Dynamic multichannel near-infrared optical imaging of human brain activity

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HOSHI, YOKO, AND MAMORU TAMURA. *Dynamic multichannel near-infrared optical imaging of human brain activity.* J. Appl. Physiol. 75(4): 1842–1846, 1993.—The present paper demonstrates functional brain mapping with an optical imaging technique by using tissue-transparent near-infrared light. With a maximal five-channel optical monitoring system, we succeeded in detecting region-specific changes in both the hemoglobin oxygenation state and blood volume during various mental tasks, in addition to visual and auditory stimulation. The time course of increases in blood supply varied with each brain region and depended on the type of internal operations occurring during the mental tasks. Changes in the hemoglobin oxygenation state were also different from region to region. This showed that there were regional variations of the oxygen delivery-oxygen utilization relationship during activation of brain activity. The usefulness of multichannel near-infrared functional imaging was well documented.

near-infrared spectroscopy; functional brain mapping; mental tasks; hemoglobin oxygenation state

THE EXISTENCE OF a tight coupling between neuronal activity and regional cerebral blood flow (rCBF) enables the use of measurements of rCBF, energy-related metabolism, and blood volume for functional brain mapping (16, 17). Detection of these changes requires a high spatiotemporal resolution. Near-infrared spectroscopy (NIRS), which is developing into a useful tool for noninvasive clinical monitoring of tissue oxygenation, achieves a high temporal resolution in <1 s (9). NIRS measures changes in concentrations of oxygenated ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) in the gas-exchange circulation and tissue blood volume, which reflect alterations in the oxygen supply-oxygen demand relationship in the illuminated volume of tissue (1, 20). NIRS is oriented toward use for clinical monitoring (2, 14). Here, we employed this technique for functional mapping of human brain activity.

SUBJECTS AND METHODS

The subjects were seven healthy male volunteers (age range 28–32 yr; median 30 yr). They were all right-handed. Informed consent was obtained from all subjects before each investigation.

The NIRS instrument (Shimadzu, Kyoto, Japan) was developed according to the method of Hazeki and Tamura (7). Validity of this method was confirmed repeatedly by both human (21) and animal investigations (13). 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 baseline values according to the following equations using the computer system at a temporal resolution of 100 ms (22)

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

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

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

where A_{780}, A_{805}, and A_{830} are the absorbance readings at 780, 805, and 830 nm, respectively. Because scattering effects prevent determination of the optical path length, the results are expressed in relative amounts rather than in absolute absorbance units. Summation of changes in [oxy-Hb] and [deoxy-Hb] gives changes in the total hemoglobin concentration ($[\text{Hb}_T]$). Under conditions with constant hematocrit, the changes in $[\text{Hb}_T]$ can be used as an indicator of changes in cerebral blood volume within the optical field (1, 4, 23). The degree of change in cerebral blood volume measured by NIRS is linearly related to changes in CBF measured by other techniques, such as the ^{133}Xe clearance technique (15). For multichannel measurements, five instruments were simultaneously operated. To confirm the absence of interference effects from the measuring lights on the brain, we first switched each instrument on and off separately and successively at an interval of a few seconds after all optodes were fixed on the subjects. We found that signals were not affected by the presence or absence of light illumination by the adjacent optodes.

The optodes were placed at a distance 1.5 cm from each other on the head adjacent to Brodmann's area 10 (frontal association field; the frontal region), area 41 (primary auditory cortex; the temporal region), and area 17 (primary visual cortex; the occipital region) (3; see Fig. 4). Spatial resolution depends on the distance between two optodes. Under the conditions of the present study, near-infrared light detected changes in the brain tissue within the depth of ~3 cm from the surface, which was confirmed by our time of flight measurement of the picosecond-length pulse (11, 12). We found that the minimum working distance was ~1 cm in our conditions. Only the left hemisphere was measured in four subjects. Measurements of the frontal and temporal region of the right hemisphere were added in three subjects. An electroencephalogram and the heart rate were monitored si-

