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Near-Infrared Optical Detection of Sequential Brain Activation in the Prefrontal Cortex during Mental Tasks

Yoko Hoshi*,† and Mamoru Tamura*

**Biophysics Group, Research Institute for Electronic Science, Hokkaido University, Sapporo 060, Japan; and †New Energy and Industrial Technology Development Organization, Tokyo 170, Japan*

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To examine the spatiotemporal differences of brain activation during mental tasks, changes in the oxygenation and hemodynamics in two regions of the prefrontal cortex were measured simultaneously by near-infrared spectroscopy (NIRS). Subjects were eight healthy adults who attempted to solve three different mathematical problems. The behavior of concentration changes in oxy-, deoxy-, and total hemoglobin in one brain region varied with the time course (more than 10 min). This suggested that regional brain activity varied during the performance of the mental task. In each single subject, the pattern of these changes varied with each problem, and this variation differed from subject to subject. When NIRS traces in two regions were compared, it was seen that activated regions moved alternatively: when in one region total hemoglobin that had first increased returned to the resting level, in the other it started to increase. These region-dependent temporal variations of brain activity might reflect mental processes. It is thus concluded that NIRS has the potential for imaging the sequence of brain activation.

A major aim of functional mapping studies of the human brain is to visualize internal operations occurring in various brain functions. To achieve this aim, elucidation of functional networks is necessary. With the advent of modern neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (FMRI), a great deal of functional mapping data has been accumulating. Since interregional correlations are not obvious through simple examination of differences in mean regional activity, however, correlational analysis of these mapping data has been used to examine the functional associations between different areas of the brain (Clark *et al.*, 1984; Horwitz *et al.*, 1984; Soncrant *et al.*, 1986). Recent computational methods, which require several assumptions, allow for the assessment of changes in the interregional correlations of entire systems (McIntosh and Gonzalez-Lima, 1991; Friston *et al.*, 1993). In contrast to these mathematical methods, detecting the sequence of brain activation is a more direct way to examine the functional networks. At the moment, echoplanar FMRI and optical imaging seem to make this possible. Near-infrared spectroscopy (NIRS), a new noninvasive optical technique, measures changes in concentrations of oxygenated and deoxygenated hemoglobin ([oxy-Hb], [deoxy-Hb]) mainly in cerebral venous blood. Summation of changes in [oxy-Hb] and [deoxy-Hb] gives changes in the total hemoglobin concentration ([t-Hb]). Changes in [t-Hb], which reflect those in blood volume within the optical field, are in general closely related to those in cerebral blood flow (CBF) (Hoshi *et al.*, 1994). Recently, NIRS has been developed into a useful tool for functional mapping of human brain activity (Hoshi and Tamura, 1993; Villringer *et al.*, 1993). With this technique, we can see the successive changes in cerebral oxygenation and hemodynamics accompanying those in neuronal activity in real time because of its high temporal resolution (1 s). In addition, unlike echoplanar FMRI, NIRS allows studies outside of specific institutions. Although NIRS does not image the brain structure, simultaneously operating multiple NIRS instruments make it possible to examine regional differences in the oxygenation and hemodynamics (Hoshi and Tamura, 1993). Here, we applied NIRS to examine the spatiotemporal differences in brain activity between two regions of the prefrontal cortex during mental tasks. The purpose of this study is to evaluate the possibility of imaging the sequence of brain activation with NIRS.

SUBJECTS AND METHODS

Subjects were eight healthy volunteers, ages 22 to 32 years (one female, seven males). They were all right-handed. Informed consent was obtained prior to the beginning of the study.

Two NIRS instruments (OM-100A, Shimadzu, Japan) were simultaneously operated. This instrument consists of three semiconductor laser diodes (wave-

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lengths of 780, 805, and 830 nm) as light sources and calculated changes in [oxy-Hb] and [deoxy-Hb] from arbitrary baseline values according to the following equations,

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

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

and

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

where A_{780}, A_{805}, and A_{830} are the absorbance recordings at 780, 805, and 830 nm, respectively. Because scattering effects prevent determination of the optical pathlength, the results are expressed in relative amounts rather than in absolute amounts.

