

# Regional changes in cerebral haemodynamics as a result of a visual stimulus measured by near infrared spectroscopy

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## SUMMARY

Near infrared spectroscopy (NIRS) is used to measure global changes in cerebral haemodynamics. We have adapted the technique to measure regional changes in response to a visual stimulus. Ten volunteers were exposed to a computer generated visual stimulus designed to activate a large area of the visual cortex, including V1, V2, V3, V4 and V5. The stimulus was on for 30 s and off for 30 s. Changes in the concentrations of oxyhaemoglobin ([HbO<sub>2</sub>]) and deoxyhaemoglobin ([Hb]) were measured using a commercial spectrometer (NIRO500), over the occipital cortex. The data were summed over ten cycles. As a control, the experiment was repeated over the frontal cortex. For each subject [HbO<sub>2</sub>] increased during stimulation, and decreased when the stimulus was off. The mean ( $\pm$ s.e.m.) change in [HbO<sub>2</sub>] was  $0.54 \pm 0.14 \mu\text{mol l}^{-1}$ . The change in total haemoglobin concentration, given by [HbO<sub>2</sub>] + [Hb] was  $0.61 \pm 0.21 \mu\text{mol l}^{-1}$ , equivalent to a rise in cerebral blood volume of  $0.04 \pm 0.01 \text{ ml } 100 \text{ g}^{-1}$  which is about 2% of the total cerebral blood volume. There was no significant change in [HbO<sub>2</sub>] over the frontal cortex, implying that the changes in blood volume originated in the occipital lobe. This demonstrates that NIRS provides a non-invasive method of measuring regional changes in cerebral haemodynamics as a result of visual stimulation.

## 1. INTRODUCTION

The past decade has seen the development of new techniques, based on changes in regional cerebral blood flow (rCBF), for detecting and localizing cerebral areas involved in different functions. The most widely used and successful of these have been positron emission tomography (PET) and magnetic resonance imaging (MRI) (Fox *et al.* 1986; Belliveau *et al.* 1991; Zeki *et al.* 1991). These have many advantages, but cannot easily be used in situations where the clinician needs information rapidly, and at the bedside, about the function of a patient's brain. This may arise, for example, in the assessment of a premature or birth asphyxiated newborn infant, or with continuous monitoring of the function of the brain during neurosurgery. Near infrared spectroscopy (NIRS) is a non-invasive and relatively inexpensive technique used for studying cerebral haemodynamics in infants and adults. This study describes the use of the method in monitoring and measuring changes in regional cerebral oxygenation in the occipital cortex of adult subjects in response to a visual stimulus.

NIRS was introduced as a method of monitoring changes in tissue oxygenation of intact organs in 1977 (Jöbsis 1977). Over the past decade it has been applied to measuring global cerebral haemodynamics in the newborn (Wyatt *et al.* 1986) and in adults (Elwell *et al.* 1994), and muscle oxygenation at rest and during exercise (Piantadosi *et al.* 1986; Hampson & Piantadosi 1988; De Blasi *et al.* 1994*a, b*). Recently the technique has been used to detect regional cerebral haemodynamic changes when the brain is activated during the execution of cognitive tasks, visual stimulation and complex-partial seizures (Hoshi & Tamura 1993*a*; Villringer *et al.* 1993).

To date, NIRS studies of visual cortical function have used photic stimulation (Hoshi & Tamura 1993*b*; Kato *et al.* 1993). There is some debate in the published literature about whether such stimulation activates cortical or sub-cortical regions (Pratt *et al.* 1982). We wanted to concentrate on the occipital cortex; so we used stimuli which were tailored to the physiology of the visual areas in the cerebral cortex. It is well established that, in addition to the primary visual receiving area (V1), the human visual cortex consists of multiple visual areas, specialized to undertake different tasks (Zeki 1990). Because we were not sure of how sensitive our method would be and because some of these areas are not accessible from the surface (for

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example, the visual areas lying in the fusiform gyrus), we designed a visual stimulus that would activate several areas and would therefore maximize our chances of detecting the haemodynamic changes in the cerebral cortex associated with visual stimulation.