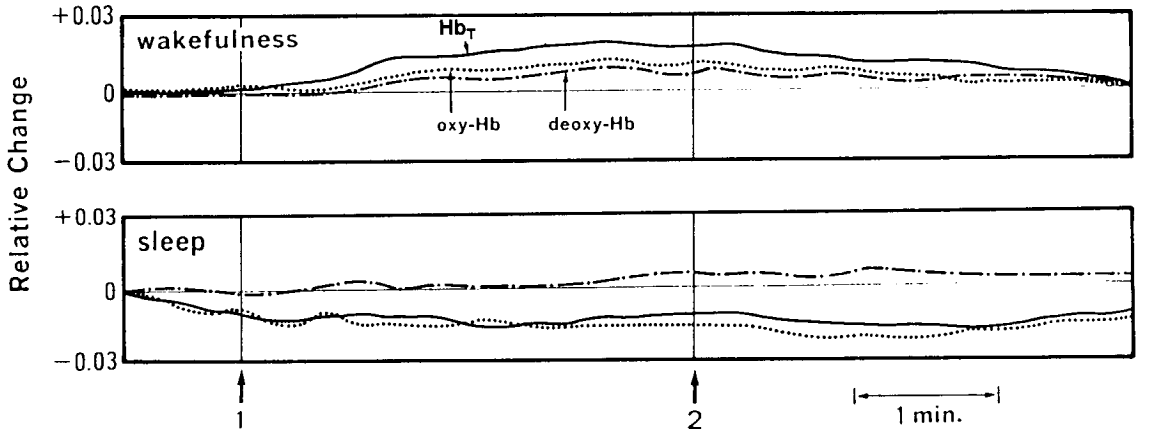

FIG. 1. Changes in oxygenated ([oxy-Hb]), deoxygenated ([deoxy-Hb]), and total ([Hb_T]) hemoglobin concentrations in left occipital region during visual stimulation in wakefulness and sleep in 29-yr-old man. Baselines were selected from resting state, and these values were taken as zero for each signal. Changes from baseline are represented as relative amounts, with 0.001 taken as order of magnitude of change for each signal. Upward (plus) and downward (minus) trends show increase and decrease in values, respectively. Stimulator was located 30 cm from subject's face and produced continuous flashes at 10 Hz (between *arrows 1* and *2*). Subject fell asleep after 1st stimulation. Effects of visual stimulation were investigated in both wakefulness (*top*) and sleep (*bottom*). Beginning of *bottom traces* was point of transition from wakefulness to sleep.

multaneously. The subjects were awake but with their eyelids closed, were relaxed in the supine position, and did not receive any stimulation while in a resting state in a dark room. After the 20-min resting state, in which α-wave activity was observed on the electroencephalogram, multiple brain regions were evaluated simultaneously by using physiological stimulations, including a 10-Hz flash photic stimulation (visual stimulation), classical music (auditory stimulation), and mental tasks, such as solving a mathematical problem and doing mental arithmetic. During photic stimulation and while solving the mathematical problem, subjects opened their eyelids. Mental tasks were performed in a light room.

RESULTS

First, we examined whether activation of Brodmann's area 17 and area 41 was specifically detectable during visual and auditory stimulation in four subjects (photic stimulation, 2 subjects; auditory stimulation, 2 subjects). The same stimuli were repeated two or three times for the same subject. Figure 1 shows changes in the hemoglobin oxygenation state and [Hb_T] in the left occipital region during visual stimulation. Within 20 s after the start of photic stimulation, a gradual increase in [Hb_T], together with increases in [oxy-Hb] and [deoxy-Hb], was observed in wakefulness (Fig. 1, *top*). After the cessation of stimulation, the levels very slowly reverted to original levels. In the frontal and temporal regions of the left hemisphere, no significant changes in hemoglobin oxygenation were observed (data not shown). When the subject closed his eyelids after the first stimulation, neither the hemoglobin oxygenation state nor blood volume changed. During the second resting state, the subject fell asleep, which was associated with decreases in both [Hb_T] and [oxy-Hb] compared with those responses in wakefulness. In stage 1 sleep, photic stimulation did not cause an increase in [Hb_T] (Fig. 1, *bottom*). The frontal and temporal regions did not show changes in hemoglobin oxygenation (data not shown). The other subject showed changes similar to those shown in Fig. 1, except that no change in [deoxy-Hb] in the occipital region was observed during the second stimulation. When these two subjects closed their eyelids in wakefulness, no increases in [Hb_T] in their occipital regions were elicited by photic stimulation.

Figure 2 shows changes in the hemoglobin oxygenation state and [Hb_T] in the temporal and occipital regions of the left hemisphere during the first auditory stimulation. The subject listening to classical music through earphones from a tape recorder was associated with an increase in [Hb_T] together with increases in [oxy-Hb] and [deoxy-Hb] in the temporal region (Fig. 2, *top*). The original levels were rapidly restored after the cessation of stimulation. In the left occipital region, [Hb_T] decreased concomitantly with a decrease in [oxy-Hb], whereas [deoxy-Hb] remained unchanged (Fig. 2, *bottom*). In the left frontal region, no significant changes in hemoglobin oxygenation were observed (data not shown). The second stimulation was associated with changes similar to those shown in Fig. 2. The other subject also showed changes similar to those shown in Fig. 2 in the temporal region, whereas no significant changes were observed in the occipital regions during either the first or second stimulation.