In four subjects, bilateral prefrontal cortices were measured. Two illuminated light guides were attached on the forehead 3.5 cm above the bilateral pupils. Two detecting light guides were attached 3 cm above each illuminated guide. In the rest of the subjects, two brain regions of the left prefrontal cortex were measured. Two pairs of light guides at a distance of 3 cm from each other, with the illuminated guides placed 3.5 cm above the horizontal line through the bilateral pupils, were placed 0.5 and 5 cm left of the midline of the forehead. Under these experimental conditions, there were no interference effects from the measuring lights on the brain, which was confirmed by the fact that when we switched each instrument on and off separately and successively at an interval of a few seconds, NIRS signals were not affected by the presence or absence of light illumination from the adjacent light guides.

The subjects, awake but with their eyelids closed, sat relaxed on a chair and did not receive any stimulation while in the resting state under dim light. Subjects attempted to solve three different mathematical problems (see Appendix) with an interval of 25–30 min between tasks. The task order was problem 1–2–3. This type of task causes large interindividual variability in the brain's reactivity. However, the present study was not designed for an anatomical description of the brain regions that participate in solving problems but to examine dynamic features of changes in regional brain activity during prolonged activated state (about 10 min). We therefore asked the subjects to solve these complicated mathematical problems. When subjects performed tasks, they opened their eyelids and were allowed to calculate on paper with a pen. Problems 1 and 2 were read by the subjects themselves, while problem 3 was read out repeatedly until the subjects understood it. Prior to each task, they were in a resting state for 15–20 min. Continuous NIRS measurement was started from the first resting state.

RESULTS

It took more than 10 min for each subject to solve each mathematical problem. The behavior of changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in one brain region varied with the time course. The pattern of changes in these parameters varied with each problem in one brain region (Figs. 1, 3, and 4). They were also different from subject to subject in the same brain region (Figs. 1 and 2). NIRS traces in the right and left prefrontal cortices were often different from each other (8 of 12 pairs of traces).

Figure 1 shows NIRS traces made during solving of problem 1. The subject read the problem between 1 and 2 and solved it between 2 and 3. Increases in [t-Hb] and [oxy-Hb] were first observed in the left prefrontal cortex (LF). When these changes returned to the resting levels, [t-Hb] and [oxy-Hb] started to increase in the right prefrontal cortex (RF). Degrees of increases in [t-Hb] and [oxy-Hb] fluctuated and relatively large increases in [t-Hb] and [oxy-Hb] were accompanied by a decrease in [deoxy-Hb]. In contrast to the RF, in the LF [t-Hb] and [oxy-Hb] started to decrease about 10 min after the start of solving the problem, and then increases in [t-Hb] and [oxy-Hb] together with a decrease

