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Localized near-infrared spectroscopy and functional optical imaging of brain activity

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SUMMARY

Changes in cerebral blood flow (CBF) and cerebral metabolic rates (CMRO₂) have been used as indices for changes in neuronal activity. Near-infrared spectroscopy (NIRS) can also measure cerebral haemodynamics and metabolic changes, enabling the possible use of multichannel recording of NIRS for functional optical imaging of human brain activity. Spatio-temporal variations of brain regions were demonstrated during various mental tasks. Non-synchronous behaviour of cerebral haemodynamics during the neuronal activation was observed. Gender- and handedness-dependent lateralization of the function between right and left hemispheres was demonstrated by simultaneous measurement using two NIR instruments during the mirror-drawing task. A lack of interhemispheric integration was observed with schizophrenic patients. These observations suggest an application for NIRS in psychiatric disease management, as an addition to clinical monitoring at the bedside.

A time-resolved 64-channel optical imaging system was constructed. This consisted of three picosecond laser diodes and 64 channels of TAC and CFD systems. Image reconstruction for phantom model systems was performed. Time-resolved quantitative optical imaging will become real in the very near future.

1. INTRODUCTION

Near-infrared spectroscopy (NIRS) has been recognized as a unique non-invasive technique for evaluating tissue oxygenation and haemodynamics. The diagnostic applications of this technique were mainly focused on the clinical field, especially in the monitoring of neonatal brains. In 1993 the possible use of NIRS for monitoring brain function was demonstrated (Hoshi & Tamura 1993*a, b*; Kato *et al.* 1993), when changes in haemoglobin oxygenation and blood volume in specific regions were shown during various physiological stimuli. Our series of cognitive studies have revealed that NIRS has the potential to be used for functional mapping of brain activity. NIRS measures changes in concentrations of oxygenated ([oxy-Hb]) and deoxygenated haemoglobin ([deoxy-Hb]), mainly in cerebral mixed venous blood. Summation of changes in [oxy-Hb] and [deoxy-Hb] gives changes in the total haemoglobin concentration ([t-Hb]), which reflects those in blood volume. Changes in [oxy-Hb] and [deoxy-Hb] are related to changes in cerebral metabolic rates (CMRO₂), and changes in [t-Hb] are related to those in cerebral blood flow (CBF).

NIRS has high temporal resolution (0.5 s), and unlike positron emission tomography (PET) and magnetic resonance imaging (MRI), is easy to perform and uses portable equipment, which allows measurement outside specific institutions. As subjects in NIRS studies do not have to have their mobility limited, they can relax, and their neuronal activity is maintained at a relatively low level in the resting state. The size of the recently available portable apparatus is only 5 cm × 10 cm × 2 cm, and continuously records the

responses over 24 h. Thus, it is expected that the use of a multichannel NIRS monitoring system will allow region-specific changes in both CBF and the oxygen supply–oxygen utilization relationship to be revealed in real-time during various physiological stimuli, such as mental tasks. Our final goal for this functional optical imaging of the human brain is to construct an optical imaging system that will give us the dynamic features of quantitative spatio-temporal variations of haemoglobin oxygenations and blood volume.

Our functional imaging by NIRS raised fundamental questions underlying the studies of PET and fMRI (Hoshi *et al.* 1994*b*). (i) Are neuronal activations always associated with increases in CBF and CMRO₂? (ii) Do increases in neuronal activity always accompany decreases in [deoxy-Hb]? (iii) Can we obtain a specific response for neuronal activation by the subtraction of the ‘resting state’ from the ‘activated state’? (iv) Is ‘resting state’ really a non-activated state?

2. SUBJECTS AND METHODS

The NIRS instrument used here is OM-100A (Shimadzu, Kyoto, Japan), which was developed according to the method of Hazeki & Tamura (1988). This instrument consists of three semiconductor laser diodes (wavelengths 780, 805 and 830 nm) as light sources and calculates changes in [oxy-Hb] and [deoxy-Hb] from arbitrary baselines according to the following equations:

$$\Delta[\text{oxy-Hb}] = -3.0 \Delta A_{805} + 3.0 \Delta A_{830}$$

$$\Delta[\text{oxy-Hb}] = 1.6 \Delta A_{780} - 2.8 \Delta A_{805} + 1.2 \Delta A_{830}$$

$$\Delta[\text{t-Hb}] = \Delta[\text{oxy-Hb}] + \Delta[\text{deoxy-Hb}]$$

Our measurements were expressed as relative values, not absolute ones, as pathlength factor (Van der Zee *et al.* 1992) was incorporated into the apparent absorption coefficients in our algorithm (Hazeki & Tamura 1988).