Next we tried to evaluate effects of mental tasks on regional cerebral oxygenation in multiple brain regions. Figure 3 shows the NIRS traces observed in the left hemisphere during the subject solving a mathematical problem. The subject read a text (between *arrows 1* and *2*) and then solved the problem (between *arrows 2* and *3*). First, [Hb_T] increased concomitantly with increases in [oxy-Hb] and [deoxy-Hb] in the occipital region (Fig. 3, *bottom*). When the subject started to solve the problem (*arrow 2*), [Hb_T] increased in both the frontal (Fig. 3, *top*) and the temporal (Fig. 3, *middle*) regions. The increase in [Hb_T] was accompanied by increases in both [oxy-Hb] and [deoxy-Hb] in the temporal region, whereas in the

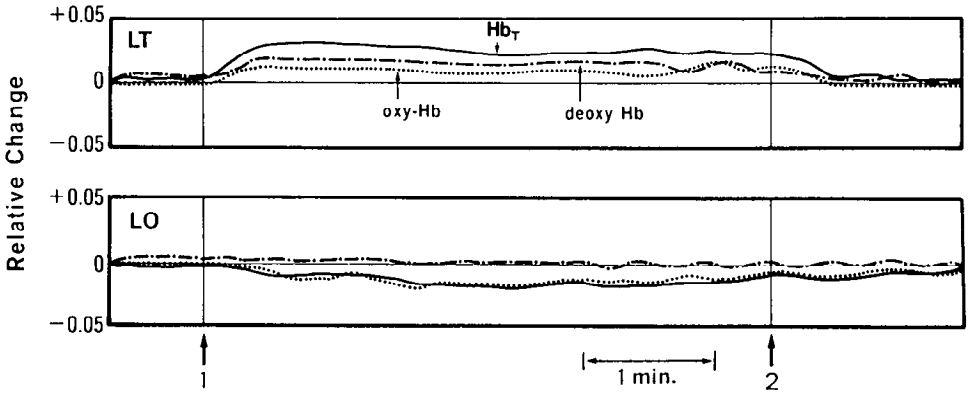

FIG. 2. Changes in [oxy-Hb], [deoxy-Hb], and [Hb_T] in left temporal and occipital regions during auditory stimulation in 28-yr-old man. Subject listened to classical music through earphones from a tape recorder (between *arrows 1* and 2). LT, traces from left temporal region; LO, traces from left occipital region.

frontal region [oxy-Hb] increased but [deoxy-Hb] decreased. When the subject completed the problem (*arrow 3*), all levels slowly returned to the original levels but in a different manner in each region.

Figure 4 shows the NIRS traces observed in five brain regions while the subject was doing mental arithmetic, in which 30 calculations were performed while he was listening to the problems. The start of mental arithmetic (*arrow 1*) caused gradual increases in [Hb_T] together with increases in [oxy-Hb] in the left temporal and bilateral frontal regions. After the subject quit doing mental arithmetic (*arrow 2*), these levels returned to the original levels rapidly in the left temporal region, whereas they returned very slowly in the bilateral frontal regions. The hemoglobin oxygenation state did not change in the right and the left occipital regions. α-Blocking was observed during the time the subject was doing mental arithmetic.

DISCUSSION

[Hb_T] increases either with an increase in CBF or with any impedance to cerebral venous return (1). In the present case, the increase in [Hb_T] reflects an increase in rCBF. As is seen in Fig. 1, a decrease in [Hb_T] in sleep is often observed in the frontal region (unpublished data), and several studies of cerebral hemodynamics in sleep with other techniques also demonstrated global decreases in rCBF (18, 19). Absence of an increase in [Hb_T] during visual stimulation in sleep might not be due to a decline in neuronal excitability but simply due to a diminution in light-intensity stimulation caused by closing the eyelids, since visual evoked potential is obtained even in sleep and an increase in CBF was not observed while the subject's eyelids were closed in wakefulness. Increases in [Hb_T] during photic stimulation were accompanied by both an increase and no change in [deoxy-Hb] in the occipital region, which meant that the oxygen supply-oxygen utilization relationship varied in the same stimulation. This relationship is discussed in detail below. As shown in Fig. 2, a decrease in [Hb_T] in the left occipital region during auditory stimulation, which seemed to be a phenomenon nonspecific to auditory stimulation because it was not observed in the other subject, reflected a relative decrease in neuronal activity compared with that in the resting state in this subject. In contrast, increases in [Hb_T] in the occipital and the temporal regions during photic and auditory stimulation, respectively, were regarded as specific responses to each

