Comparison of blood-oxygen-level–dependent functional magnetic resonance imaging and near-infrared spectroscopy recording during functional brain activation in patients with stroke and brain tumors

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Abstract. Blood-oxygen-level–dependent contrast functional magnetic resonance imaging (BOLD-fMRI) has been used to perform functional imaging in brain disorders such as stroke and brain tumors. However, recent studies have revealed that BOLD-fMRI does not image activation areas correctly in such patients. To clarify the characteristics of the evoked cerebral blood oxygenation (CBO) changes occurring in stroke and brain tumors, we have been comparing near-infrared spectroscopy (NIRS) and BOLD-fMRI recording during functional brain activation in these patients. We review our recent studies and related functional imaging studies on the brain disorders. In the primary sensorimotor cortex (PSMC) on the nonlesion side, the motor task consistently caused a decrease of deoxyhemoglobin (deoxy-Hb) with increases of oxyhemoglobin (oxy-Hb) and total hemoglobin (t-Hb), which is consistent with the evoked CBO response observed in normal adults. BOLD-fMRI demonstrated robust activation areas on the nonlesion side. In stroke patients, severe cerebral ischemia (i.e., misery perfusion) caused an increase of deoxy-Hb during the task, associated with increases of oxy-Hb and t-Hb, in the PSMC on the lesion side. In addition, the activation volume of BOLD-fMRI was significantly reduced on the lesion side. The BOLD signal did not change in some areas of the PSMC on the lesion side, but it tended to decrease in other areas during the tasks. In brain tumors, BOLD-fMRI clearly demonstrated activation areas in the PSMC on the lesion side in patients who displayed a normal evoked CBO response. However, the activation volume on the lesion side was significantly reduced in patients who exhibited an increase of deoxy-Hb during the task. In both stroke and brain tumors, false-negative activations (i.e., marked reductions of activation volumes) in BOLD imaging were associated with increases of deoxy-Hb, which could cause a reduction in BOLD signal. BOLD-fMRI investigations of patients with brain disorders should be performed while giving consideration to atypical evoked CBO changes. © *2007 Society of Photo-Optical Instrumentation Engineers.*
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1 Introduction

Blood-oxygen-level–dependent functional magnetic resonance imaging (BOLD-fMRI) has been used to perform functional imaging in brain disorders such as stroke[1–3] and brain tumors,[4–6] under the assumption that such patients exhibit normal evoked cerebral blood oxygenation (CBO) changes in the activation areas. Recent studies have revealed, however, that BOLD-fMRI does not image activation areas correctly in these patients.[7–18] Nevertheless, BOLD-fMRI cannot elucidate the precise mechanisms underlying the failure of BOLD imaging, because BOLD-fMRI provides information mainly about concentration changes of deoxyhemoglobin (deoxy-Hb), which is paramagnetic.[19,20]

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In contrast, near infrared spectroscopy (NIRS) can measure the concentration of oxyhemoglobin (oxy-Hb) as well as that of deoxy-Hb: changes in total hemoglobin (the sum of oxy-Hb and deoxy-Hb; t-Hb) indicate cerebral blood volume (CBV) changes.[21] NIRS thus provides more information about the evoked CBO changes than does BOLD-fMRI. To clarify the mechanisms underlying the failure of BOLD imaging in stroke and brain tumors, we have been comparing NIRS and BOLD-fMRI recording during functional brain activation in these patients.[22–25] This paper reviews the results of functional imaging studies on the brain disorders including our recent studies. In our functional studies, we measured the evoked CBO responses in the primary sensorimotor cortex (PSMC) contralateral to the motor task performance using a NIRO-300 (Hamamatsu Photonics K.K., Hamamatsu, Japan). The BOLD-fMRI signals were measured with a 1.5 T MRI (Symphony, Siemens, Munich, Germany) employing an echoplanar technique. The task paradigm consisted of 40 sec of rest and 40 sec of self-paced hand grasping; this task-rest cycle was repeated six times. The patients studied could perform the motor task similarly to the control subjects at the time of the examination.