The distance between the input and output optodes was between 2.0 cm and 3.0 cm (3.0 cm was most frequently used), a distance for which the contribution of the skull, skin and subcutaneous tissue to the absorption signals is very small. The subjects were healthy adult volunteers, except for the studies on individuals with psychiatric diseases.

3. RESULTS

(a) Changes in oxy-, deoxy and total haemoglobins during mental tasks

The well-known phenomenon of 'overcompensation' can be observed by NIRS. Figure 1 shows typical traces observed in subjects who found difficulty in solving a mathematical problem (Hoshi & Tamura 1993*b*). There were no significant changes in the traces during listening to the mathematical problem, suggesting that the left frontal region measured was not activated for understanding the meaning of the problem. Within 15 s of starting to solve the problem, [t-Hb] together with [oxy-Hb] began to increase; [deoxy-Hb] showed no changes in the early stage and later decreased slightly. When the subject stopped solving the problem (arrow 3), [t-Hb] and [oxy-Hb] decreased abruptly, but remained higher than the

original levels. After short-term rest, the subject tried to solve the same problem again. Both [t-Hb] and [oxy-Hb] increased again, and then decreased. At arrow 5, the subject finally stopped trying to solve the problem.

Interesting observations that question the principle of functional mapping of brain activity based on 'overcompensation' are given in figure 2 (Hoshi & Tamura 1993*b*). This demonstrates an increase in [deoxy-Hb] and a reciprocal decrease in [oxy-Hb] during the mental task, where blood flow ([t-Hb]) remained unchanged. This is explained by the lack of coupling between the neuronal activation and blood flow, that is, the increase in CMRO₂ due to neuronal activation was not compensated for by an increase in CBF resulting in the increase in [deoxy-Hb]. In our series of investigations we have encountered several unexpected results with NIRS. For example, mental tasks were accompanied by decreases in both CBF and CMRO₂ in the frontal region of the dominant hemisphere. This unexpected response was confirmed by simultaneous measurements of CBF with PET (Hoshi *et al.* 1994*b*). Thus, NIRS gave rise to the question: are mental tasks always associated with increases in CBF and CMRO₂? This question is critical for the various imaging techniques based on the activation-flow coupling in cerebral tissue. The relatively poor spatial resolution of NIRS must be overcome to answer this question.

NIRS could also detect the haemodynamic changes in specific areas caused by simple physiological stimuli,

