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Evoked-cerebral blood oxygenation changes in false-negative activations in BOLD contrast functional MRI of patients with brain tumors

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Blood oxygenation level dependent contrast functional MRI (BOLD-fMRI) has been used to define the functional cortices of the brain in preoperative planning for tumor removal. However, some studies have demonstrated false-negative activations in such patients. We compared the evoked-cerebral blood oxygenation (CBO) changes measured by near-infrared spectroscopy (NIRS) and activation mapping of BOLD-fMRI in 12 patients with brain tumors who had no paresis of the upper extremities. On the nonlesion side, NIRS demonstrated a decrease in deoxyhemoglobin (Deoxy-Hb) with increases in oxyhemoglobin (Oxy-Hb) and total hemoglobin (Total-Hb) during a contralateral hand grasping task in the primary sensorimotor cortex (PSMC) of all patients. On the lesion side, NIRS revealed a decrease in Deoxy-Hb in five patients (Deoxy-decrease group), and an increase in Deoxy-Hb in seven patients (Deoxy-increase group); the Oxy-Hb and Total-Hb were increased during activation in both groups, indicating the occurrence of rCBF increases in response to neuronal activation. BOLD-fMRI demonstrated clear activation areas in the PSMC on the nonlesion side of all patients and on the lesion side of the Deoxy-decrease group. However, in the Deoxy-increase group, BOLD-fMRI revealed only a small activation area or no activation on the lesion side. Intraoperative brain mapping identified the PSMC on the lesion side that was not demonstrated by BOLD-fMRI. The false-negative activations might have been caused by the atypical evoked-CBO changes (i.e. increases in Deoxy-Hb) and the software employed to calculate the activation maps, which does not regard an increase of Deoxy-Hb (i.e., a decrease in BOLD-fMRI signal) as neuronal activation.

Keywords: Cortical mapping; CBF; Hemodynamic response; Hemoglobin; Near-infrared spectroscopy; Oxygen metabolism; Primary sensorimotor cortex

Introduction

Blood oxygenation level dependent contrast functional MRI (BOLD-fMRI) is regarded as a well-established noninvasive diagnostic method for imaging activated cortical areas. BOLD-fMRI images the activated areas by detecting the reduced concentration of deoxyhemoglobin (Deoxy-Hb) (Kwong et al., 1992; Ogawa et al., 1990, 1992), which is caused by a larger increase in regional cerebral blood flow (rCBF) as compared to the cerebral metabolic rate for oxygen (CMR_{O_2}) in normal adults (Fox and Raichle, 1986; Fox et al., 1988). Based on the assumption that normal adults and patients with brain tumors exhibit similar cerebral blood oxygenation (CBO) changes in the activated areas, BOLD-fMRI has been used to define the functional cortices of the brain in preoperative planning for tumor removal (Atlas et al., 1996; Mueller et al., 1996; Nelson et al., 2002).

Several BOLD-fMRI studies have, however, cast doubt on the reliability of its functional imaging in patients with brain tumors (Holodny et al., 1999, 2000; Inoue et al., 1999; Lurito et al., 2000; Schreiber et al., 2000). Holodny et al. (1999, 2000) reported that BOLD-fMRI indicated that patients with brain tumors in or adjacent to the primary sensorimotor cortex (PSMC) displayed significantly less activation of the PSMC on the lesion side than on the nonlesion side, although these patients had only mild sensorimotor deficits. Inoue et al. (1999) found that the fMRI-defined central sulcus did not coincide with the central sulcus as defined by magnetoencephalography. These observations suggest that BOLD-fMRI cannot image activated areas accurately in some patients with brain tumors. However, the underlying mechanism of such false-negative activations remains unclear.

Near-infrared spectroscopy (NIRS) is an optical method for measuring changes of oxyhemoglobin (Oxy-Hb) and Deoxy-Hb concentration in cerebral vessels with the characteristic absorption spectra of hemoglobin in the near-infrared range (Jöbsis, 1977; Reynolds et al., 1988). Changes in total hemoglobin (sum of Oxy-Hb and Deoxy-Hb; Total-Hb) indicate blood volume (CBV) changes and correlate with CBF changes under conditions of constant hematocrit and perfusion pressure (Ferrari et al., 1992;

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Pryds et al., 1990; Sakatani et al., 1995). NIRS thus allows us to measure changes of CBO and hemodynamics noninvasively. NIRS has been applied to the evaluation of evoked-CBO changes in normal adults (Hock et al., 1995; Hock et al., 1997; Hoshi and Tamura, 1993a,b, 1994; Kato et al., 1993; Kleinschmidt et al., 1996; Sakatani et al., 1999a,b,c) and patients with brain disorders (Hock et al., 1997; Murata et al., 2002; Sakatani et al., 1998, 1999b).