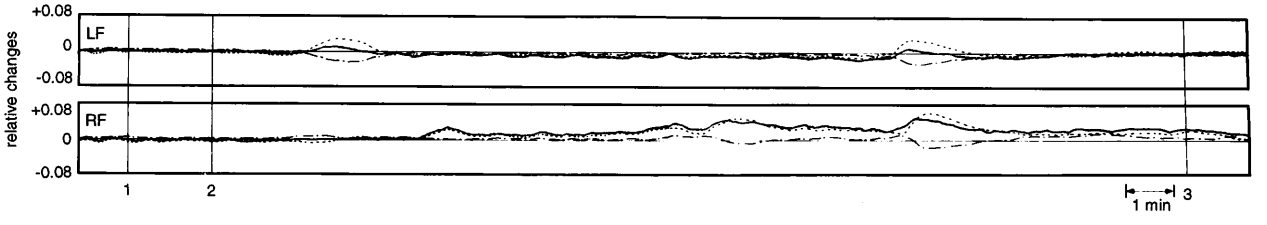


FIG. 1. Changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in the bilateral prefrontal cortices during solving of problem 1. The subject was a 26-year-old male student. Baselines were selected from resting state, and these values were taken as 0 for each signal. Changes from baseline are represented as relative 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. He read a text between 1 and 2 and then solved the problem between 2 and 3. He found the correct answer at line 3. NIRS traces in the LF and RF were different from each other. The behavior of changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in each brain region varied with the time course. LF, traces from left prefrontal cortex; RF, traces from right prefrontal cortex; dotted line, [oxy-Hb]; broken line, [deoxy-Hb]; solid line, [t-Hb].

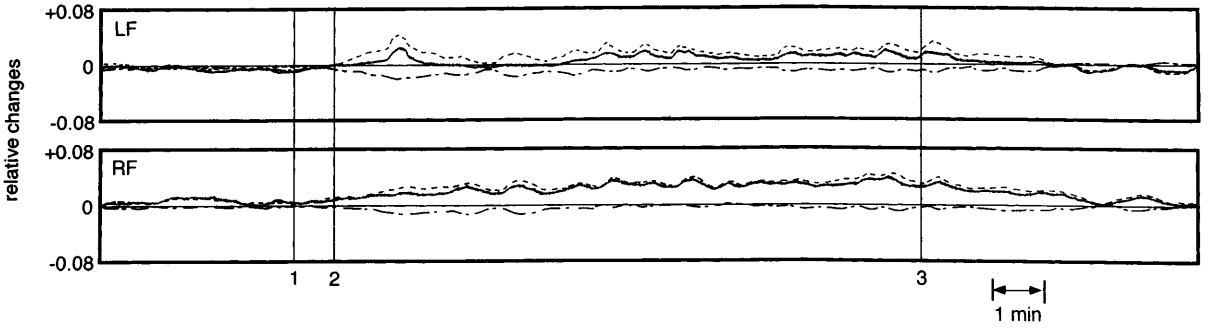


FIG. 2. Changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in the bilateral prefrontal cortices prior to, during, and after solving of problem 1. The subject was 24-year-old male student. He read a text between 1 and 2 and then solved the problem between 2 and 3. He found the correct answer at line 3. Unlike Fig. 1, NIRS traces in the LF and RF were similar to each other. It should be noted that task-unrelated changes in the hemoglobin oxygenation state existed prior to and after solving of problem.

in [deoxy-Hb] occurred for 1.5 min. After that, these parameters returned to the resting levels. At line 3, he found the correct answer.

When problem 1 was solved by another subject different patterns of changes were observed (Fig. 2). In this subject, the NIRS traces in bilateral prefrontal cortices were similar to each other. Increases in [t-Hb] and [oxy-Hb] with a decrease in [deoxy-Hb] occurred immediately after the start of solving the problem. These changes were observed throughout the task, except that [t-Hb] returned once to the resting level in the LF for about 3 min. Degrees of changes in NIRS parameters fluctuated while the problem was being solved. This subject also found the correct answer at line 3. NIRS parameters returned to the original levels 2.7 and 3.3 min after finding the correct answer in the LF and RF, respectively. After that, however, [t-Hb] and [oxy-Hb] started to decrease in the LF, while increases in [t-Hb] and [oxy-Hb] were observed in the RF. Task-unrelated increases in [t-Hb] and [oxy-Hb] were also observed in the RF before the subject read the problem. The degrees of task-unrelated changes were less than those of the changes observed during solving the problem. Since these fluctuations of the hemoglobin oxygenation state were observed in all resting records, we asked the subjects to start performing a task when all NIRS parameters were on the baselines.