2 Technical Differences between NIRS and BOLD-fMRI

NIRS is an optical method for measuring concentration changes of both oxy-Hb and deoxy-Hb in the cerebral vessels by means of the characteristic absorption spectra of hemoglobin in the near infrared range.[21] In contrast, BOLD-fMRI detects neuronal activity by measuring changes in BOLD signal (i.e., the T_2^* signal), which is caused by concentration changes of paramagnetic deoxy-Hb in the cerebral vessels.[19,20] NIRS studies on normal adults have revealed that neuronal activation generally induce a decrease of deoxy-Hb with increases of oxy-Hb and t-Hb in the activated cortical area,[26–32] and this is consistent with the physiological basis of BOLD imaging.[19,20] Simultaneous measurements of NIRS and BOLD-fMRI have demonstrated correlations between NIRS parameters and the BOLD signal;[33–36] however it has not yet been established which NIRS parameter correlates best with the BOLD signal in population with altered vasculature.

When comparing the data obtained by NIRS and BOLD-fMRI, the following technical differences between NIRS and BOLD-fMRI need to be taken into account. First, there is a large difference in spatial resolution between NIRS and BOLD-fMRI. NIRS measures the averaged blood oxygenation changes within the illuminated area, including the intracranial and extracranial tissues. Therefore, NIRS not only underestimates the CBO changes occurring in the activation area, but also mixes brain-related changes with changes occurring in overlaying tissue.[37] In contrast, BOLD-fMRI can selectively detect the blood oxygenation changes in the brain with high spatial resolution. Second, NIRS may not permit measurements of CBO changes in the deep structure of the brain; recent simulation studies have suggested that NIRS measures the CBO changes only at the surface of the cortex due to light reflection at the cerebrospinal fluid layer.[38,39] Third, NIRS is sensitive to all compartments of the cerebral vessels (i.e., arterial, capillary, and venous compartments) within the illuminated area; for deoxy-Hb changes, NIRS is sensitive to the venous and capillary compartments, because changes of deoxy-Hb occur in these compartments. In contrast, BOLD-fMRI is thought to be sensitive mainly to the venous compartment.[40]

3 Comparison of NIRS and BOLD-fMRI in Stroke Patients

NIRS studies on chronic stroke patients have provided conflicting data concerning the evoked CBO response patterns.[3,22,23,30,41] Kato et al.[3] and Miyai et al.[41] found that chronic stroke patients exhibited a normal evoked CBO response pattern in the activated areas. In contrast, Sakatani et al. revealed that a number of chronic stroke patients exhibited an atypical evoked CBO response pattern (i.e., an increase of deoxy-Hb associated with increases of oxy-Hb and t-Hb) in the left prefrontal cortex during language tasks.[30] In addition, we have observed similar atypical evoked CBO changes in the PSMC of stroke patients during contralateral motor tasks.[22] Interestingly, despite normal motor function, BOLD-fMRI showed small activation areas in the PSMC on the lesion side, suggesting that altered evoked CBO responses induced by cerebral ischemia cause failure of BOLD imaging in stroke patients.

Recently, we have evaluated the quantitative relationships among cerebral ischemic levels, evoked CBO responses, and BOLD imaging in chronic stroke patients displaying different cerebral circulatory conditions, that is, moderate cerebral ischemia [slight reduction of regional CBF (rCBF) and cerebrovascular reserve capacity (CVRC)] and severe cerebral ischemia (marked reduction of rCBF and CVRC), which corresponds to "misery perfusion."[23] The evoked CBO responses in the PSMC were measured by NIRS during contralateral motor tasks and compared with the activation volumes and BOLD signal changes of BOLD-fMRI in the PSMC.

In the PSMC on the nonlesion side, the motor task consistently caused a decrease of deoxy-Hb with increases of oxy-Hb and t-Hb, which is consistent with the evoked CBO response observed in normal adults [Fig. 1(a)]. In addition, BOLD-fMRI demonstrated robust activation areas in the PSMC on the nonlesion side [Fig. 1(b)]. In the moderate cerebral ischemia group, the evoked CBO response pattern on the lesion side was similar to that in the control subjects [Fig. 2(a)]; however, in the severe cerebral ischemia group, the deoxy-Hb concentrations increased during the entire course of the task concomitantly with increases of oxy-Hb and t-Hb [Fig. 2(b)].

