Language-Activated Cerebral Blood Oxygenation and Hemodynamic Changes of the Left Prefrontal Cortex in Poststroke Aphasic Patients

A Near-Infrared Spectroscopy Study

Kaoru Sakatani, MD, DMSc, PhD; Yuxiao Xie, MD; Wemara Lichty, PhD; Sunwei Li, MD; Huancong Zuo, MD

Background and Purpose—In normal subjects, regional cerebral blood flow (rCBF) is greatly increased by neuronal activity, whereas the cerebral metabolic rate for O₂ is increased only slightly. However, it is not clear what kinds of cerebral blood oxygenation and hemodynamic changes can be induced by language activities in language-relevant areas of poststroke aphasics. In the present study, we investigated the difference in the changes of cerebral blood oxygenation and hemodynamics in the left prefrontal cortex induced by language activities between normal subjects, poststroke nonaphasic patients, and nonfluent aphasic patients using near-infrared spectroscopy (NIRS).

Methods—Twenty-nine participants performed speech tasks, such as confrontational naming, to evaluate changes among poststroke nonfluent (Broca’s) aphasia patients (10 cases; mean ± SEM, 56.9 ± 2.2 years), age-matched normal subjects (13 cases; 50.7 ± 2.2 years) and poststroke nonaphasic patients (6 cases; 52.5 ± 3.9 years). The optodes of NIRS were placed over the left prefrontal cortex. We analyzed the NIRS parameter (oxyhemoglobin [oxy-Hb], deoxyhemoglobin [deoxy-Hb], and total hemoglobin [total-Hb]) changes by qualitative pattern analysis of the parameter changes and quantitative analysis of the parameter values among the groups.

Results—The most common NIRS parameter change was an increase in oxy-Hb and total-Hb, with a slight decrease or no change in deoxy-Hb in the normal subjects (5 of 13 cases, 38.5%) and the nonaphasic cerebrovascular disease (CVD) patients (3 of 6 cases, 50.0%). In contrast, the most common pattern in the aphasic patients was an increase of deoxy-Hb, with an increase of oxy-Hb and total-Hb (5 of 10 cases, 50%). However, this pattern was observed in only 3 of 13 cases (23.1%) in the normal subjects and 1 of 6 cases (16.7%) in the nonaphasic CVD patients. The mean (±SEM) changes of deoxy-Hb of the aphasic patients, the normal subjects, and the nonaphasic CVD patients were 0.78 ± 0.29, 0.06 ± 0.16, and −0.18 ± 0.22, respectively. The statistical analysis demonstrated a significant effect for deoxy-Hb (P < 0.05), with the aphasic patients differing significantly from the normal subjects and the nonaphasic CVD patients, while the 2 nonaphasic groups did not differ from each other.

Conclusions—The present results demonstrate a multiplicity of language-activated cerebral blood oxygenation and hemodynamic changes in the left prefrontal cortex in the nonaphasic and aphasic groups. The increase of deoxy-Hb with increases of oxy-Hb and total-Hb in the aphasics during language tasks suggests that the left prefrontal cortex of the aphasics utilizes more oxygen than the nonaphasics during language tasks. Finally, functional MRI, which images the activation area in the brain by detecting the reduced concentration of deoxy-Hb during neuronal activation, should be performed on the patients with cerebral dysfunction, giving special consideration to the possible multiplicity of the rCBF and cerebral oxygen metabolism responses to functional tasks. (Stroke. 1998;29:1299-1304.)

Key Words: aphasia ■ cerebral blood flow ■ cognition ■ language ■ spectroscopy, near-infrared

Aphasia is a disorder of language functions and 1 of the major symptoms caused by CVD. To address the processing mechanism of language functions, PET or fMRI has been performed on normal subjects to image activation areas during language tasks.¹⁻⁵ These studies have demonstrated that several cortical areas outside the classic language centers such as Broca’s area and Wernicke’s area are also activated by language processing, associated with an activation of the language centers. In addition, recent PET activation studies on aphasics demonstrated that cortical areas, which are not

Received December 16, 1997; final revision received March 5, 1998; accepted March 26, 1998.