## 2. MATERIALS AND METHODS

The theory of *nirs* has been described elsewhere (Cope & Delpy 1988). Briefly, the technique depends on absorption by the chromophores oxyhaemoglobin ( $\text{HbO}_2$ ) and deoxyhaemoglobin (Hb) of near infrared light transmitted through the cranium. The absorption spectra of  $\text{HbO}_2$  and Hb are shown in figure 1. There is a ten-fold decrease in light absorption from the visible to the near infrared spectrum. Other biological tissues scatter rather than absorb near infrared light, resulting in relative transparency. Thus light at a given wavelength incident on the head can be detected emerging at some distance away with an intensity which varies primarily with changes in the concentration (and therefore light absorption) of  $\text{HbO}_2$  and Hb. Use of light at more than one wavelength allows the calculation of the relative proportions of the two chromophores. The near infrared spectrometer used in this study (NIRO500, Hamamatsu Photonics KK, Japan) has four pulsed laser diodes with wavelengths of 779 nm, 821 nm, 855 nm and 908 nm, each with a fullwidth half maximum of 3 nm.

The optical attenuation in a highly scattering medium such as the brain can be expressed by a modified Beer-Lambert law which states:

$$\text{attenuation} = \text{adB} + G,$$

where  $a$  is the absorption coefficient of the chromophore ( $\mu\text{mol}^{-1}\text{l}^{-1}\text{cm}^{-1}$ ),  $c$  is the concentration of chromophore ( $\mu\text{mol l}^{-1}$ ),  $d$  is the distance between the points where light enters and leaves the tissue (cm),  $B$  a 'pathlength factor' that takes account of the increase in optical pathlength as a result of scattering of light in the tissue, and  $G$  is a constant attenuation factor related to the optical properties and geometry of the tissue. If  $d$ ,  $B$  and  $G$  remain constant, changes in chromophore concentration can be calculated from the changes in optical absorption divided by the product of  $adB$ . The 'differential pathlength factor' ( $B$ ) has been measured by phase resolved spectroscopy (Duncan *et al.* 1994), and the value for the adult head at 807 nm is 6.26. The continuous *nirs* measurements of  $\text{HbO}_2$  and Hb concentration changes are expressed as absolute concentration changes in  $\mu\text{mol l}^{-1}$  from an arbitrary zero for each study at the start of the measurement period.

As  $\text{HbO}_2$  and Hb have different absorption spectra, simultaneous changes in  $[\text{HbO}_2]$  and  $[\text{Hb}]$  can be measured, thus obtaining information not only about the total blood volume, but about oxygenation. The sum of the two signals,  $\text{Hb}_{\text{sum}}$ , is therefore the change in total haemoglobin concentration in  $\mu\text{mol l}^{-1}$ .  $\text{Hb}_{\text{sum}}$  can be used to calculate changes in cerebral blood volume (cbv) in  $\text{ml } 100 \text{ g}^{-1}$ .

The study was approved by the University College London Faculty of Clinical Sciences Committee on the Ethics of Clinical Investigation. Ten healthy adult volunteers took part, of whom six were female and two were left handed. Light from a near infrared spectrometer was conveyed via a fibre-optic bundle to an 'optode' positioned over the right occipital region, placed 1 cm to the right of the midline (to avoid the sagittal sinus) and 1 cm beneath the occipital ridge. The second optode, conveying transmitted light to a photomultiplier tube was placed 3-4 cm laterally. A black cloth was wrapped over the optodes to reduce noise from ambient light. The subjects were seated in a dental chair, using the headrest to minimize head movement. A venous blood sample was taken from the cubital vein of each volunteer, to measure venous haemoglobin concentration.

