

idly increased with but a mild increase in  $HbR$ . Thus, the increase of CBV was caused more by oxygenated hemoglobin than by deoxygenated hemoglobin. After PS stopped, CBV promptly decreased and then slightly increased again. Cyt did not show any change during or after PS, suggesting a nonreactive redox state in mitochondria. These phenomena reappeared in repeated PS examinations. PC darkness, which monitors contaminations of extraneous light, did not show any change with PS. There was no background noise generated by PS.

Figure 2 shows the changes of  $HbO_2$ ,  $HbR$ , and  $HbT$  on NIRS in five subjects. The responses of NIRS parameters to PS were found to be similar in all five subjects. The average  $HbO_2$  concentration values were  $3.40 \pm 2.46$  (mean  $\pm$  SD)  $\mu\text{mol L}^{-1}$  after 3 min,  $4.28 \pm 1.99$  after 5 min, and  $4.64 \pm 1.94$  after 10 min of PS. After PS stopped,  $HbO_2$  decreased  $47.5 \pm 22.4\%$  from  $4.64 \pm 1.94$  during PS to  $2.49 \pm 1.98$   $\mu\text{mol L}^{-1}$  1 min after PS.  $HbT$  decreased by  $40.5 \pm 17.8\%$  and showed a similar pattern to that of  $HbO_2$ .  $HbR$ , however, only slightly increased, by  $1.67 \pm 1.38$  and  $1.78 \pm 0.79$   $\mu\text{mol L}^{-1}$  during and after PS, respectively.

## DISCUSSION

NIRS was able to monitor the change of  $HbO_2$  and  $HbR$  in the visual cortical area during and after

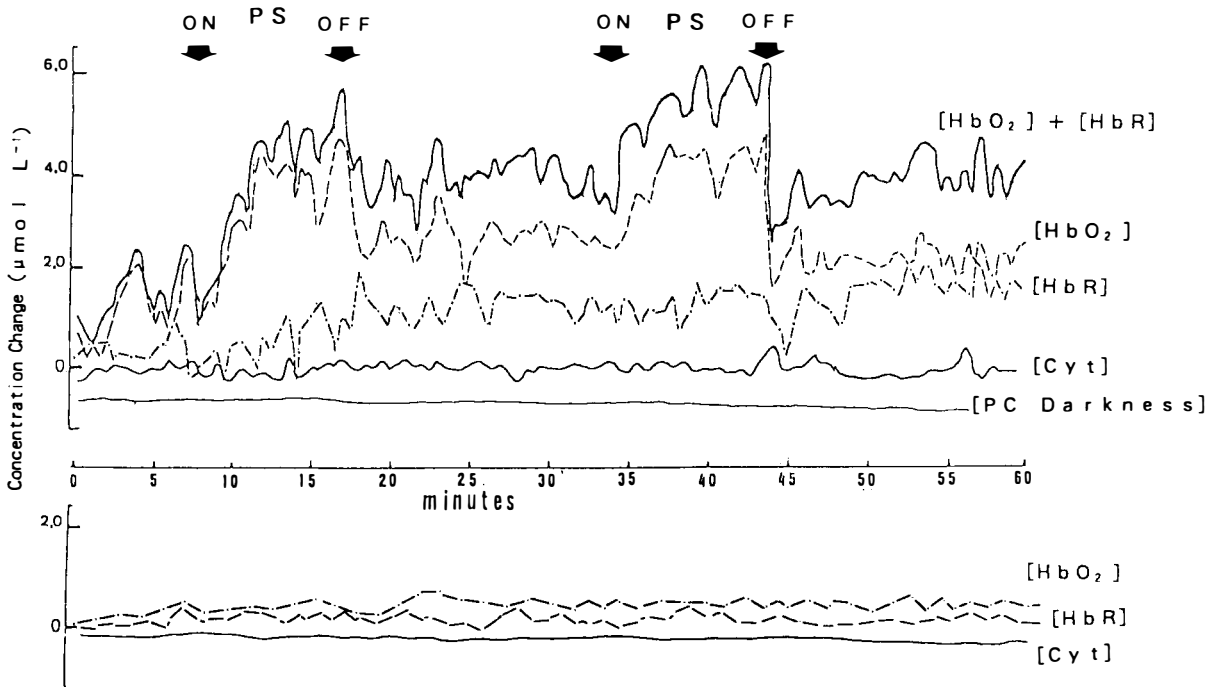
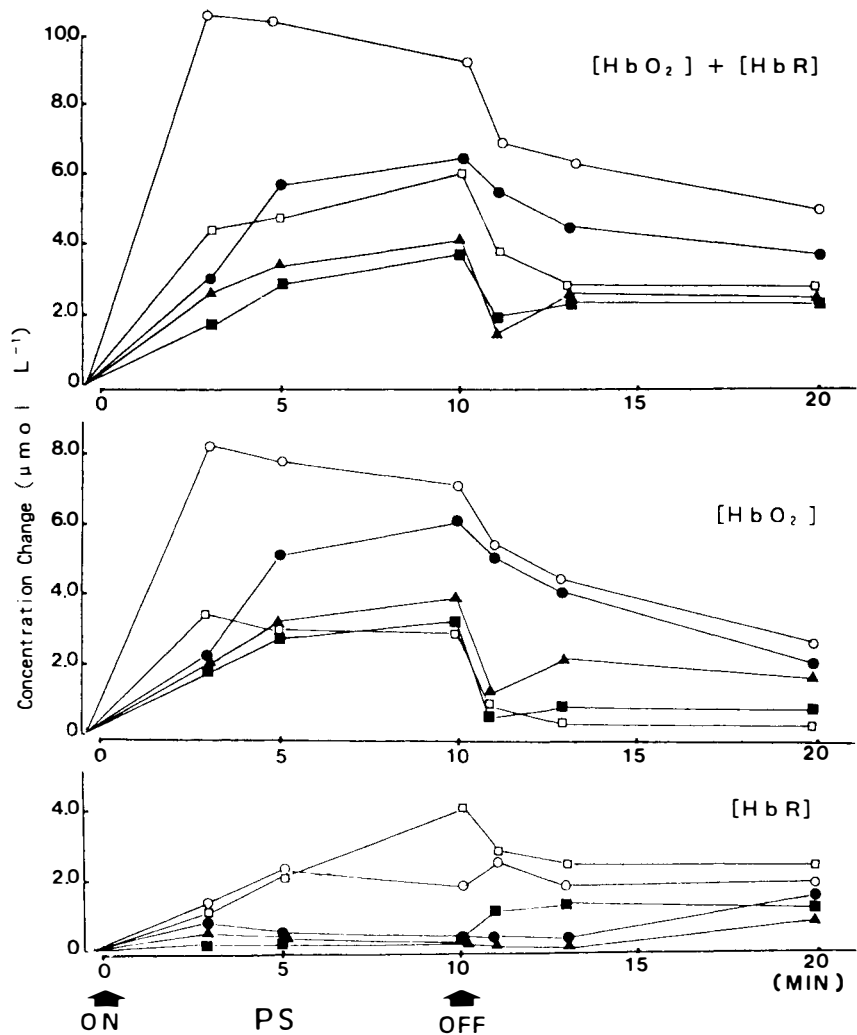