NIRS activation studies on normal adults have demonstrated that neuronal activation generally causes a decrease of Deoxy-Hb with increases of Oxy-Hb and Total-Hb in the activated cortical area (Hock et al., 1995; Hoshi and Tamura, 1993a,b, 1997, Hoshi et al., 1994; Kleinschmidt et al., 1996; Sakatani et al., 1999a); this CBO change is consistent with that obtained by PET (Fox and Raichle, 1986; Fox et al., 1988). However, the evoked-CBO changes occurring in brain disorders differ from those of normal adults (Hock et al., 1997; Murata et al., 2002; Sakatani et al., 1998). Recently, in patients with cerebral ischemia, we compared the evoked-CBO changes measured by NIRS and the activation maps of BOLD-fMRI (Murata et al., 2002). We found that the focal concentration of Deoxy-Hb in the PSMC on the lesion side was increased during activation in the patients. In addition, BOLD-fMRI failed to image the activated areas in the PSMC of the patients. These observations suggested that the evoked-CBO changes occurring in brain disorders differ from those of normal adults resulting in false-negative activations on BOLD-fMRI.

In the present study, employing NIRS, we evaluated the evoked-CBO changes in the PSMC of patients with brain tumors who had no paresis of the upper extremities. We compared the evoked-CBO changes and the activation maps of BOLD-fMRI.

Materials and methods

Subjects

We investigated 12 patients (five males and seven females) ranging in age from 27 to 65 years (mean, 48 years). All patients had suffered from brain tumors; eight cases had glioma (five cases of astrocytoma, two cases of glioblastoma, and one case of oligodendroglioma) and four cases had meningioma. We classified the relations between the tumors and the PSMC into three categories. First, the tumor was located within the PSMC (three cases). Second, the tumor was located close to the PSMC, which was associated with edema (three cases). Third, there was no direct relation between the tumor and the PSMC. The subjects were all strongly right-handed, as confirmed by the Edinburgh Handedness Inventory. Patients with motor deficits of the upper extremities were not included in the present study. Table 1 summarizes the patient profiles. Informed consent to participate in the study was obtained from each subject.

Intraoperative brain mapping of the PSMC

In the patients with glioma, to reduce any postoperative motor deficits, the PSMC on the lesion side was defined by electrical stimulation of the cortex during resection of the lesions. For intraoperative brain mapping, the methodology outlined in previous papers was employed (Katayama et al., 1988). Briefly, a pair of flexible, platinum wire electrodes insulated except at the tip (Medtronic Co. M-8483) was inserted into the epidural space of the cervical and/or upper thoracic vertebrae before surgery. During intracranial surgery under general anesthesia, the motor cortex and other cortical areas were directly stimulated with multicontact plate electrodes (Medtronic Co. M-3586). The corticospinal direct (D) response was recorded monopolarly from the spinal epidural electrodes, with the reference electrodes placed at the paravertebral muscles. The D response was obtained from stimulation of restricted areas of the cerebral cortex, viz., the hand, trunk, and thigh areas of the motor cortex. We defined the motor cortex by recording these D responses. None of the patients displayed neurological deficits after the surgery.

NIRS measurements

We measured the evoked-CBO changes in the PSMC contralateral to the task performance using NIRO-300 (Hamamatsu Photonics K.K., Japan), which has been applied in previous NIRS studies (Murata et al., 2002; Sakatani et al., 1999a,b,c). The NIR light from four laser diodes was directed at the head, and the reflected light was transmitted to a multisegment photodiode detector array (Matcher et al., 1995). The concentration changes

Table 1
Clinical profiles of the patients

Case no.	Age/sex	Pathology	Symptoms	Location of tumor	Relation between PSMC and tumor
1	65/M	Glioblastoma	Dysarthria	Lt-frontal	E
2	27/M	Astrocytoma, II	Convulsion	Lt-frontal	N
3	58/M	Astrocytoma, II	None	Lt-temporal	N
4	61/F	Meningioma	Convulsion	Lt-frontal	T
5	33/F	Astrocytoma, III	Headache	Rt-frontal	E
6	54/M	Meningioma	LOC	Lt-temporal	E
7	53/M	Glioblastoma	Gerstman	Lt-temporal	N
8	51/F	Meningioma	Focal seizure	Rt-frontal	T
9	51/F	Astrocytoma, III	None	Rt-frontal	N
10	38/F	Oligodendroglioma	Convulsion	Lt-frontal	N
11	52/F	Meningioma	Headache	Rt-temporal	N
12	33/F	Astrocytoma, III	Headache	Lt-parietal	T

T indicates the tumor located within the PSMC. E indicates the tumor located close to the PSMC, which was associated with edema. N indicates no direct relation between the tumor and the PSMC.

of Oxy-Hb, Deoxy-Hb, and Total-Hb were analyzed continuously, and were expressed in arbitrary units (Cope et al., 1988).