The stimulus was displayed on a monitor placed 2 m from the subject at eye level by an Amiga microcomputer (Commodore Business Machines Inc., West Chester, Pennsylvania). It consisted of randomly moving 1 cm diameter red, blue and green discs on a grey background. The speed of the moving discs was set at  $5 \text{ cm s}^{-1}$ . Here each disc subtended an angle of  $0.06^\circ$  at the eye. By using coloured stimuli, we hoped to be able to stimulate V4; the motion component would stimulate V5 and the edges on the discs would stimulate the cells of V3. The stimulus would also excite the cells of V1 and V2, which represent all attributes of vision (Baizer *et al.* 1977; Zeki & Shipp 1988; Livingstone & Hubel 1985).

The study took place in a dark room so that no extraneous visual stimuli were present, and each subject had an initial period of at least 5 min looking at the blank grey screen until a flat baseline for  $[\text{Hb}]$  and  $[\text{HbO}_2]$  was obtained. The image was shown for 30 s, followed by the blank grey screen for 30 s. This one minute cycle was repeated ten times. Each time the stimulus was shown an analogue signal was simultaneously sent to the NIRO500. This allowed the haemodynamic changes to be directly related to the timing of the stimulus.

Changes from baseline in  $[\text{HbO}_2]$  and  $[\text{Hb}]$  in  $\mu\text{mol l}^{-1}$  were measured every 2 s. The data were displayed on a spreadsheet and summed over ten consecutive cycles. The total changes in  $[\text{HbO}_2]$  and  $\text{Hb}_{\text{sum}}$  with the stimulus on and off were compared. For each subject  $\text{HbO}_2$  rose to a maximum during the period of stimulation (see figure 2).

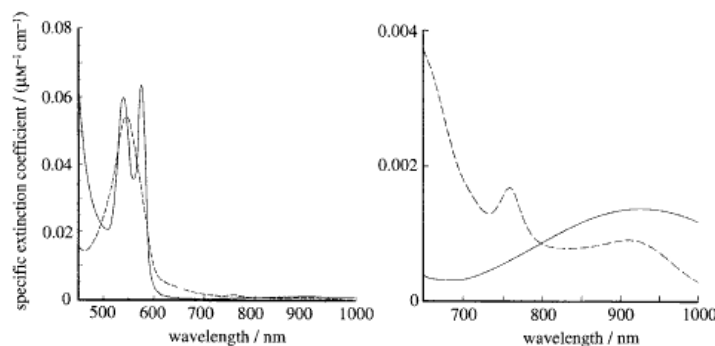


Figure 1. Absorption spectra of  $\text{HbO}_2$  and Hb in the near infrared region.  $\text{HbO}_2$  (line) and Hb (broken line).

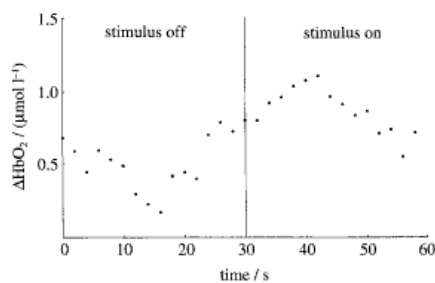


Figure 2. Sum of changes in  $\text{HbO}_2$  concentration over ten cycles for one subject.

The 6 s period of maximum change in  $\text{HbO}_2$  was measured from inspection of the data, for each subject, and the analysis was repeated over this period. As a control, the experimental procedure was repeated for each subject on a later occasion with the optodes over the frontal region, positioned 2–3 cm above the right eyebrow, beneath the hairline.

In addition,  $\text{cbv}$  was measured in one subject over the occipital region, using the change in  $[\text{HbO}_2]$  induced by a slow change in inspired oxygen fraction (Elwell *et al.* 1994). This allowed us to compare the volume changes observed to a total regional volume measured using the same technique. Previous measurements of  $\text{cbv}$  with  $\text{NIRS}$  on adults have been performed with the optodes on the frontal region and the value obtained is  $2.85 \pm 0.97 \text{ ml } 100 \text{ g}^{-1}$  (Elwell *et al.* 1994). The single occipital value was measured to ensure that there was no large difference in  $\text{cbv}$  between the two regions.