FIG. 1. Changes in  $[HbO_2]$  (---),  $[HbR]$  (-·-·-),  $[HbO_2] + [HbR]$  (—),  $[Cyt]$  (· · ·), and  $[PC\ Darkness]$  (—) taken before, during, and after PS over the frontal (bottom) and occipital (top) surfaces in a healthy 38-year-old man.

**FIG. 2.** Responses of NIRS parameters to PS in five subjects (ages 27 ○—○, 28 ●—●, 30 ▲—▲, 31 □—□, and 38 ■—■). **Top:**  $[\text{HbO}_2] + [\text{HbR}]$ . **Middle:**  $[\text{HbO}_2]$ . **Bottom:**  $[\text{HbR}]$ .



PS. These NIRS results suggest that PS causes an increase of  $\text{HbO}_2$  with but a small change of  $\text{HbR}$  and with no change of mitochondrial oxygenation in the visual cortex. Thus, the increase of CBV was caused more by oxygenated hemoglobin than by deoxygenated hemoglobin.

Belliveau et al. (1991) reported that during PS, localized increases of CBV (mean  $\pm$  SD  $32 \pm 10\%$ ) were also detected in the primary visual cortex by the magnetic resonance technique. The 40.5% reduction of CBV after PS may correlate with visual cortical function and neural activity. An increase in regional CBF and  $\text{CMR}_{\text{glc}}$ , and a decrease in  $\text{CMRO}_2$  during PS in the visual cortex was demonstrated by PET (Fox et al., 1988). The mismatch between glucose uptake and oxidation was confirmed in the human visual system by proton magnetic resonance spectroscopy (Prichard et al., 1991). Our NIRS technique in the human visual system may be useful in assessing cerebral vascular regulatory components of the cortical function and

in investigating these mismatches and function-related energy costs using the PET and magnetic resonance techniques (Kato et al., 1992).