The NIRS probes were placed over the PSMC. The method of probe placement over the PSMC was as described by us in a previous NIRS activation study (Murata et al., 2002). Briefly, the probes were placed at a distance of 3 or 4 cm on the head over the PSMC so that the axis of the probes could be aimed so as to superimpose on the central sulcus; 3 cm posterior to the bregma, and 30° outside from the median line of the head (Greenberg, 1997). We did not shave the hair at the site of the NIRS probes, which might tend to obstruct light penetration into the skull, because we found that NIRS measurements of the evoked-CBO were easily possible when the probes were placed on the skull by separating the hair without shaving (Murata et al., 2002). After performing the initial setting using this method, the position of the probes was adjusted so that the maximum responses of Oxy-Hb and Total-Hb were obtained during the task performance. The location of the probes was identified by MRI employing vitamin E capsules. With an optode distance of 4 cm, the correlations of the Oxy-Hb and Total-Hb measured by NIRS and the rCBF measured by PET suggested that the reliable penetration depth of NIR light into the brain tissue is about 1.3 cm (Hock et al., 1997), so that the NIRS measurement area in the present study corresponded to the PSMC.

We measured the evoked-CBO changes in the PSMC on the nonlesion side and the lesion side during contralateral hand grasping tasks. The task paradigm consisted of 40 s of rest and 40 s of self-paced hand grasping; this task–rest cycle was repeated six times. The patients were observed directly to make sure that they performed the task paradigm accurately. No difference in task performance was detected between the right and left hands.

BOLD-fMRI

The BOLD-fMRI signals were measured with a 1.5-T MRI (Symphony, Siemens, Germany) employing an echo-planar technique (TE, 50 ms; TR, 4 s; slice thickness, 3 mm; matrix size, 40 × 40; FOV, 192 × 192 mm). One hundred twenty frames of 40 axial slices (acquisition time of one frame, 4 s) through the PSMC were acquired during repeated motor task periods (40 s) and resting periods (40 s); the task paradigm was the same as in the NIRS measurements. Activation maps were calculated by Statistical Parametric Mapping (SPM; Z score > 1.5).

Data analysis

We evaluated the changes in NIRS parameters (Oxy-Hb, Deoxy-Hb, and Total-Hb) by subtracting the mean baseline values (40 s) from the mean stimulation values (40 s), as described in our previous studies (Murata et al., 2002; Sakatani et al., 1999a,b,c). Comparisons were made for each of the NIRS parameters using paired t tests ($P < 0.05$ was defined as a significant level).

To quantify the activation areas on BOLD-fMRI, we calculated the activated volumes in the PSMC on the nonlesion side and lesion side by counting the activated voxels in these areas. In addition, the activated volumes on the lesion side were normalized to the activated volumes on the nonlesion side (=activated volumes on the lesion side/activated volumes on the nonlesion side); =1 as expected in hemispheric symmetry in activation.

To evaluate the differences in activated volumes between the nonlesion side and lesion side, comparisons were made for the activated volumes on the nonlesion side and lesion side using paired t tests ($P < 0.05$ was defined as a significant level).

Results

Comparison of evoked-CBO changes and activation maps of BOLD-fMRI

On the nonlesion side, the contralateral motor task consistently caused a decrease of Deoxy-Hb with increases of Oxy-Hb and Total-Hb in the PSMC of all patients. After the beginning of the task, the Oxy-Hb and Total-Hb were increased during the task, and Deoxy-Hb decreased below the baseline. These changes showed a return to the control level after the end of the task (Fig. 1A). BOLD-fMRI demonstrated robust activation areas in the PSMC on the nonlesion side during the task (Fig. 1B).