### 3. RESULTS

Figure 3 shows the  $\text{NIRS}$  data collected during the ten cycles for one subject. The change in  $[\text{HbO}_2]$  from an arbitrary baseline is shown plotted against time with the 'ON' epochs shown separately from the 'OFF'

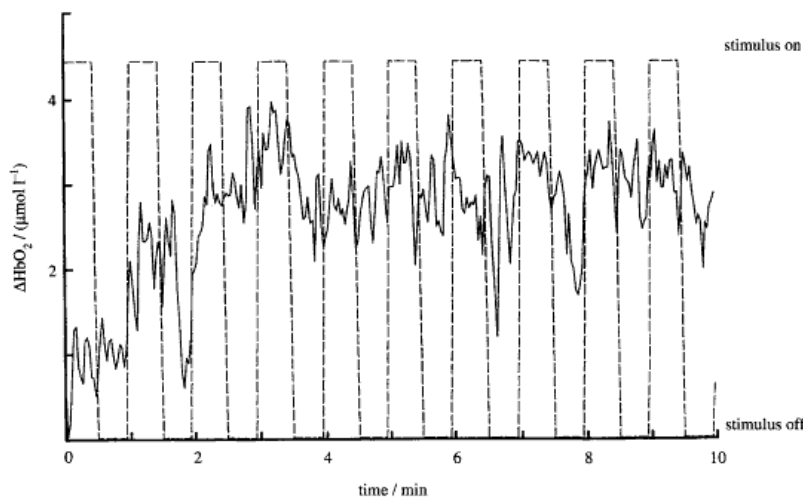


Figure 3. Changes in  $\text{HbO}_2$  concentration with visual stimulation for one subject.

Table 1. Mean differences in  $[\text{Hb}]$ ,  $[\text{HbO}_2]$  and  $\text{Hb}_{\text{sum}}$  between 30 s of stimulus on and 30 s of stimulus off

subject	$\Delta[\text{Hb}]/$ ( $\mu\text{mol l}^{-1}$ )	$\Delta[\text{HbO}_2]/$ ( $\mu\text{mol l}^{-1}$ )	$\Delta\text{Hb}_{\text{sum}}/$ ( $\mu\text{mol l}^{-1}$ )
1	0.04	0.54	0.58
2	-0.17	0.41	0.24
3	0.00	0.49	0.49
4	-0.09	0.14	0.05
5	0.15	0.34	0.49
6	-0.15	0.44	0.29
7	-0.15	0.69	0.54
8	0.16	0.34	0.50
9	0.13	0.32	0.45
10	0.72	1.70	2.42
mean	0.06	0.54	0.61
s.e.m.	0.08	0.14	0.21

epochs. The graph shows that the  $[\text{HbO}_2]$  increases when the stimulus is on and decreases when it is off. These changes are superimposed upon an overall increase in  $[\text{HbO}_2]$ , which is especially marked during the first 3 min, suggesting a cumulative increase. Figure 2 shows the same data summed over ten cycles. For each subject  $[\text{HbO}_2]$  rose to a maximum between 6–16 s after the start of stimulation, and decreased when the stimulus was off. There was a difference between  $[\text{HbO}_2]$  and  $[\text{Hb}]$ . For every subject the sum of changes in  $[\text{HbO}_2]$  was positive, whereas no consistent pattern was seen for  $[\text{Hb}]$ , although the overall  $\text{Hb}_{\text{sum}}$  increased (table 1). The mean ( $\pm$  standard deviation) change in  $[\text{HbO}_2]$  was  $0.54 \pm 0.14 \mu\text{mol l}^{-1}$ . This was significantly different from zero ( $p = 0.003$ ,  $t$ -test with nine degrees of freedom). The mean change in  $\text{Hb}_{\text{sum}}$  was  $0.61 \pm 0.21 \mu\text{mol l}^{-1}$ , which is equivalent to a rise in cerebral blood volume of  $0.04 \pm 0.01 \text{ ml } 100 \text{ g}^{-1}$ . Using