BOLD-fMRI clearly demonstrated activation areas on the lesion side in the moderate cerebral ischemia group [Fig. 2(c)]; however, the activation volume on the lesion side was slightly smaller than that on the nonlesion side. In the severe cerebral ischemia group, BOLD-fMRI revealed only small activation areas [Fig. 2(d)]. (It should be noted that none of the patients had motor paresis at the time of examination.) We found that significant correlations existed between the normalized activation volume (activation volume on the lesion side divided by that on the nonlesion side), and the baseline rCBF ($p<0.01$) and % CVR ($p<0.01$; Fig. 3). The BOLD signal increased consistently during the tasks in the PSMC on the nonlesion side in severe cerebral ischemia, where NIRS

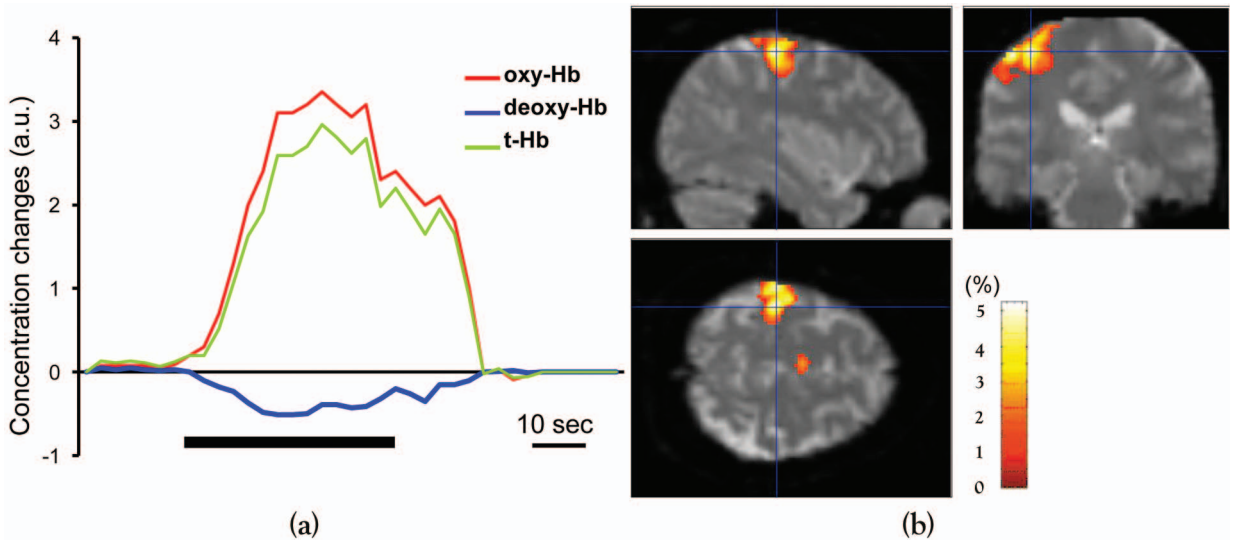

Fig. 1 Evoked CBO responses in the PSMC on the nonlesion side (a) and activation maps of BOLD-fMRI (b) during contralateral motor tasks in a severe cerebral ischemia patient (Ref. 23). The ordinate indicates the concentration changes of the NIRS parameters in arbitrary units. Horizontal thick bars denote the task period (40 sec).