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activated in normal subjects, are functioning in aphasics during language tasks.6,7

PET activation studies on visual8 or somatosensory functions8,9 demonstrated that rCBF is greatly increased by focal increases in neuronal activity, whereas the CMRO2 increases only slightly, leading to a decrease in the extracted fraction of available O2.8–10 Therefore, the rCBF increase induced by neuronal activity decreases the concentration of deoxy-Hb in the cerebral vessels. By detecting the reduced concentration of the paramagnetic species, deoxy-Hb, during neuronal activation, fMRI images the activation area in the brain.11,12 However, it is not clear whether language activity in the language-relevant areas of poststroke aphasics is associated with similar changes of cerebral blood oxygenation and hemodynamics induced by relatively simple physiological stimulations such as visual or somatosensory stimulation. This is particularly important in the fMRI studies on cerebral function, since the activation area in the brain may be overlooked by fMRI if the activation area is not associated with the reduction of deoxy-Hb.

NIRS is an optical method to measure concentration changes of oxy-Hb and deoxy-Hb in cerebral vessels by means of the characteristic absorption spectra of hemoglobin in the near-infrared range.7,13,14 Changes in total-Hb (sum of oxy-Hb and deoxy-Hb) indicate blood volume changes and correlate with CBF changes under conditions with constant hematocrit levels and perfusion pressures.15–17 Thus, NIRS can measure both blood oxygenation and hemodynamics in the brain noninvasively. NIRS has been applied to the evaluation of cerebral blood oxygenation and hemodynamic changes during neuronal activities including cognitive functions.18–24 Simultaneous measurements made with NIRS and PET demonstrated that neuronal activation during mental tasks resulted in changes in cerebral oxygenation and hemodynamics measured by NIRS that were consistent with PET results.20

In the present study, we used NIRS to investigate the difference in the changes of cerebral blood oxygenation and hemodynamics induced by language activities between normal subjects, poststroke nonaphasics patients, and nonfluent aphasic patients. We evaluated these changes in the left prefrontal cortex, which plays an important role in language function in normal subjects.1

Subjects and Methods

Subjects

Twenty-nine participants performed speech tasks to evaluate changes among poststroke aphasics (10 cases; age [mean±SEM], 56.9±2.2 years), age-matched normal subjects (13 cases; age, 50.7±2.2 years), and poststroke nonaphasic patients (6 cases; age, 52.5±3.9 years). The groups did not differ in age (P=0.20). The poststroke aphasics was caused by infarction in 4 cases, hemorrhage in 5, and mixed (infarction and hemorrhage) in 1. CT or MRI was taken of each poststroke patient to obtain morphological information before the NIRS study. The clinical profiles of the patients are shown in Table 1. The subjects were all strongly right-handed, as confirmed by the Edinburgh Handedness Inventory. Each poststroke aphasic patient underwent the WAB before the NIRS study. The nonfluent (Broca’s) aphasics were of varying severity, ranging from mild impairment to severe global aphasia. Four of the poststroke nonaphasic patients had suffered an infarction, and 2 had suffered a hemorrhage. The NIRS measurement area (see next section) in the left frontal lobe was morphologically normal in all the subjects. Informed consent to participate in the study was obtained from each subject.

Three speech tasks that are commonly difficult for aphasics to perform were administered. The primary task confrontational naming is included in most aphasia test batteries25 because of its sensitivity to nonfluent (Broca’s) aphasia. To further evaluate the ability of NIRS to detect aphasia-related differences, 2 additional speaking tasks were given that are not generally included in standard aphasia tests. These were counting (from 1 to 50) and talking about what happened yesterday. The evaluation included a rest period (5 to 10 minutes), followed by the cognitive performance. Participants were seated and had their eyes open during the entire experiment.