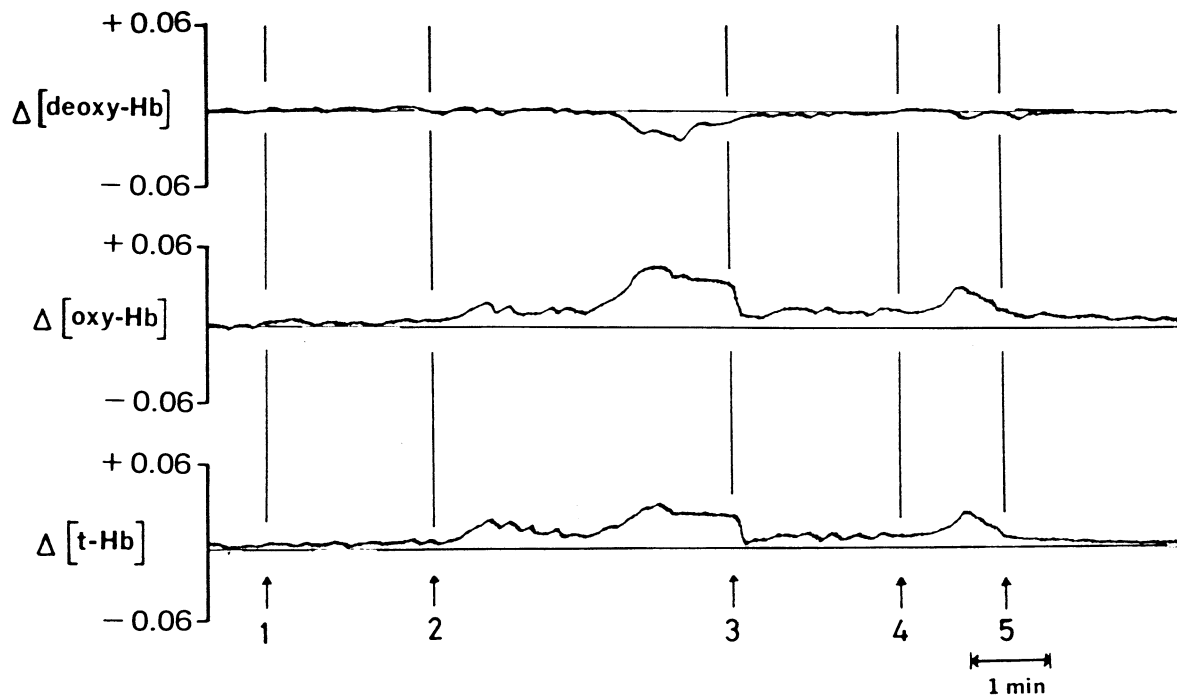


Figure 1. Changes in concentrations of oxy-Hb, deoxy-Hb and t-Hb in the frontal region of the dominant hemisphere, the left frontal region, during problem-solving. The ordinate is the relative amount; the abscissa is the time. Baselines were selected from the resting state, and these values were taken as zero in each signal. The upward (plus) and the downward (minus) trends show the increase and the decrease in values, respectively. The subject was a 26-year-old right-handed male student. The arithmetic problem was read out between the points shown by arrows 1 and 2. At the point shown by arrow 2, he started to solve it. Arrows 3 and 5 show the points at which he said 'I stopped trying to solve the problem'. Arrow 4 shows the point at which he said 'I will try to solve the problem again'. He stopped and failed to obtain the correct answer at the point shown by arrow 5.