Figure 3 shows the NIRS traces when the same subject as in Fig. 1 solved problem 2. Increases in [t-Hb] and [oxy-Hb] with no change in [deoxy-Hb] were observed soon after solving the problem in the RF. About 6 min after the start of solving the problem they returned to the resting levels. In contrast, no changes were first observed in the LF. About 5 min after the start of solving the problem [t-Hb] and [oxy-Hb] started to decrease, while [t-Hb] and [oxy-Hb] returned to the resting level in the RF. About 10 min after the start of solving the problem, increases in [t-Hb] and [oxy-Hb] accompanying a decrease in [deoxy-Hb] occurred transiently in the LF, and then [t-Hb] and [oxy-Hb] decreased again. About 2 min before finding the correct answer (line 3), [t-Hb] and [oxy-Hb] increased concomitantly with a decrease in [deoxy-Hb] in the RF.

Figure 4 shows the NIRS traces when the same subject as in Figs. 1 and 3 solved problem 3. In contrast to what occurred when solving problems 1 and 2, almost synchronous behavior of NIRS traces was observed in the LF and RF. In the beginning, solving the problem caused immediate increases in [t-Hb] and [oxy-Hb] together with decreases in [deoxy-Hb], the degree of which fluctuated. He found the correct answer at line 3.

Comparison of NIRS traces between two regions of the left prefrontal cortex also gave different patterns in

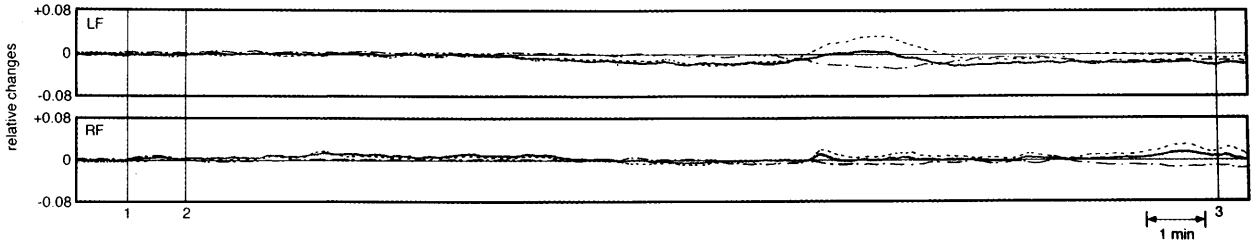


FIG. 3. Changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in the bilateral prefrontal cortices during solving of problem 2. The subject was the same as in Fig. 1. He read a text between 1 and 2 and then solved the problem. He found the correct answer at line 3. NIRS traces in the LF and RF were different from each other. The behavior of changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in each brain region varied with the time course.

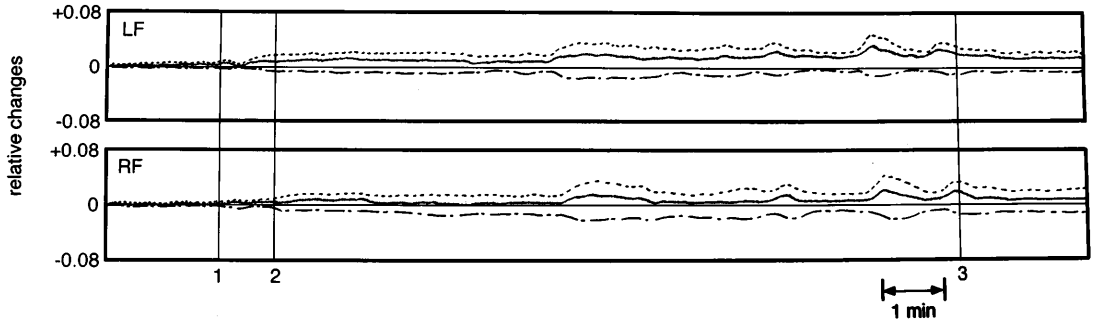


FIG. 4. Changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in the bilateral prefrontal cortices during solving of problem 3. The subject was the same as in Figs. 1 and 3. The problem was read out between 1 and 2 and then the subject solved it between 2 and 3. He found the correct answer at line 3. Almost synchronous behavior of NIRS traces was observed in the LF and RF.