Near-Infrared Spectroscopy

We measured cerebral blood oxygenation and hemodynamics with NIRO-500 (Hamamatsu Photonics K.K.), which has been used in previous NIRS activation studies.21–24 Near-infrared light from laser diodes (wavelengths, 775, 825, 850, and 904 nm) was directed at the head through a fiberoptic bundle (“optode”), and reflected light was collected in the receiving fiberoptic bundle and transmitted to a photomultiplier tube. With the use of an algorithm developed by Cope et al.,20 absolute concentration changes of oxy-Hb, deoxy-Hb, and total-Hb (equal to oxy-Hb plus deoxy-Hb) were continuously analyzed by means of a computer interfaced with the apparatus. NIRS data are expressed in arbitrary units. If the differential path length factor of the adult head is assumed to be 5.9, which was determined by time-of-flight measurement of a picosecond-length optical pulse through the tissues, 1 arbitrary unit equals 1 μmol/L.27 The optodes were placed at a distance of 3 or 4 cm on the left forehead; the center of the 2 optodes was identical to the Fp2 position of the international EEG 10–20 system. In 5 subjects, the location of the optodes was identified by MRI with use of vitamin E capsules. MRI showed that the optodes were placed over the left prefrontal cortex with an optode distance of 3.5 cm, the maximum depth of the region is 4 cm,27 and thus the NIRS measurement area in the present study corresponded to the left prefrontal cortex.

Data Analysis

In many NIRS studies on neuronal activation using NIRO-500, the values of NIRS parameters were compared between different individuals.21–24 However, the values of NIRS parameters can be affected by individual differences in anatomic structures through which light passes, including skull thickness, skin absorption, and scattering properties of underlying brain structures such as subarachnoid space. Therefore, some of the NIRS activation studies analyzed only qualitative changes of NIRS parameters, such as pattern changes of NIRS parameters, with an NIRS instrument that does not indicate absolute values of the parameter changes.18–20 In the present study, we mainly analyzed the changes of NIRS parameters (oxy-Hb, deoxy-Hb, and total-Hb) induced by the language tasks by qualitative pattern analysis of the parameter change: we classified several common patterns according to the changes of the NIRS parameters during the language tasks.

In addition to the pattern analysis, we analyzed the quantitative data of the NIRS parameters for the following reasons. First, the path length factor is constant once the interoptode distance exceeds 2.5

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**Selected Abbreviations and Acronyms**

<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CMRO2</td>
<td>Cerebral metabolic rate for O2</td>
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<td>CVD</td>
<td>Cerebrovascular disease</td>
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<td>deoxy-Hb</td>
<td>Deoxyhemoglobin</td>
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<td>fMRI</td>
<td>Functional MRI</td>
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<td>NIRS</td>
<td>Near-infrared spectroscopy</td>
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<tr>
<td>oxy-Hb</td>
<td>Oxyhemoglobin</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>rCBF</td>
<td>Regional cerebral blood flow</td>
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<tr>
<td>total-Hb</td>
<td>Total hemoglobin</td>
</tr>
<tr>
<td>WAB</td>
<td>Western Aphasia Battery</td>
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in view of the fact that the interoptode distance was 3 or 4 cm in the present study, intersubject variability related to path length factor was minimal. Second, the reported NIRS studies, including our study on the CO2 response of normal adults, support the feasibility of analyzing the absolute values of NIRS parameters as measured by NIRO-500 when comparing groups of subjects. We analyzed the maximum value from the preactivation baseline rather than the average value during task performance, since the NIRS parameters tended to return toward the preactivation baseline after reaching the maximum value or to fluctuate during the task, possibly because of attention changes. One-way ANOVAs were conducted to compare age-matched normal subjects, nonaphasic CVD patients, and aphasic patients, and the Student-Newman-Keuls test was performed to compare group means.

**Results**

In the normal subjects, the language task significantly altered oxygen metabolism and hemodynamics in the left prefrontal cortex. The changes measured by NIRS were classified into 4 patterns. Figure 1 summarizes these patterns of NIRS parameter changes during the task. "A through E" on the abscissa represent the patterns of NIRS parameter change during the task. "+" and "−" below A through E indicate an increase and a decrease, respectively, of the NIRS parameters designated in the left during the task. The ordinate indicates percentage of the patterns in normal age-matched control subjects (M), nonaphasic CVD patients (m), and aphasic patients (f).