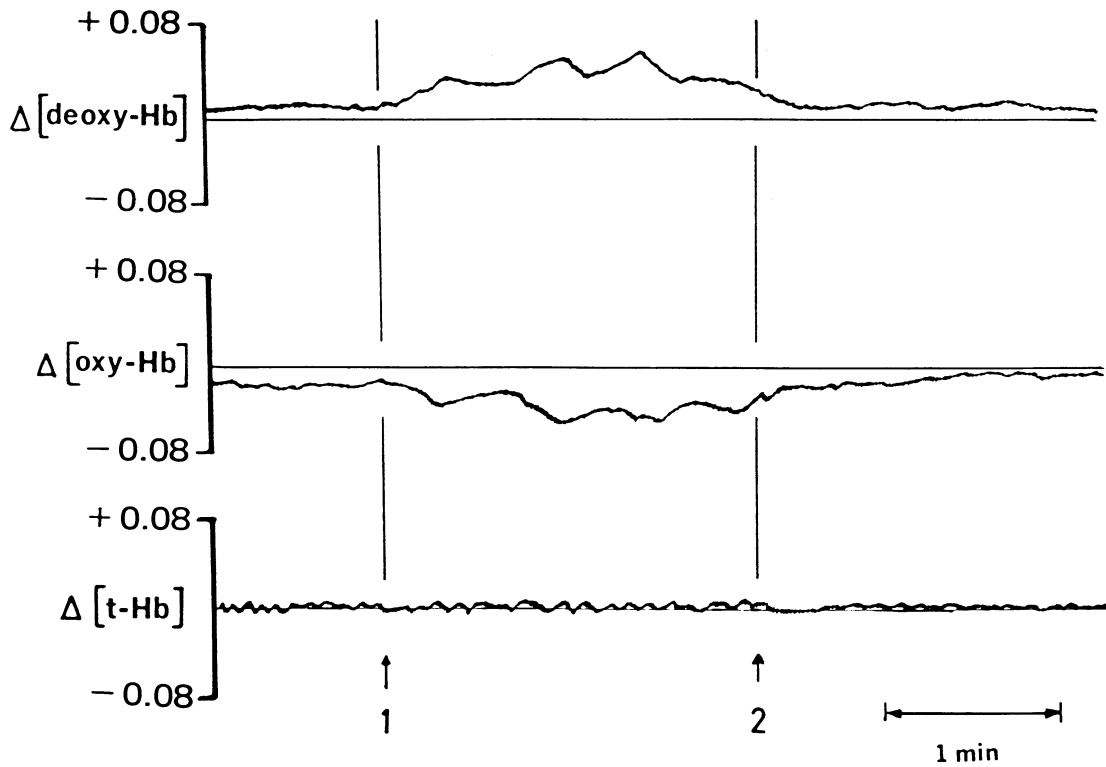


Figure 2. Changes in concentrations of oxy-Hb, deoxy-Hb and t-Hb in the frontal region of the dominant hemisphere, the left frontal region, during mental arithmetic in a middle-aged man (47 years old). Arrow 1 denotes the start of mental arithmetic. Arrow 2 denotes the end of mental arithmetic.

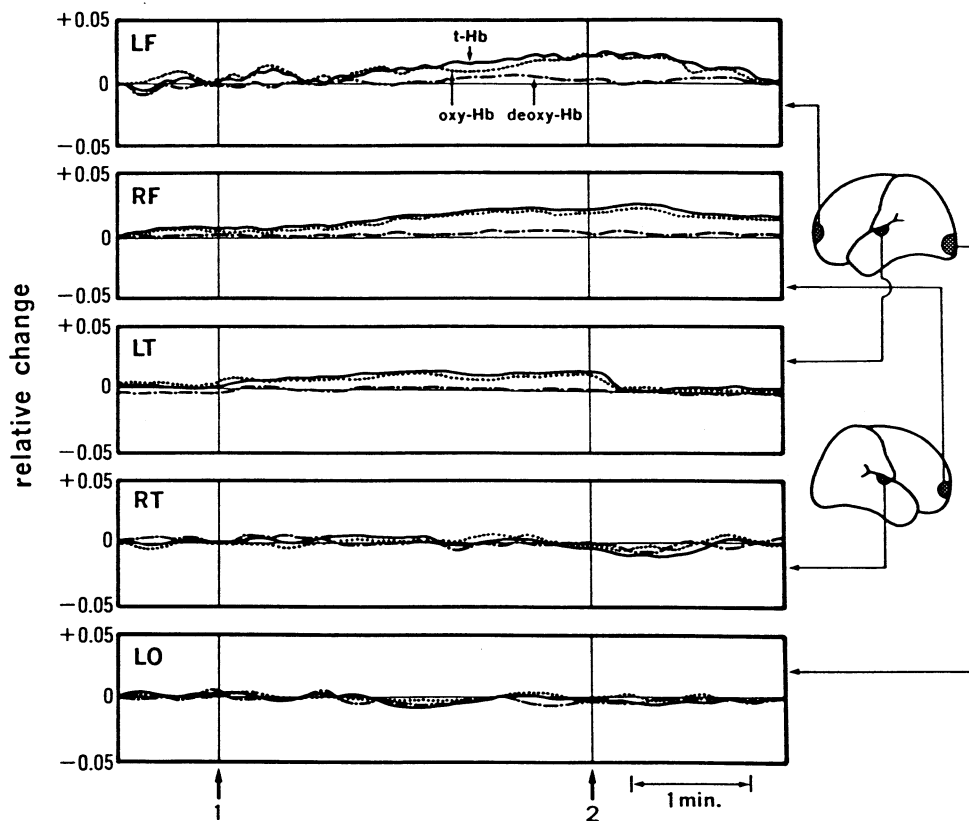


Figure 3. Changes in regional cerebral oxygenation during mental arithmetic in a 30-year-old male subject. Arrows 1 and 2 denote the beginning and end of mental arithmetic, respectively. RF, traces from the right frontal region; RT, traces from the right temporal region. LF, LT and LO traces from the left frontal, left temporal and left occipital regions, respectively.