Table 2. Mean peak [ $\text{HbO}_2$ ] changes per cycle over the occipital and frontal regions of each subject

subject	[ $\text{HbO}_2$ ] change over occipital region/ ( $\mu\text{mol l}^{-1}$ )	[ $\text{HbO}_2$ ] change over frontal region/ ( $\mu\text{mol l}^{-1}$ )
1	0.54	-0.17
2	0.41	-0.13
3	0.49	0.10
4	0.14	0.15
5	0.34	-0.08
6	0.44	-0.26
7	0.69	0.08
8	0.34	-0.21
9	0.32	-0.13
10	1.70	0.39
mean	0.54	-0.03
s.e.m.	0.14	0.06

the value of  $\text{CBV}$  measured over the occipital region ( $2.2 \text{ ml } 100 \text{ g}^{-1}$ ), this is approximately a 2% change in blood volume.

The responses measured over the frontal region are shown in table 2. The mean change in [ $\text{HbO}_2$ ] was  $-0.03 \pm 0.06 \mu\text{mol l}^{-1}$ . This change was not significantly different from zero, but was significantly different from the occipital value, with  $p < 0.001$ .

#### 4. DISCUSSION

This study demonstrates that it is possible to use near infrared spectroscopy to measure regional changes in cerebral haemodynamics resulting from visual stimulation. There was a wide variation in the magnitude of the change in [ $\text{HbO}_2$ ] between subjects, but all showed an increase in [ $\text{HbO}_2$ ] and [ $\text{Hb}_{\text{sum}}$ ] with stimulation. Whereas the overall [ $\text{Hb}_{\text{sum}}$ ] changed, [ $\text{HbO}_2$ ] was a more reliable indicator than [ $\text{Hb}$ ].  $\text{Hb}_{\text{sum}}$  was used to derive change in  $\text{CBV}$ . The mean fractional change in  $\text{CBV}$  was 2%. Belliveau *et al.* (1991) have measured a  $32 \pm 10\%$  change in functional  $\text{CBV}$  as a result of photic stimulation in the primary visual cortex (V1) by MRI. Kato *et al.* (1993) have used NIRS to measure changes in [ $\text{HbO}_2$ ] as a result of photic stimulation. The mean [ $\text{HbO}_2$ ] change after 3 min of photic stimulation in five subjects was  $3.4 \pm 2.46 \mu\text{mol l}^{-1}$ , compared with the change reported in this study after a 30 s stimulus of  $0.54 \pm 0.14 \mu\text{mol l}^{-1}$ . Although changes in  $\text{CBV}$  are not directly comparable to changes in  $\text{rCBF}$  it is interesting to note  $\text{rCBF}$  changes of 17–24% in area V1–V2 (Zeki *et al.* 1991), and of 2.6–11% in area V5, measured by PET (Watson *et al.* 1993).

There was no significant rise in [ $\text{HbO}_2$ ] over the frontal area when the subjects viewed the stimulus. Therefore the changes observed over the occipital region are unlikely to be the result of: increased blood flow in extracerebral tissue such as skull and skin; a movement artefact; or a generalized increase in cerebral activation. Previous studies in which skin blood flow has been simultaneously monitored by laser doppler velocimetry, or has been rendered constant by application of a chemical vasodilator have shown that there is little change in skin blood flow, and negligible effect on the NIRS signal (Villringer *et al.* 1993).