The patterns of the NIRS parameter changes observed in the nonaphasic CVD patients were similar to those in the normal subjects (Figure 1). The most common pattern of NIRS parameter in the nonaphasic CVD patients was the same as that in the normal subjects; 3 of 6 cases (50%) showed an increase in oxy-Hb and total-Hb, with no change or a slight decrease in deoxy-Hb (pattern A). A decrease of oxy-Hb, total-Hb, and deoxy-Hb (pattern B) was observed in 2 of 6 cases (33.3%). An increase of deoxy-Hb associated

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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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<tbody>
<tr>
<td>Oxy-Hb</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Deoxy-Hb</td>
<td>-</td>
<td>0</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Total-Hb</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</table>

**Figure 1.** Patterns of NIRS parameter changes induced by naming task in normal age-matched control subjects, nonaphasic CVD patients, and aphasic patients. "A through E" on the abscissa represent the patterns of NIRS parameter change during the task. "+" and "−" below A through E indicate an increase and a decrease, respectively, of the NIRS parameters designated in the left during the task. The ordinate indicates percentage of the patterns in normal age-matched control subjects ( ), nonaphasic CVD patients ( ), and aphasic patients ( ).
with an increase in oxy-Hb and total-Hb (pattern C) was observed in only 1 of 6 cases (16.7%).

Although aphasic patients had some difficulty performing the language task, the task altered the oxygen metabolism and hemodynamics in the left prefrontal cortex for all of the aphasic patients except 1.

In contrast to the normal subjects and the nonaphasic CVD patients, the most common pattern in the aphasic patients was an increase of deoxy-Hb with an increase of oxy-Hb and total-Hb (pattern C). This pattern was observed in 5 of 10 cases (50%). Figure 2B shows a typical example of the NIRS parameter change during the language task. Within 10 seconds from the start of the task, first oxy-Hb began to increase, and then deoxy-Hb gradually increased. These increases in oxy-Hb and deoxy-Hb led to an increase of total-Hb.

The second most frequent pattern was an increase in oxy-Hb and total-Hb with a slight decrease or no change in deoxy-Hb (pattern A). This pattern was observed in 3 of 10 cases (30%) from the aphasic patient group. One of the aphasic patients showed an increase in deoxy-Hb with a decrease in oxy-Hb and total-Hb. Another aphasic patient (No. 10) could perform the language task to some degree; however, no changes of the NIRS parameters were observed during the task.

Table 2 summarizes the mean changes of oxy-Hb, deoxy-Hb, and total-Hb in the aphasic patients, the normal subjects, and the nonaphasic CVD patients. Results of a 1-way ANOVA comparing the performance of the 3 groups in the naming task demonstrated a significant effect for deoxy-Hb [F(2,27) = 4.47, P < 0.05], with aphasic patients differing significantly from normal subjects and nonaphasic CVD patients, while the 2 nonaphasic groups did not differ from each other. In contrast, there were no significant differences in oxy-Hb or total-Hb among the groups (P > 0.05). Generalizability about the results was supported by the statistical analyses for the talking and counting tasks. As evident in Table 2, the results of the 1-way ANOVAs support the naming findings in that significance was attained for deoxy-Hb (P < 0.05) but not for oxy-Hb or total-Hb. Outcomes of the naming task were replicated in that aphasia patients differed significantly from the 2 nonaphasic groups only on deoxy-Hb and that for deoxy-Hb the normal subjects and CVD patients without aphasia did not differ.

Finally, we evaluated a variety of possible reasons for the NIRS parameters of the aphasic patients. These include types of CVD (ie, infarction or hemorrhage), the degree of aphasia, the Aphasia Quotient from the WAB test, age, lesion location, and interval between stroke and NIRS measurements. None of these factors illuminate the findings.

**Discussion**

The left prefrontal cortex is related to various higher brain functions including language processing.1–4,29 Recent fMRI studies have demonstrated that the left prefrontal cortex outside the classic “Broca’s area” is also activated by language processing that is associated with activation of Broca’s area.1 In the present study in which NIRS was used, we demonstrated that the language task caused changes in the oxygen metabolism and hemodynamics of the left prefrontal cortex. The second most frequent pattern was an increase in oxy-Hb and total-Hb with a slight decrease or no change in deoxy-Hb (pattern A). This pattern was observed in 3 of 10 cases (30%) from the aphasic patient group. One of the aphasic patients showed an increase in deoxy-Hb with a decrease in oxy-Hb and total-Hb. Another aphasic patient (No. 10) could perform the language task to some degree; however, no changes of the NIRS parameters were observed during the task.