In contrast, the evoked-CBO changes in the PSMC on the lesion side could be classified into two groups according to the changes of Deoxy-Hb during activation: five patients (Deoxy-decrease group; cases No. 1–5) showed a decrease of Deoxy-Hb, while seven patients (Deoxy-increase group; cases No. 6–12)

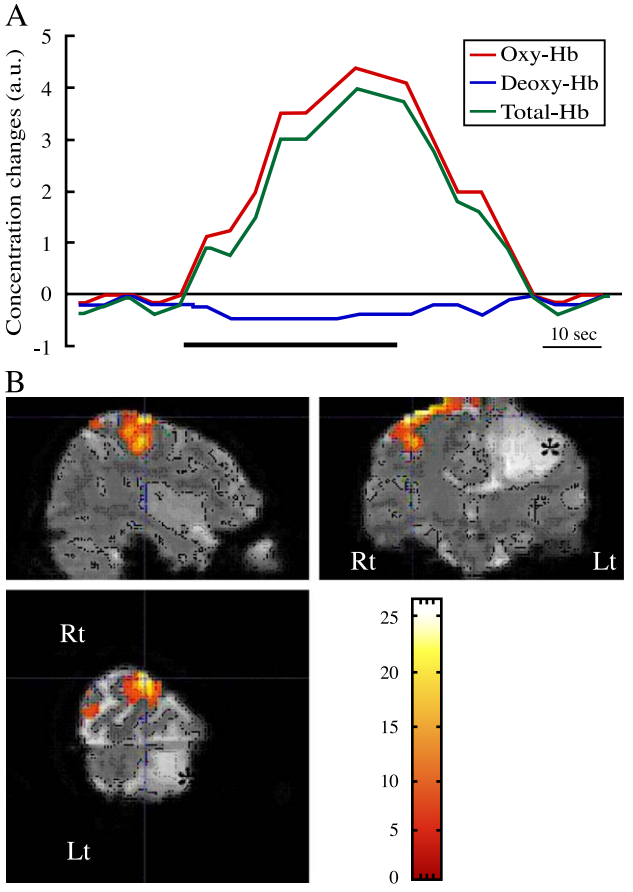

Fig. 1. Comparison of the evoked-CBO changes in the PSMC on the nonlesion side and the activation maps of BOLD-fMRI in a patient with glioma (case No. 12). (A) Evoked-CBO changes in the PSMC on the nonlesion side during the task. The ordinate indicates the concentration changes of the NIRS parameters in arbitrary units. The horizontal thick bar denotes the task period. (B) Activation maps of BOLD-fMRI for the left grasping task in the patient. The asterisk indicates the tumor.

showed an increase of Deoxy-Hb. Figs. 2A and B compare the evoked-CBO changes in the Deoxy-decrease group and Deoxy-increase group. Note that the increase of Deoxy-Hb in the Deoxy-increase group was evident during the entire course of the task. In addition, the Oxy-Hb and Total-Hb were increased during the task in both the Deoxy-decrease group and Deoxy-increase group, indicating the occurrence of rCBF increases in response to neuronal activation.

In the Deoxy-decrease group, BOLD-fMRI clearly demonstrated activation areas in the PSMC on the lesion side (Fig. 2C). However, in the Deoxy-increase group, BOLD-fMRI demonstrated only small activation areas or no activation (Fig. 2D); three patients in the Deoxy-increase group (cases No. 6–8) showed no activated areas. Table 2 compares the activated volumes of BOLD-fMRI in the Deoxy-decrease group and Deoxy-increase group. There was no significant difference in activated volume between the nonlesion side and the lesion side in the Deoxy-decrease group. However, in the Deoxy-increase group, the activated volumes on the lesion side were significantly smaller than those on the nonlesion side ($P < 0.0001$). In addition, the normalized activated volumes in the Deoxy-increase group were significantly smaller than those in the Deoxy-decrease group ($P < 0.0001$).

Table 2
Comparison of the activated volumes in the PSMC on the nonlesion side and lesion side of the Deoxy-decrease group and Deoxy-increase group

Group		Activated volumes (voxels)	Normalized activated volumes
Deoxy-decrease ($n = 5$)	Nonlesion side	294 ± 213	1.58 ± 0.82
	Lesion side	359 ± 256	
Deoxy-increase ($n = 7$)	Nonlesion side	213 ± 152	0.23 ± 0.30*
	Lesion side	33 ± 34†	

* $P < 0.0001$ compared to Deoxy-decrease group.
† $P < 0.0001$ compared to nonlesion side of Deoxy-increase group.