The increase in oxygenated hemoglobin in the visual cortical area may be interpreted as indicating cerebral vascular dilatation, increased regional CBF, or decreased oxygen consumption in relation to an increase in  $\text{HbO}_2$ . The vascular site of the hemoglobin measurement is undetermined. Arterial dilatation increases the venous blood volume and, depending upon the level of  $\text{CMRO}_2$ , may increase the amount of oxyhemoglobin within the venous compartment. The increase of signal attributed to  $\text{HbO}_2$  does not guarantee arterial dilatation. The small change of deoxyhemoglobin in relation to the increased  $\text{HbO}_2$  during PS suggests decreased oxygen consumption in relation to an increase in  $\text{HbO}_2$  or arteriolar dilatation with a regional CBF increase.

The NIRS parameters did not change on the frontal sagittal sinus surface during PS. However, little

reference is made to the potential contribution from the sagittal sinus which presumably is within the field of the NIR photodetector used in the occipital location. The potential contribution of a large volume of venous blood from the occipital and other lobes should be considered in an interpretation of these data. Specifically, these experiments might best be repeated over the parietal cortex with vibratory stimulation as performed by Fox and Raichle (1986). Such a localization would remove the confounding influences of the sagittal sinus. Recently, NIRS was used to monitor from the temporal surface the increase in CBV in the stimulated human auditory cortex (Kato, unpublished data).

Rapidly decreased CBV due to increased HbO<sub>2</sub> and the incomplete recovery of CBV and HbO<sub>2</sub> after PS may be correlated with a recovering state of visual function after PS, associated with any combination of diminished neural activity, increased oxidative metabolism, or, more probably, increased blood flow which accelerates lactate washout (Sap- pey-Mariner, 1992). NIRS under different photic stimulating conditions (i.e., duration and strength of stimulation) must be further studied.

In our studies, cytochrome aa<sub>3</sub> did not show any changes due to PS, but cytochrome-hemoglobin divergence must be more clearly demonstrated by a quantitative method (Kline et al., 1990). With the NIRS technique, it is difficult to estimate hemoglobin concentration because of the difficulty of defining the assumptions needed to calculate hemoglobin concentration. These include (a) path length; (b) extinction coefficients; (c) overlap matrix for signal subtraction; and (d) age-related changes in chromophores. The work of Ferrari et al. (1990) supports the hypothesis that it is possible to quantify the cytochrome *c* oxidase copper band in the near-infrared spectral region.

It is difficult to define accurately the sensitive volume of the detector using the various distances of probe separations. In the 2.5-cm probe separations used in our study, the sensitive depth from the occipital surface is estimated to be ~2.5–4.0 cm, because the path length is  $14.8 \pm 1.1$  cm. The exact sensitive volume of the detector should be determined in future work.

In previous reports on human patients using NIRS (Wyatt et al., 1986; Delpy et al., 1987), an increase in HbO<sub>2</sub> was usually associated with a reduction of HbR, but our results showed that CBV increases with the elevation of HbO<sub>2</sub>, whereas HbR does not decrease much, neither during nor after PS. These specific NIRS parameter patterns may indicate a normal response to physiologic stimulation, as demonstrated by the lactate elevation in the

rat somatosensory cortex upon forepaw stimulation (Ueki et al., 1988) as well as by the stimulated human auditory cortex (Singh et al., 1991). The general conclusion of our results should be tested by study of auditory, somatosensory, and motor systems.

To our knowledge, this is the first report detecting a human visual cortical function during PS by means of NIRS. In addition, PS studies by means of NIRS may be useful in evaluating the remaining cerebral function in the brain-dead, vegetative state (Kato et al., 1991) and in blind patients. Studies in young infants and children could be contemplated, because of the truly safe nature of the approach. Our results are the first step in the development of NIRS imaging. The occipital surface attachment technique of NIR probes used in our study allowed sampling of the regional changes in cerebral oxygenation in the human brain. However, the development of a new technique for spatially selective high resolution NIRS is desirable.

Paramagnetic deoxyhemoglobin in venous blood is a naturally occurring contrast agent for magnetic resonance imaging (MRI). By accentuating the effects of this agent through the use of gradient-echo techniques in high fields, Ogawa et al. (1989; 1990) demonstrated in vivo images of brain microvasculature with image contrast reflecting the blood oxygen level. The NIRS technique can be used to provide measurement in vivo of real-time oxygenated hemoglobin, deoxyhemoglobin, and the redox state of cytochrome aa<sub>3</sub> at the bedside. We believe that a NIRS study using the new MR functional imaging technique will confirm the cortical functional site under normal physiological conditions related to regional neural activity.

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