Table 2 summarizes the mean changes of oxy-Hb, deoxy-Hb, and total-Hb in the language task. The ordinates indicate concentration changes of oxy-Hb, deoxy-Hb, and total-Hb in arbitrary units (a.u.). Horizontal thick bars indicate the period of the task. Note the difference in changes of deoxy-Hb between A and B during the task.

**Figure 2.** A, Typical example of the most common pattern of NIRS parameter change in the normal subjects during naming task. B, Typical example of the most frequent pattern of NIRS parameter change in the aphasic patients (No. 5; see Table 1) during the task. The ordinates indicate concentration changes of oxy-Hb, deoxy-Hb, and total-Hb in arbitrary units (a.u.). Horizontal thick bars indicate the period of the task. Note the difference in changes of deoxy-Hb between A and B during the task.

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Age-Matched Controls</th>
<th>Nonaphasic CVD Patients</th>
<th>Aphasics</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Naming</td>
<td>Oxy-Hb</td>
<td>0.43±0.54</td>
<td>0.58±0.64</td>
<td>1.41±0.39</td>
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<tr>
<td></td>
<td>Deoxy-Hb</td>
<td>0.06±0.16*</td>
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<td>Talking</td>
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<td>Deoxy-Hb</td>
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<td>−0.58±0.33*</td>
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<td>Total-Hb</td>
<td>0.41±0.31</td>
<td>−0.09±0.64</td>
<td>0.63±0.32</td>
</tr>
</tbody>
</table>

Values are mean±SEM in arbitrary units. P < 0.05 for values with different letters using 1-way ANOVA with Student-Newman-Keuls test.
cortex. In addition, these changes of the oxygen metabolism and hemodynamics measured by NIRS showed several different patterns in subjects.

In the normal subjects and nonaphasic CVD patients, increases of oxy-Hb and total-Hb were the most commonly observed changes during the language tasks. These changes are consistent with the reported NIRS parameter changes induced by various neuronal activations including mental tasks. Although increases of oxy-Hb and total-Hb can be induced by either an increase in CBF or any impedance to cerebral venous return, the changes induced by neuronal activations reflect an increase in rCBF. The increase of rCBF induced by neuronal activity decreases the concentration of deoxy-Hb in the cerebral vessels since the increase of CMRO₂ is much less than that of rCBF.

In the present study, however, the decrease of deoxy-Hb was not observed consistently in the subjects who showed increases of oxy-Hb and total-Hb. A lack of deoxy-Hb responses during neuronal activity was reported in the NIRS study on cognitive function. It was suggested that if an increase of CMRO₂ was sufficient to compensate for the decrease of deoxy-Hb induced by increased rCBF during the task, a decrease of deoxy-Hb might not be observed. Another possibility was the relationship between the optodes and the activating foci. Kleinschmidt et al found a similar lack of deoxy-Hb responses during sensorimotor stimulation; slight mispositioning of the optodes with respect to activation foci, which were detected by fMRI, caused the lack of deoxy-Hb responses. Further studies are necessary to clarify the physiological mechanism of the lack of deoxy-Hb responses.

Although the aphasic patients had difficulty performing the task, 30% of them showed alterations similar to those seen in most nonaphasic patients, specifically increases of oxy-Hb and total-Hb with little or no change in deoxy-Hb during the language task. These results indicate that despite the poor language function the left prefrontal cortex outside Broca’s area was activated by the language task in those aphasic patients, with preservation of coupling of rCBF and neuronal activity and a normal relationship between oxygen delivery and oxygen utilization during neuronal activity.