Intraoperative brain mapping of the PSMC

Intraoperative brain mapping, which was performed in the patients with glioma, identified the primary motor cortex on the lesion side in the patients. Fig. 3 presents an example of the

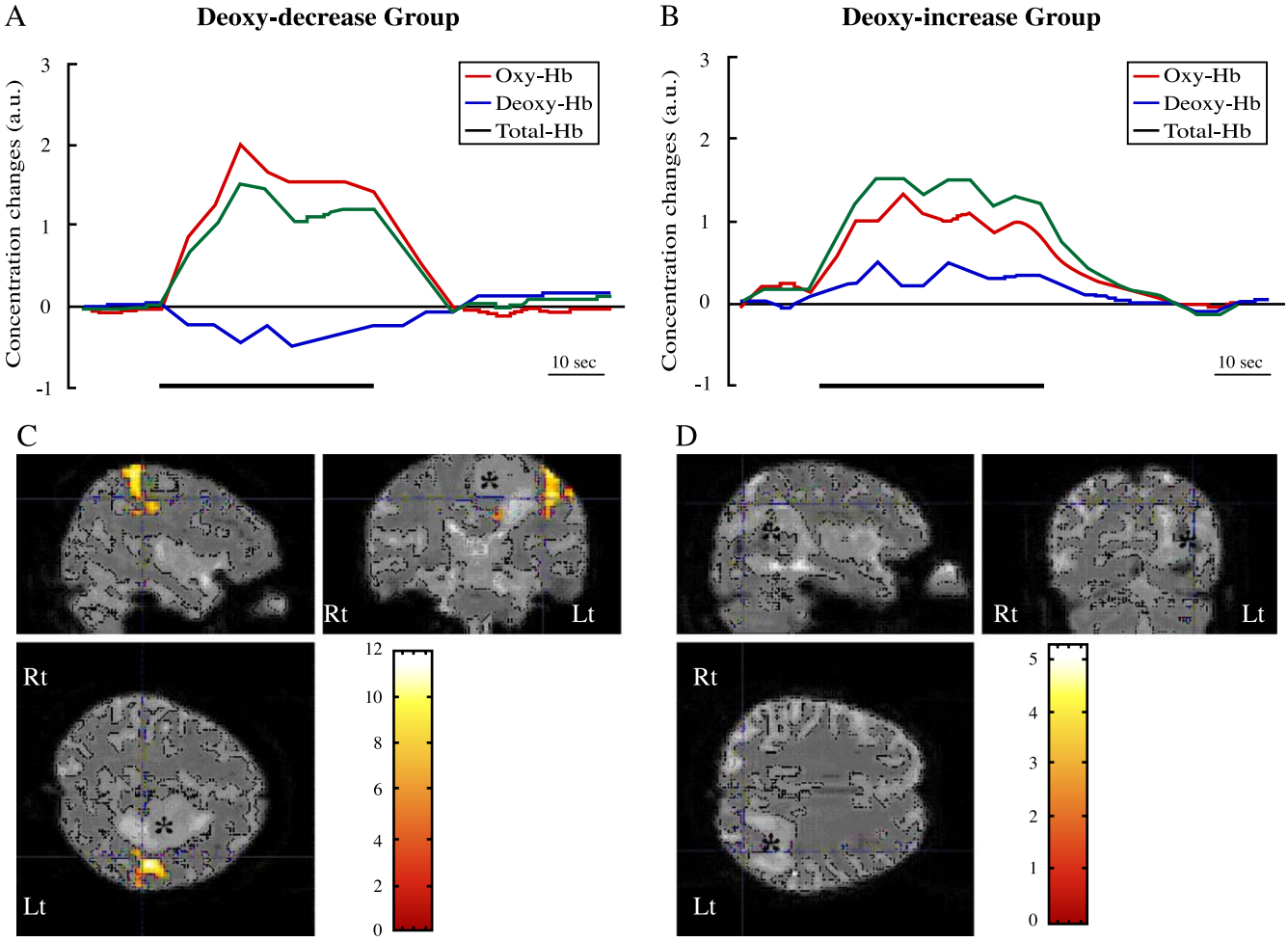

Fig. 2. Comparison of the evoked-CBO changes in the PSMC on the lesion side and the activation maps of BOLD-fMRI between the Deoxy-decrease group and Deoxy-increase group. (A,B) Evoked-CBO changes in the PSMC on the lesion side in the Deoxy-decrease group (case No. 4) and Deoxy-increase group (case No. 6). (C,D) Activation maps of BOLD-fMRI in the Deoxy-decrease group and Deoxy-increase group. The asterisks indicate the tumors. Note that NIRS demonstrated an increase of Deoxy-Hb with increases of Oxy-Hb and Total-Hb during the task, while BOLD-fMRI did not image an activation area in the Deoxy-increase group.