The variability in the magnitude of the responses between subjects reflects variations both in individual  $\text{rCBF}$  changes and in anatomy. It was not possible to define the precise anatomical area studied, because near infrared light is highly scattered in tissue. Modelling studies show that this scattering produces considerable spreading of light between the optodes. Exact prediction of the region interrogated is therefore difficult (Arridge *et al.* 1993; Hiraoka *et al.* 1993; Schotland *et al.* 1993), especially in an optically heterogeneous structure like the adult head. However, in a recent combined PET–NIR evoked response study of the motor cortex (Villringer *et al.* 1994) it was reported that lateral misplacement of the optodes by only 2 cm away from the activated region led to a significant decrease in the NIRS signal. This implies that the interrogated volume may be limited to a band 1–2 cm width either side of the optodes. Validation studies of functional NIRS using MRI also indicate that precise anatomical location may be critical (Nakajima *et al.* 1994; Obrig *et al.* 1994). In this study it is likely that the interrogated region would have included more than areas V1–V5, resulting both in a variation between subjects, and an underestimation of the change in  $\text{CBV}$  in the occipital cortex. However, it is feasible that refinement of the technique may enable measurements to be made from individual areas of the visual cortex, using appropriate stimuli.

The results show that there were consistent increases in [ $\text{HbO}_2$ ], but not in [ $\text{Hb}$ ]. This may have been the result of an increased  $\text{CBF}$  leading to reduced oxygen extraction. These changes are also consistent with the results from both PET and MRI studies that functionally induced increases in  $\text{rCBF}$  are associated with an increase in glucose rather than oxygen consumption (Pritchard *et al.* 1991). This increase in [ $\text{HbO}_2$ ] has also been demonstrated by BOLD (blood oxygenation-level dependent) functional MRI (Kwong *et al.* 1992; Ogawa *et al.* 1992; Nakajima *et al.* 1994).

The time course of the rise in [ $\text{HbO}_2$ ] peaking between 6–16 s after the onset of stimulation is comparable to the results of studies using BOLD fMRI. Bandettini (1993) has demonstrated a maximum change at 4–10 s, and Friston *et al.* (1994) have found that the optimal delay time of the response function (and therefore the peak of the haemodynamic response) is 6.6 s. *In vivo* direct optical imaging of the exposed visual cortex of monkeys in both the visible and infrared parts of the spectrum, has shown an initial increase of oxygen delivery, with a rise in [ $\text{Hb}$ ] after 200–400 ms. This is followed by an increase in blood volume 300–400 ms later, and after 1000 ms by a substantial rise in [ $\text{HbO}_2$ ] (Frostig *et al.* 1990). These changes are very localized, even to the size of individual blood vessels, compared with the field interrogated by the NIRS technique.

The changes in [ $\text{HbO}_2$ ] and [ $\text{Hb}$ ] observed by NIRS are small. One reason for this is that the concentration calculation requires data for the optical pathlength in tissue. This is taken as the inter-optode spacing multiplied by a differential pathlength factor (DPF) which has previously been measured for the adult head (van der Zee *et al.* 1992; Duncan *et al.* 1994). The use

of this pathlength factor assumes that all tissues in the light path contribute to the changes in [Hb] and [HbO<sub>2</sub>]. However, there is a significant thickness of the relatively avascular skin, bone and muscle, especially in the occipital region, which reduces the proportion of brain tissue in the light path. This may lead to an underestimation of CBV and CBF by a factor of the order of 2 (Elwell *et al.* 1994), if the effective cerebral pathlength is only approximately 50% of the total, although this would not affect the size of the proportional volume change, as the same DPF is used in the calculation of both CBV and ΔCBV.

In certain situations NIRS would have several advantages over other techniques currently used for cerebral functional monitoring. The spectrometer is portable and does not use ionizing radiation, thus allowing repeated measurements, and no exogenous tracer is required. This is advantageous for potential applications in assessing visual function in infants, and neonates or in adults undergoing intensive care or neurosurgery. Although the spatial resolution is not yet accurately defined, the temporal resolution is currently as high as 0.5 s, which compares favourably with the current temporal resolution of functional MRI, and technical developments should reduce this to less than 100 ms. NIRS provides a simple, relatively inexpensive and non-invasive method of detecting and measuring changes in cerebral haemodynamics resulting from visual stimuli. The technique could be adapted for use as a bedside method for clinical assessment of the function of the brain.

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