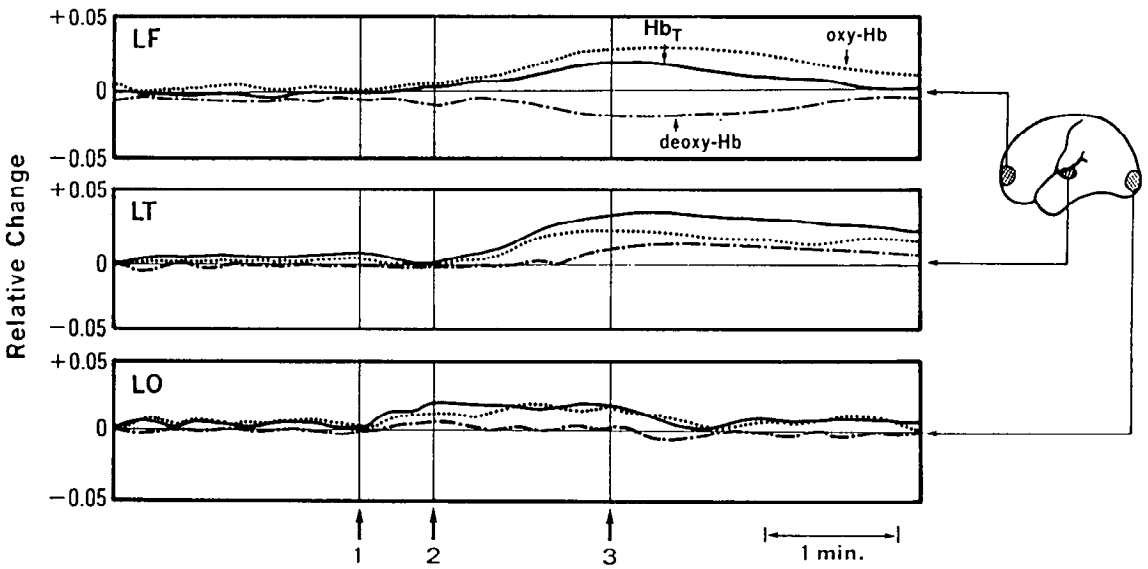

FIG. 3. Changes in regional cerebral oxygenation in left hemisphere while 29-yr-old male subject solved mathematical problem. Subject read a text (between *arrows 1* and 2) and then solved a mathematical problem (between *arrows 2* and 3). LF, traces from frontal region. Schematic drawing of left cerebral hemisphere shows detectable areas marked by shading.