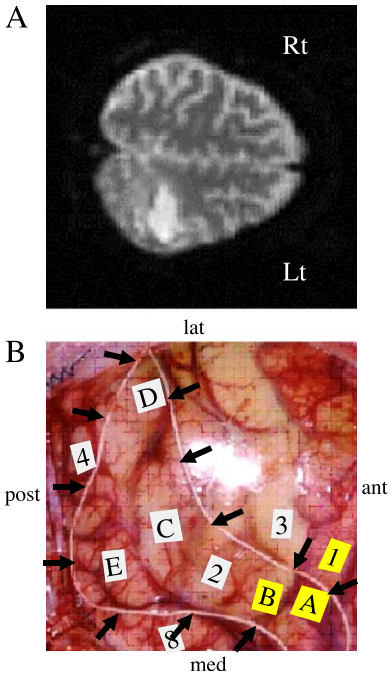

Fig. 3. Activation maps of BOLD-fMRI for the right grasping task (A) and cortical mapping (B) of the left motor cortex in case No. 12. The activation maps demonstrated only limited areas, but the cortical mapping detected the motor cortex (arrows) during surgery.

intraoperative view of the primary motor cortex, which could not be detected by BOLD-fMRI.

Discussion

Technical considerations regarding NIRS and BOLD-fMRI

The present study is the first NIRS activation study to be performed on patients with brain tumors. We compared the evoked-CBO changes measured by NIRS and the activation maps of BOLD-fMRI in the patients. When comparing such data, the following technical differences between NIRS and BOLD-fMRI need to be considered.

First, NIRS provides more information about the evoked-CBO changes than does BOLD-fMRI. NIRS measures the concentration changes of both Oxy-Hb and Deoxy-Hb in the cerebral vessels by the absorption spectra of hemoglobin (Jöbsis, 1997; Reynolds et al., 1988). Changes in Total-Hb (sum of Oxy-Hb and Deoxy-Hb) indicate CBV changes and correlate with the CBF changes under conditions of constant hematocrit and perfusion pressure (Ferrari et al., 1992; Pryds et al., 1990; Sakatani et al., 1995). Thus, NIRS allows the real-time changes in CBO and hemodynamics at the activated area to be continuously characterized. In contrast, BOLD-fMRI measures only the concentration changes of Deoxy-Hb, which is paramagnetic (Kwong et al., 1992; Ogawa et al., 1990, 1992); it images the activation area by detecting the reduced concentration of Deoxy-Hb during activation.

Second, the spatial resolution of NIRS is poor due to light scattering in the tissues. NIRS measures the blood oxygenation changes within the illuminated area, which includes both intracranial and extracranial tissues when the probe is placed on the scalp (Al-Rawi et al., 2001). Although NIRS parameter changes can therefore be caused by changes in the blood flow of the scalp, the changes induced by neuronal activation are believed to reflect the changes in CBO and hemodynamics at the activated cortices (Hock et al., 1995, 1997; Hoshi and Tamura, 1993a,b, 1997; Hoshi et al., 1994; Kato et al., 1993; Kleinschmidt et al., 1996; Murata et al., 2002; Sakatani et al., 1998, 1999a,b). In addition, the NIRS parameter changes reflect the average changes of CBO within the illuminated area, which is much larger than the voxel size of BOLD-fMRI. In the present study, therefore, the CBO changes measured by NIRS indicated the average CBO changes in the part of the PSMC through which the NIR light passed.

Third, there is a difference in the compartments of vessels (i.e., arterial, capillary, and venous compartments) to which NIRS and BOLD-fMRI are sensitive. NIRS is sensitive to all compartments within the illuminated area; for Deoxy-Hb changes, NIRS is sensitive to the venous and capillary compartments because Deoxy-Hb changes occur in these compartments. In contrast, BOLD-fMRI is sensitive to the venous compartment (Lee et al., 2001). Thus, depending on the contribution of the capillary compartments to the optical changes, a mismatch in spatial sensitivities of NIRS and BOLD-fMRI may exist, although the NIRS probes are placed over the activated area which BOLD-fMRI demonstrated (Strangman et al., 2002).