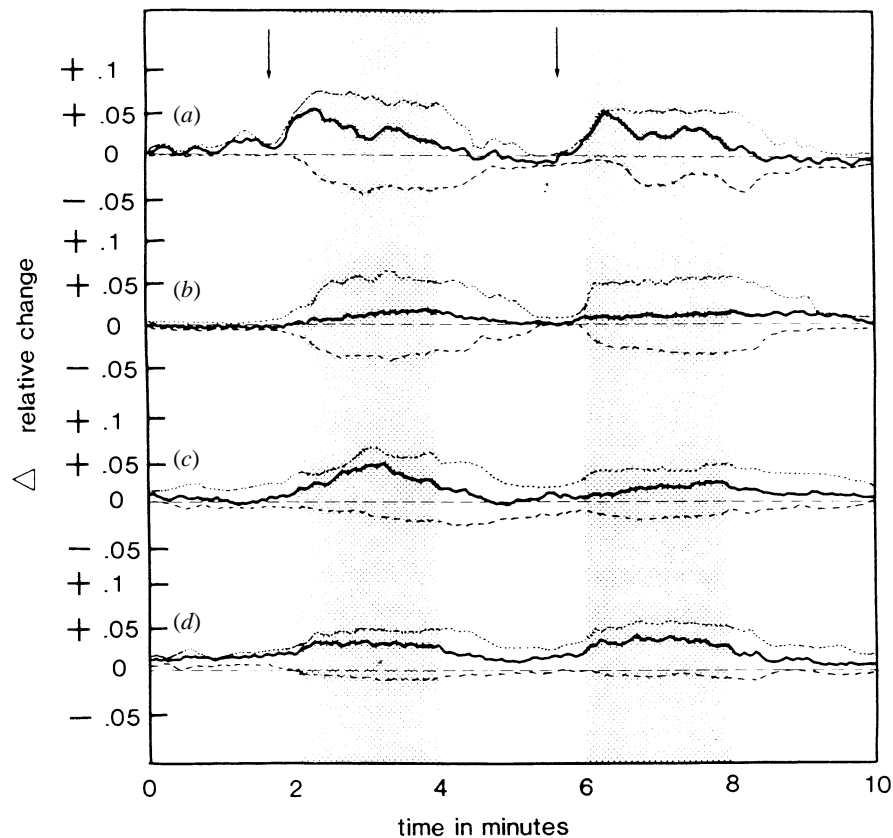


Figure 4. Typical continuous recording patterns of changes in [oxy-Hb] (dotted line), [deoxy-Hb] (broken line) and [t-Hb] (solid line) during mirror-drawing tasks (MDT) in right-handed volunteers. The MDTs were performed during the period shown by the shaded areas (the first column with right hand, the second with left hand). Vertical arrows indicate the beginning of instructions on how to carry out the MDT. (a) A typical recording from supposedly dominant (left) hemisphere of a volunteer of dominant hemisphere response pattern (26 years old, female); (b) a typical recording from non-dominant (right) hemisphere of the same subject; (c) a typical recording from dominant (left) hemisphere of a volunteer of bilateral response pattern (27 years old, male); (d) a typical recording from non-dominant (right) hemisphere of the same subject.

such as acoustic stimulation (Hoshi & Tamura 1993*a*). Simultaneous measurements of the left temporal and occipital regions showed an increase in [t-Hb] in the left temporal region during the auditory stimulation. In contrast, a decrease in [t-Hb] was observed in the left occipital region. The decrease in [t-Hb] reflected a relative decrease in neuronal activity compared with the resting period. The interesting feature in this observation is that both [t-Hb] and [deoxy-Hb] increased in the left temporal region. Photic stimulation causes an increase in [t-Hb] in the occipital region (Kato *et al.* 1993). It was, therefore, concluded that NIRS could detect the increase in CBF caused by a specific stimulation in its primary projection area. Similarly, NIRS responses to somatosensory stimulation by finger tapping were also reported (Villringer & Dirnagl 1995).

Figure 3 shows multichannel recordings of NIRS responses observed in five brain regions while the subject was doing mental arithmetic. The start of mental arithmetic caused gradual increases in [t-Hb] together with increases in [oxy-Hb] in the left temporal and bilateral frontal regions. The haemoglobin oxygenation state did not change in the right temporal and left occipital regions. Thus, multichannel recording could reveal spatio-temporal variations of neuronal

activity during various physiological stimuli (Hoshi & Tamura 1993*a*).

Very rapid (1 s) neuronal activation caused by emotional stress in the frontal region was also demonstrated by NIRS (Hoshi & Tamura 1993*b*). Similarly, rapid responses to stimuli were observed in the visual cortex (Villringer *et al.* 1993) and motor cortex (Maki *et al.* 1995; Villringer & Dirnagl 1995) by NIRS, which agreed with the results of fMRI. However, we could not find such rapid responses during either photic (Hoshi & Tamura 1993*a*) or somatosensory stimulation (unpublished data). Our algorithm is based on the principle of dual wavelength photometry, which minimizes the artefacts due to the light scattering change and volume change. Therefore, some of these rapid NIR responses might be due to contamination by an unknown optical artefact related to the neuronal activation.