7 of 12 pairs of traces. Figure 5 shows the traces obtained during solving of problem 3. In the beginning the problem caused immediate decreases in [t-Hb], [oxy-Hb], and [deoxy-Hb] in the left medial prefrontal cortex (LFm). These NIRS parameters transiently returned to the resting levels 2 min after the subject began to solve the problem. Then they decreased again and lasted for about 2.5 min after the subject found the correct answer at line 3. In contrast, in the left lateral prefrontal cortex (LFl), an increase in [oxy-Hb] and a reciprocal decrease in [deoxy-Hb] with no change in [t-Hb] were first observed. About 2.5 min after beginning to solve the problem, [t-Hb] and [oxy-Hb] started to increase. Further increases in [t-Hb] and [oxy-Hb] with a decrease in [deoxy-Hb] were observed within 1 min before finding the correct answer.

When this subject solved problem 2, NIRS traces different from those in Fig. 5 were observed (Fig. 6). In the LFm, [t-Hb] and [oxy-Hb] started to increase about 4 min after beginning. These changes lasted about 7 min. In the later phase of this period, [t-Hb] and [oxy-Hb] returned once to the resting levels and then increased again. After this period, no significant changes were observed until he gave up (line 3). In the LFl, about 5 min after starting to work on the problem, [t-Hb] and [oxy-Hb] began to increase. The [deoxy-Hb] level first showed no change and later increased. When he said that he was shocked because he could not find the answer, [t-Hb], [oxy-Hb], and [deoxy-Hb] suddenly increased in the LFm, though there were no changes in the LFm.

DISCUSSION

Since NIRS measures changes in [oxy-Hb] and [deoxy-Hb] mainly in cerebral mixed venous blood, it provides information about changes in the oxygen supply–oxygen utilization relationship, that is, oxygen metabolism and hemodynamics in brain tissue. In a typical case, brain activation is accompanied by increases in [t-Hb] and [oxy-Hb] with a decrease in [deoxy-Hb], while deactivation is associated with decreases in [t-Hb] and [oxy-Hb] with no change or a decrease in [deoxy-Hb]. The present study demonstrated that the direction of these changes was not constant but varied with the time course in the activated state. This meant that one brain region in the prefrontal cortex was activated in certain periods while performing a mental task, while

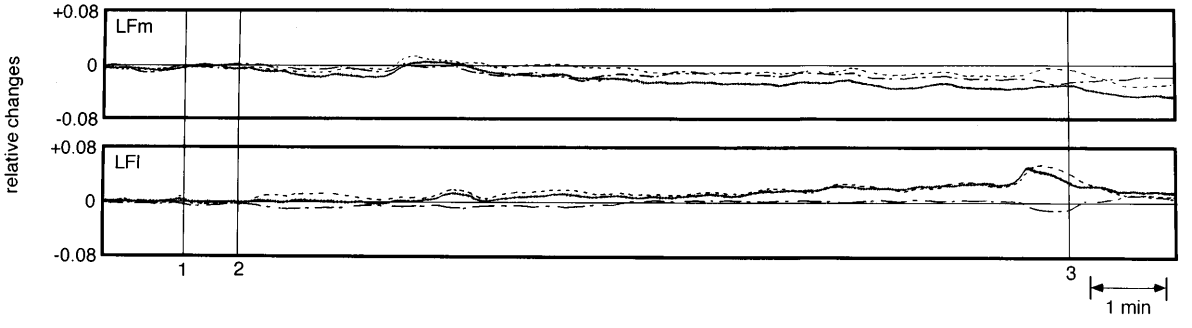


FIG. 5. Changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in two regions of the left prefrontal cortex during solving of problem 3. The subject was a 25-year-old male student. The problem was read out between 1 and 2 and then the subject solved it between 2 and 3. He found the correct answer at line 3. NIRS traces in the LFm and LFl were different from each other. In the LFm [oxy-Hb], [deoxy-Hb], and [t-Hb] decreased, while in the LFl increases in [oxy-Hb] and [t-Hb] were observed. LFm, traces from left medial prefrontal cortex; LFl, traces from left lateral prefrontal cortex.