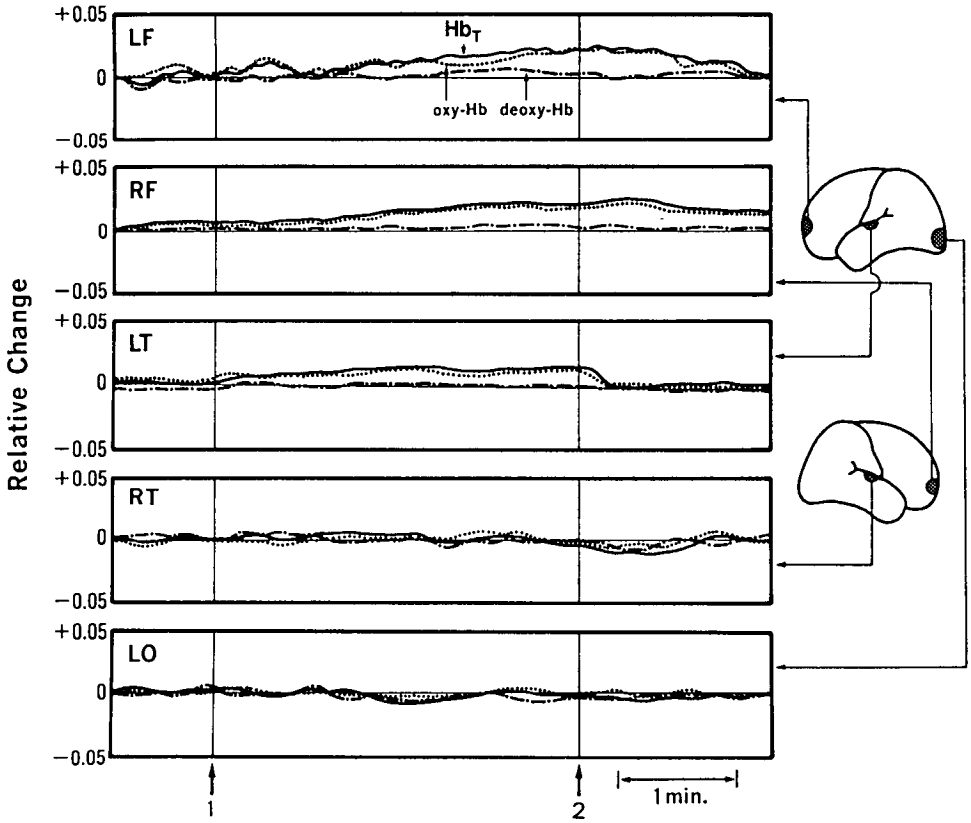

FIG. 4. Changes in regional cerebral oxygenation during mental arithmetic by 30-yr-old male subject. *Arrows 1* and *2* denote beginning and end of mental arithmetic, respectively. RF, traces from right frontal region; RT, traces from right temporal region.

stimulation. Thus, NIRS could detect the increase in CBF caused by a specific stimulation in its primary projection field.

As shown in Figs. 3 and 4, the time courses of increases in [Hb_T] varied with each brain region and depended on the type of internal operation occurring during the mental task. Because in the present study we did not measure subjects with other techniques, such as positron emission tomography, simultaneously with NIRS, we could not precisely identify the illuminated regions. However, the fact that the activation of the temporal region did not occur while the subject was reading the text but rather occurred while he was solving the problem, as shown in Fig. 3, suggests that near-infrared illumination of the temporal region passed through the very limited area of the secondary auditory association field, i.e., the area responsible for the retrieval of the verbal memory required to solve a problem. Activation of the left temporal region observed in Fig. 4 might be attributable to the subject listening to problems (auditory stimulation). Impulses from the cochlea of each ear are conveyed to the bilateral primary auditory cortices, although the association field in the dominant hemisphere is mainly responsible for higher brain function (5). Thus, near-infrared illumination of the right temporal region might pass through the auditory association field rather than through the primary auditory cortex.

Changes in the hemoglobin oxygenation state, which mainly reflect those in cerebral mixed venous blood (24), also behaved in a different manner from region to region. This meant that there were regional variations of the oxygen delivery-oxygen utilization relationship during activation of brain activity. In Fig. 3, where a typical example can be seen, [Hb_T] increased concomitantly with an increase in [oxy-Hb] in both the frontal and temporal regions, which meant that increases in cerebral blood supply exceeded increases in neuronal oxygen consumption. Such physiological overcompensation of the flow was also demonstrated by Fox and Raichle (6). In contrast, the behavior of [deoxy-Hb] was quite different between the frontal and temporal regions. The [deoxy-Hb] decreased in the frontal region, whereas in the temporal region it first showed no change and then increased concomitantly with a further increase in [Hb_T]. These changes meant that the degree of overcompensation in the frontal region was greater than in the temporal region and that oxygen consumption increased more in the later period than in the first period. Thus the oxygen supply-oxygen utilization relationship not only varied with each brain region but even varied in the same region during activation of brain activity, which could not have been found by measuring CBF alone.

In a previous study, we observed that emotional stress activated neurons in the frontal region of the dominant hemisphere immediately (within 1 s) and that NIRS could detect that CBF increase simultaneously (8). Such a rapid response of CBF was seen also in the present study. The only difference between the present and the previous data was that activation of neurons occurred gradually in the present study, whereas it was momentary in the previous study. Because NIRS can detect changes in the oxidative metabolism accompanying neuronal activation at a time scale similar to the hemodynamic response time, we have an opportunity to differentiate between neuronal and metabolic control of hemodynamic changes associated with neuronal activation (10). Moreover, NIRS requires neither large expensive equipment nor an exogenous contrast medium, unlike

positron emission tomography and magnetic resonance imaging. The apparatus is easy to handle and portable. Thus, this will allow functional imaging of brain activity outside of specific institutions. As the next step, we will employ near-infrared optical imaging in an attempt to achieve deeper understanding of human brain activity in both temporal and spatial domains.

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