One of the important findings in the present study is that 50% of the aphasic patients showed an increase of deoxy-Hb during the language task that can be associated with increases in oxy-Hb and total-Hb, whereas this pattern was observed in only 23.1% and 16.7%, respectively, of the normal subjects and the nonaphasic CVD patients. In addition, the statistical analysis demonstrated a significant effect for deoxy-Hb, with the aphasic patients differing significantly from the normal subjects and the nonaphasic CVD patients. In the aphasic patients with an increase of deoxy-Hb, the rCBF in the left prefrontal cortex must be increased by the language task since both oxy-Hb and total-Hb were increased by the task, indicating the presence of coupling between rCBF and neuronal activity. However, the mean increase of total-Hb in the aphasic patients was larger than that seen in normal subjects and nonaphasic CVD patients, suggesting that a larger increase of rCBF is induced by the language task in the aphasic patients. On the other hand, the increase of deoxy-Hb indicates that the oxygen consumption in the left prefrontal cortex of the aphasic patients was increased more by neuronal activity than seen in the nonaphasic patients. These observations suggest that the left prefrontal cortex, in most of the aphasic patients, is more activated during language processing, resulting in more oxygen delivery and oxygen utilization compared with the nonaphasic patient group. However, several of the normal subjects and the nonaphasic CVD patients showed a similar increase of deoxy-Hb with an increase of oxy-Hb and total-Hb during the language task. Therefore, the increase of deoxy-Hb should not be interpreted as an abnormal cerebral oxygenation metabolism during neuronal activity. Finally, it should be emphasized that fMRI, which assesses neuronal activation as a decrease of deoxy-Hb, may misinterpret such an increase of deoxy-Hb with an increase of oxy-Hb and total-Hb as deactivations.

Another interesting finding is that both oxy-Hb and total-Hb decreased with a decrease or no change of deoxy-Hb in some of the normal adults and the nonaphasic CVD patients during the language task. Similar changes of NIRS parameters in the left frontal lobe were reported in some normal adults during mental tasks; simultaneous measurements with NIRS and PET demonstrated that the decreases in oxy-Hb and total-Hb were associated with a decrease in rCBF at the NIRS recording region. The physiological mechanisms and roles of the rCBF decrease during neuronal activity are not yet clear; however, several possible mechanisms should be considered. First, the baseline CBF before tasks may affect the rCBF response induced by neuronal activity. Second, neuronal activities near the NIRS recording area may steal the blood flow at the NIRS measurement area, resulting in a decreased rCBF. Finally, the synaptic activity in the measurement area might be depressed by the language task; PET studies have demonstrated that regional depressions of synaptic activity decreased rCBF and CMRO₂. Indeed, in most cases with decreases of oxy-Hb and total-Hb, deoxy-Hb decreased or did not change during the task; however, 1 normal subject and 1 aphasic patient showed an increase of deoxy-Hb associated with decreases of oxy-Hb and total-Hb, suggesting that relative ischemia was induced by the neuronal activation. Further studies are necessary to clarify the physiological mechanisms and roles of the rCBF decrease during neuronal activity.

In summary, the present results demonstrated that the language-activated cerebral blood oxygenation and hemodynamic changes of the left prefrontal cortex showed several response patterns in the nonaphasic and aphasic patients. The multiplicity of the language-activated responses differs from the responses induced by visual or somatosensory stimulation; visual or somatosensory stimulation evokes predictable and consistent neuronal activities in corresponding cortical areas associated with relatively consistent changes of rCBF and cerebral oxygen metabolism. This difference suggests that neuronal activities such as participation of inhibitory and facilitatory synaptic activities in the language-relevant area varies in subjects during language processing, resulted in the multiplicity of the language-activated responses of cerebral blood oxygenation and hemodynamics. In addition, the difference in the response patterns between the aphasic and nonaphasic groups suggests that neuronal activ-
ities induce different activity-dependent changes of rCBF and cerebral oxygen metabolism compared with those during normal function. Finally, it should be emphasized that MRI should be performed, giving special considerations to the possible multiplicity of the rCBF and cerebral oxygen metabolism responses to cognitive tasks.

Acknowledgment
This research was partially funded by Japan International Cooperation Agency (JICA).

References
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Stroke. 1998;29:1299-1304
doi: 10.1161/01.STR.29.7.1299

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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