Finally, it should be emphasized that continuous wave NIRS, such as with NIRO-300 in the present study, may not yield precise absolute values for changes in the hemoglobin chromophore concentrations. That is, NIRS is based on the modified Beer–Lambert law in which the hemoglobin chromophore concentration changes are assumed to be proportional to the changes in light absorbance divided by the extinction coefficients of the chromophores and the optical pathlength in the tissue, which is the average distance that light travels between the source and detector through the tissue (Delpy et al., 1988). For the measurement of the absolute values, it is necessary therefore to determine the optical pathlength, which can be estimated by a time-resolved or frequency domain NIRS. Recently, employing a time-resolved NIRS, Zhao et al. (2002) found that the optical pathlength varied with individual subjects, regions of the head, and wavelength, indicating that continuous wave NIRS does not provide absolute values of the hemoglobin chromophore concentration changes. In the present study, therefore, we did not evaluate the mean changes of the NIRS parameters among the subjects.

CBO responses to neuronal activation in the brain tumor

NIRS activation studies on normal adults have demonstrated that neuronal activation generally causes a decrease of Deoxy-Hb with increases of Oxy-Hb and Total-Hb during activation (Hock et al., 1995; Hoshi and Tamura, 1993a,b, 1997, Hoshi et al., 1994; Kleinschmidt et al., 1996; Sakatani et al., 1999a). In the present study, NIRS demonstrated a similar CBO change in the PSMC on the nonlesion side of all patients and on the lesion side of the Deoxy-decrease group, indicating that the evoked-CBO changes were essentially normal in these areas. However, in the PSMC on the lesion side of the Deoxy-increase group, the Deoxy-Hb was increased during activation associated with increases of Oxy-Hb and Total-Hb. The increase of Deoxy-Hb was evident during the entire course of the task, so that it differs from the Deoxy-Hb rise occurring within a few seconds after the start of neuronal activation (Malonek and Grinvald, 1996), or the “post stimulus overshoot” of

Deoxy-Hb occurring in the visual cortex (Heekeren et al., 1997). Increases of Oxy-Hb and Total-Hb during activation imply an increase of rCBF in response to neuronal activation. This differs therefore from "deactivation", which is a decrease of BOLD-fMRI signal during the task, because the deactivation is associated with a decrease of rCBF (Harel et al., 2002).

NIRS activation studies have demonstrated a similar increase of Deoxy-Hb during activation in patients with cerebral ischemia (Murata et al., 2002; Sakatani et al., 1998). Sakatani et al. (1998) reported that, in many post-stroke aphasics, language tasks caused an increase of Deoxy-Hb with increases of Oxy-Hb and Total-Hb in the left prefrontal cortex. Recently, we observed similar evoked-CBO changes in the PSMC of the patients with cerebral ischemia (Murata et al., 2002). However, it should be noted that several cases of normal adults displayed a similar increase of Deoxy-Hb with increases of Oxy-Hb and Total-Hb during cognitive tasks (Hoshi and Tamura, 1993a,b; Sakatani et al., 1998, 1999a). The increase of Deoxy-Hb should therefore not be interpreted as an abnormal evoked-CBO change during neuronal activity. Interestingly, newborn infants exhibit an increase of Deoxy-Hb with increases of Oxy-Hb and Total-Hb in the visual cortex (Meek et al., 1998) and the frontal lobe (Sakatani et al., 1999c) during activation.

The physiological mechanisms and roles of the Deoxy-Hb increase during neuronal activity remains unclear; however, the following possible mechanisms should be considered. First, a decrease of oxygen delivery during neuronal activity may be involved. Quantitative models of oxygen delivery during activation have predicted that disproportionately large increases of rCBF are required to produce small increases of CMR_{O_2} (Buxton and Frank, 1997). Thus, a small decrease in rCBF response can cause oxygen deficiency during activation. Second, there could be a large increase of oxygen consumption during activation. This possibility has been proposed in cerebral ischemia (Murata et al., 2002; Sakatani et al., 1998). However, the oxygen metabolism during neuronal activity in brain disorders, including brain tumors, remains unclear since most examinations have been made in normal adults (Fox and Raichle, 1986; Fox et al., 1988; Hoge et al., 1999). It has also been proposed that the changes of Deoxy-Hb measured by NIRS may be determined by changes in both venous oxygenation and venous blood volume; thus, the concentration of Deoxy-Hb could be increased without changes in oxygen metabolism (Hoshi et al., 2001). Further studies are needed to clarify in detail the oxygen metabolism and hemodynamics during neuronal activity in brain disorders.