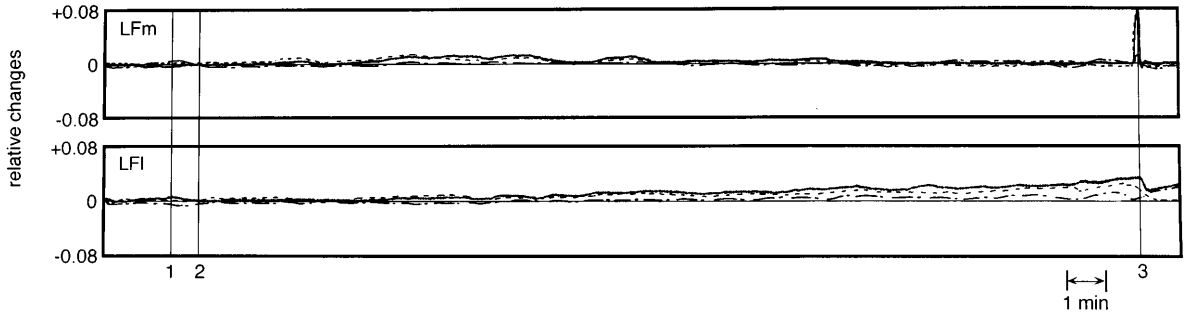


FIG. 6. Changes in [oxy-Hb], [deoxy-Hb], and [t-Hb] in two regions of the left prefrontal cortex during solving of problem of 2. The subject was the same as in Fig. 5. He read a text between 1 and 2 and then solved the problem between 2 and 3. He could not find the correct answer and gave up (line 3). When he said that he was shocked because he could not find the answer, [oxy-Hb], [deoxy-Hb], and [t-Hb] suddenly increased in the LFm (line 3).

in the rest periods brain activity was not changed or actually decreased. The prefrontal cortex is considered to perform higher levels of neural processing, and the interchange of information between modalities is accomplished in this cortex (Benson, 1994). Such complexity of neural processing in the prefrontal cortex accounts for the temporal variation of neuronal activities observed here.

It is widely recognized that the prefrontal cortex plays a major role in the control of human mental functions (Goldman-Rakic, 1987). Five higher control functions, that is, sequencing, drive, executive (cognitive) control, future memory, and self-awareness, can be attributed to the prefrontal cortex (Stuss and Benson, 1984; Ingvar, 1985). Animal and clinical observations indicate that prefrontal functions are localized. For example, the lateral aspects of the prefrontal cortex control sequential processing (Fuster, 1985). In addition, the results shown in Fig. 6 suggest that the left medial prefrontal cortex includes neurons controlling emotion. It is thus expected that multiple regions are activated serially during mental tasks in the prefrontal cortex. In the present study, NIRS could show that activated regions moved during problem solving, that is, the activation occurred first in one region and thereafter in another (Figs. 1 and 3).

Differences in NIRS traces between two regions can be explained by functional heterogenity in the prefrontal cortex. As shown in Fig. 4, however, nearly synchronous behavior of changes in NIRS parameters was also observed in the bilateral prefrontal cortices, while the same subject showed nonsynchronous behavior when solving two other problems. Such synchronous behavior of NIRS traces was also observed in two regions in the left prefrontal cortex. The prefrontal cortex has extensive neuronal networks that include multiple connections to both nearby and distant heteromodal and unimodal regions. It is thus conceivable that the two brain regions measured here influenced each other through such connections and, as a result, synchronous behavior of changes in neuronal activity was observed.