(b) Lateralization of right and left hemispheres

Using multichannel recording NIRS (Okada *et al.* 1993), we systematically measured the gender- and handedness-dependent difference between right and left hemispheres. During a mirror-drawing task (MDT), bilateral simultaneous increases in [oxy-Hb] and decreases in [deoxy-Hb] in the forebrain occurred

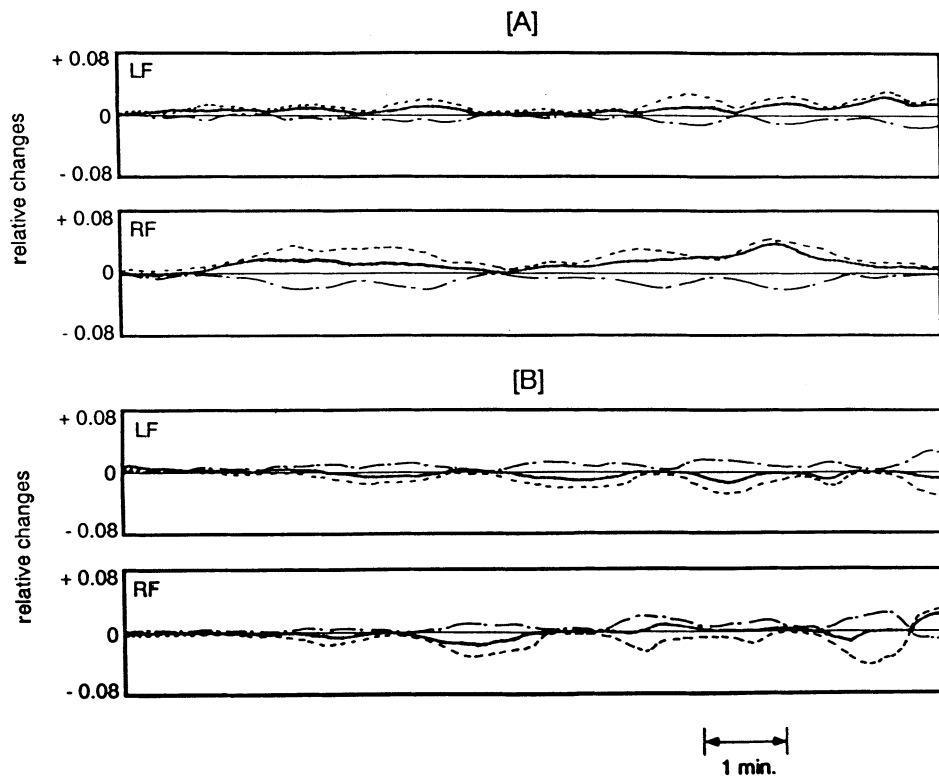


Figure 5. Fluctuations of [oxy-Hb], [deoxy-Hb] and [t-Hb] in the bilateral frontal regions during the resting state. [A] and [B] denote traces from different subjects. Dotted line denotes [oxy-Hb]; broken line denotes [deoxy-Hb]; solid line denotes [t-Hb].

in all volunteers (figure 4). The response patterns were classified into a 'dominant pattern' and a 'bilateral pattern' by the behaviour of changes in [t-Hb]. In the dominant pattern, [t-Hb] increased in the dominant hemisphere, but there was no significant change in [t-Hb] in the non-dominant hemisphere. In the bilateral pattern, [t-Hb] increased in both hemispheres. NIRS results showed that most women used both sides of the brain (bilateral pattern) when concentrating on carrying out the MDT test, whereas most men, especially left-handed ones, used mainly the dominant hemisphere.

Hemispheric lateralization in brain function is well known, but there have been few studies that monitored real-time simultaneous oxygenation and haemodynamics of brain hemispheres. By the use of NIRS, we could demonstrate that there were region-dependent symmetric or asymmetric variations in the oxygenation and haemodynamics of the brain hemispheres due to different types of mental stimuli (Okada *et al.* 1995).