Relationship between evoked-CBO changes measured by NIRS and activation maps of BOLD-fMRI

NIRS consistently revealed a decrease of Deoxy-Hb with increases of Oxy-Hb and Total-Hb during activation in the PSMC on the nonlesion side of all patients and on the lesion side of the Deoxy-decrease group. BOLD-fMRI clearly demonstrated the activation areas in the PSMC of these patients. In contrast, in the Deoxy-increase group, BOLD-fMRI disclosed relatively small activation areas or no activations in the PSMC on the lesion side, where NIRS demonstrated an increase of Deoxy-Hb. This was not due to dysfunction of the PSMC on the lesion side because the intraoperative brain mapping detected the PSMC (Fig. 3). Several BOLD-fMRI studies on patients with brain tumors have shown similar false-negative activations in such patients (Holodny et al., 1999, 2000; Inoue et al., 1999; Lurito et al., 2000; Schreiber et al., 2000). It has been hypothesized that the false-negative activations may be caused by an absence of vasodilatory response to neuronal activation (Holodny et al., 1999, 2000). However, a vasodilatory response to neuronal activation must have been present in the patients of the Deoxy-increase group because the Oxy-Hb and Total-Hb were significantly increased during activation. In cerebral ischemia without motor paresis, the vasodilatory response to neuronal activation is maintained in the PSMC, although the vasodilatory response to acetazolamide is reduced (Inao et al., 1998; Murata et al., 2002). We suggest that the false-negative activations in BOLD-fMRI were caused by the atypical evoked-CBO changes (i.e. increases in Deoxy-Hb) and the software employed to calculate the activation maps. That is, most of the software packages such as the SPM used in the present study do not regard an increase of Deoxy-Hb (i.e. a decrease in BOLD-fMRI signal) as neuronal activation.

It should be emphasized that, in four cases of the Deoxy-increase group (cases No. 9–12), BOLD-fMRI demonstrated small, but distinct activated areas in the PSMC, where NIRS showed an increase of Deoxy-Hb. This is inconsistent with the BOLD theory, because the activated area demonstrated by BOLD-fMRI should be associated with a decrease of Deoxy-Hb (i.e., positive BOLD signal) (Kwong et al., 1992; Ogawa et al., 1990, 1992). However, Hess et al. (2000) observed over the activated area a positive BOLD signal and increases of Deoxy-Hb and Total-Hb in the gerbil barrel cortex. At the activated area, the BOLD-fMRI signal is determined by the total amount of Deoxy-Hb as well as by the ratio of Deoxy-Hb to free water within the voxel (Boxerman et al., 1995; Ogawa et al., 1990). Positive changes of the BOLD-fMRI signal could therefore be caused not only by washout of Deoxy-Hb from the voxel but also by an increase of the water fraction around the Deoxy-Hb in the vessels. Indeed, in the present study, NIRS demonstrated an increase of Total-Hb (=CBV) during activation in cases of the Deoxy-increase group. This mechanism of BOLD signal generation might explain the paradoxical correlation between BOLD signal and Deoxy-Hb changes in the four cases of the Deoxy-increase group. However, it cannot explain why BOLD-fMRI failed to demonstrate the activated area in the other three cases of the Deoxy-increase group (cases No. 6–8), because the Total-Hb (=CBV) was increased during activation in these cases.

We propose an alternative explanation for the paradoxical relationship between the BOLD signal and Deoxy-Hb changes. This is based on the assumption that the evoked-CBO changes might be heterogeneous within the affected PMSC; that is, some areas of the PSMC displayed a decrease of Deoxy-Hb, while other areas exhibited an increase or no changes in Deoxy-Hb during activation. NIRS measures the average changes of the CBO in the brain tissue through which the NIR light passes. Thus, if the amount of brain tissue with a Deoxy-Hb increase was larger than that with a Deoxy-Hb decrease, NIRS would demonstrate an increase of Deoxy-Hb, while BOLD-fMRI would demonstrate the activated area with a Deoxy-Hb decrease.

In summary, the present results indicated that false-negative activations in the BOLD-fMRI of patients with brain tumors were associated an increase of Deoxy-Hb during activation. An increase of rCBF in response to activation was present in these patients, although the degree of rCBF increase was relatively small as compared to that on the nonlesion side. We suggest that the false-negative activations in BOLD-fMRI may be caused by the

atypical evoked-CBO changes (i.e., increases in Deoxy-Hb) and the software employed to calculate the activation maps, which does not regard an increase of Deoxy-Hb (i.e., a decrease in BOLD-fMRI signal) as neuronal activation. Finally, it should be emphasized that if, based on the assumption that patients with brain tumors exhibit normal evoked-CBO changes, the software is applied to define the functional cortices, important cortical activation areas may be overlooked in such patients.

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