The present data demonstrated considerable variability in patterns of changes in NIRS parameters between subjects and within subjects during the activated state. Since thought processing varies with kind of mental task, the variability within subjects is explainable. As for the variability between subjects, there are two possible explanations. One is that thought processing can be different from subject to subject. The other is that NIRS does not measure the same brain regions in all subjects because the use of the pupils as landmarks for optode positioning is not precise enough to account for the individual anatomic variability.

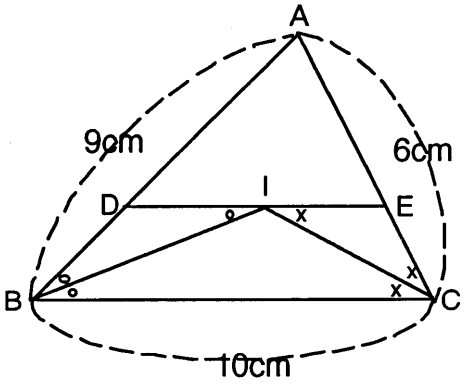
After the subjects solved mathematical problems, NIRS parameters slowly returned to the baselines in a different manner in each brain region. This slow returning has been often observed in our series of cognitive studies, while it contrasted with the observations during other physiological stimuli such as the finger-moving task, where changes returned to the original levels immediately after the cessation of stimulation (Kleinscmidt *et al.*, 1996). At the moment, we have no explanation for the reason why mental tasks had residual effects on the oxygenation and hemodynamics in the prefrontal cortex. A PET study, however, has reported that visual stimulation had a large residual effects on CBF, while quick recovery of rCBF was seen in auditory stimulation and the finger-moving task (Momose *et al.*, 1991). This difference between the visual and the other tasks was explained by a difference in the sensory receptor-specific adaptation system.

Imaging information flow among various processes is another future direction for functional mapping studies. The present study has demonstrated that NIRS is suitable for this purpose, while it also has several problems. First, anatomical information is lacking in NIRS studies. Thus, simultaneous measurements in multiple brain regions are necessary. In addition, the combined measurement by NIRS and MRI is required. Second, NIRS cannot measure subcortical structures such as basal ganglia and thalamus. Under these circumstances, the proper design of the tasks is crucial

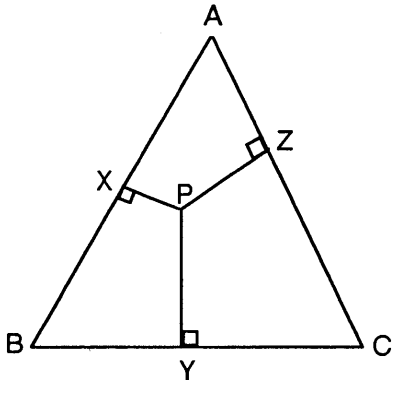
to the application of NIRS to the study on functional connectivity between cerebral cortices. The third is not a NIRS-specific problem. As is shown in Fig. 2, there are task-unrelated changes in the hemoglobin oxygeantion state during the resting period. Our previous study has demonstrated that in some instances, the degrees of changes caused by mental tasks were within this resting variation (Hoshi and Tamura, 1997). Thus, taking account of these fluctuations of the hemoglobin oxygenation is critical for the interpretation of data. NIRS enables the continuous measurements of hemodynamic and metabolic changes in both the resting and the activated state. It is thus concluded that the combined measurement by multichannel NIRS and structural MRI will be a novel approach to the sequence of brain activation.

APPENDIX

Problem 1: How long is the circumference of Triangle **ADE?**



Problem 2: Prove that $\mathbf{PX} + \mathbf{PY} + \mathbf{PZ} = K$ (constant value).



Problem 3: Determine the values of natural numbers p, q, r, s, and t that satisfy the following equation,

$$1/p + 1/q + 1/r + 1/s + 1/t = 1,$$

where $p \neq 2$, $p < q < r < s < t$.

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