(c) Application of NIRS in the study of psychiatric diseases

Extension of multichannel NIRS to the study of psychiatric diseases was attempted for schizophrenia (Okada *et al.* 1994). In response to the MDT, normal volunteers showed distinct and well-integrated dominant and bilateral patterns. On the other hand, half the schizophrenics showed 'dysregulated patterns' between hemispheres which never appeared in normal volunteers. From these data, it can be said

that certain schizophrenic symptoms may be related to defective interhemispheric integration. No alcoholics showed the dysregulated pattern. In conclusion, NIRS has wide applicability in the study of psychiatric disease; it is easy to perform; and the equipment required is portable.

(d) Sleep study

When we applied NIRS to the study of human sleep, we found two distinct and unique responses that had not been observed by simple EEG (electroencephalograph) analysis or conventional monitoring of haemodynamics (Hoshi *et al.* 1994a). During the first transition from the awake stage to non-REM (rapid eye movement) sleep the volunteers showed decreases in CBF. This response is a well-known phenomenon. However, several volunteers clearly showed an increase in oxygen consumption at this first transition, where cerebral oxygenation decreased. Such increases in $CMRO_2$ were not observed during the later non-REM sleep periods of the night. Thus, the transition from wakefulness to sleep seemed to be a distinct state, differing from other sleep and waking states in neurophysiological activity. During REM sleep both CBF and $CMRO_2$ were practically the same as the awake level, whereas during the transition from REM sleep to arousal a disproportionate increase in CBF compared with $CMRO_2$ was observed. These data suggested that the flow-metabolic coupling mechanism is reset to a new level during sleep. It must be noted that our NIRS measurement was very close to the conditions of normal all-night sleep, when com-

pared with those studies using PET or f-MRI. Thus, various sleep-associated diseases can be easily monitored even at home.

(e) Fluctuations in the cerebral oxygenation state during the resting period

During our series of functional mapping studies, we found the existence of significant fluctuations in cerebral [oxy-Hb], [deoxy-Hb] and [t-Hb] during the resting period. The interval of the fluctuations was 0.6–4.5 min. A typical example is shown in figure 5, where left–right differences were observed. The behaviour of changes in [oxy-Hb] and [t-Hb] in the left frontal region was quite different from that in the right frontal region: frequency in the left frontal region was faster than that in the right (Figure 5[A]. Figure 5[B] shows the traces where the phases of these fluctuations differed between left and right frontal regions. The time-course and frequency of the fluctuations also differed among the various regions, such as the temporal and occipital regions. It is unlikely that these fluctuations are a result of alterations of systemic circulation. Changes in cerebrospinal fluid pressure might also be unrelated, as the interval of the fluctuations was longer than that of changes in cerebrospinal fluid pressure. We also found that there were fluctuations of [oxy-Hb] and [deoxy-Hb] without fluctuation of [t-Hb]. Such fluctuations mean that the CMRO₂ fluctuates. We believe, therefore, that the fluctuations are related to those in neuronal activity specific for the brain area monitored. The absence of the fluctuations in the bilateral frontal regions during sleep (Hoshi *et al.* 1994*a*) and under general anaesthesia supports this hypothesis. However, neurophysiological evidence for our interpretation is lacking, and therefore further study combined with EEG and MEG is required.

4. DISCUSSION

Though quantification of the changes of NIRS responses is still lacking, the advantages of functional mapping by NIRS are well demonstrated. Because of the non-interfering nature of near-infrared light with various electromagnetic radiations, simultaneous measurements by PET, fMRI and SPECT are possible. An example is our cognitive study (Hoshi *et al.* 1994*b*), where if NIRS or PET was performed alone, decreases in CBF and CMRO₂ during the mental task would not have been accepted. Simultaneous measurements with SPECT (single photon emission computed tomography) and NIRS were also performed in neurosurgery, where changes in [t-Hb] measured by NIRS were well correlated with those in CBF measured by SPECT. Combined measurements of NIRS and other techniques will allow quantitative interpretation of the change in NIRS parameters.

In the present paper, we have focused mainly on the ‘unexpected’ results obtained by NIRS imaging. The increase in [deoxy-Hb] induced by stimulation is critical, and may conflict with results obtained by f-

MRI. The existence of possible fluctuations of brain activity during the resting state is also critical with respect to functional mapping studies, in which the resting state was compared to the activated state. These ‘unexpected’ results are one of the proofs of the usefulness of NIR imaging.

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