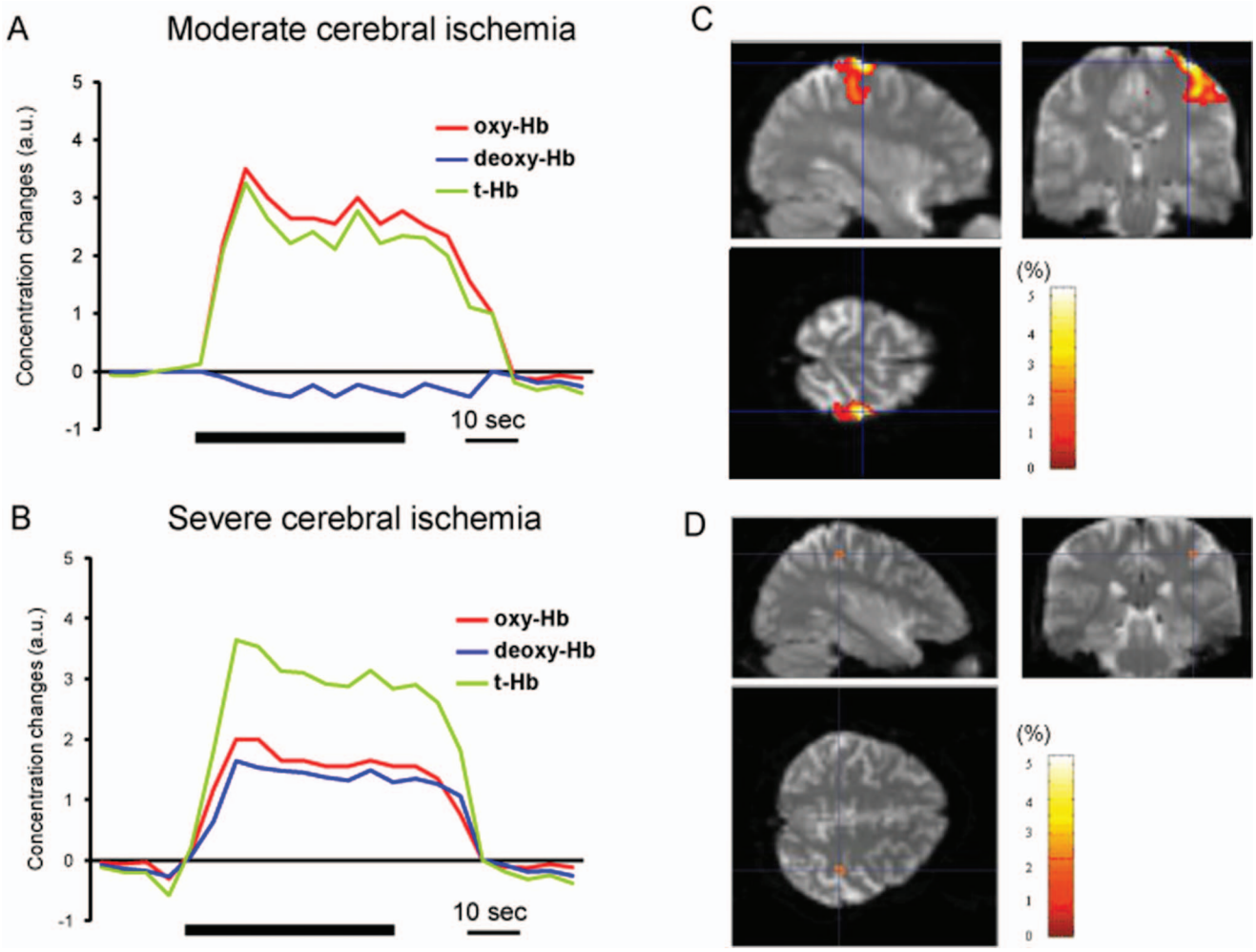

Fig. 2 Comparison of evoked CBO responses in the PSMC on the lesion side and activation maps of BOLD-fMRI between patients with moderate cerebral ischemia and severe cerebral ischemia (Ref. 23). (a), (b) Evoked CBO responses in moderate cerebral ischemia (a) and severe cerebral ischemia (b). (c), (d) Activation maps in the moderate cerebral ischemia (c) and severe cerebral ischemia (d). The ordinates indicate the changes of the NIRS parameters in arbitrary units. Horizontal thick bars denote the task period (40 sec).

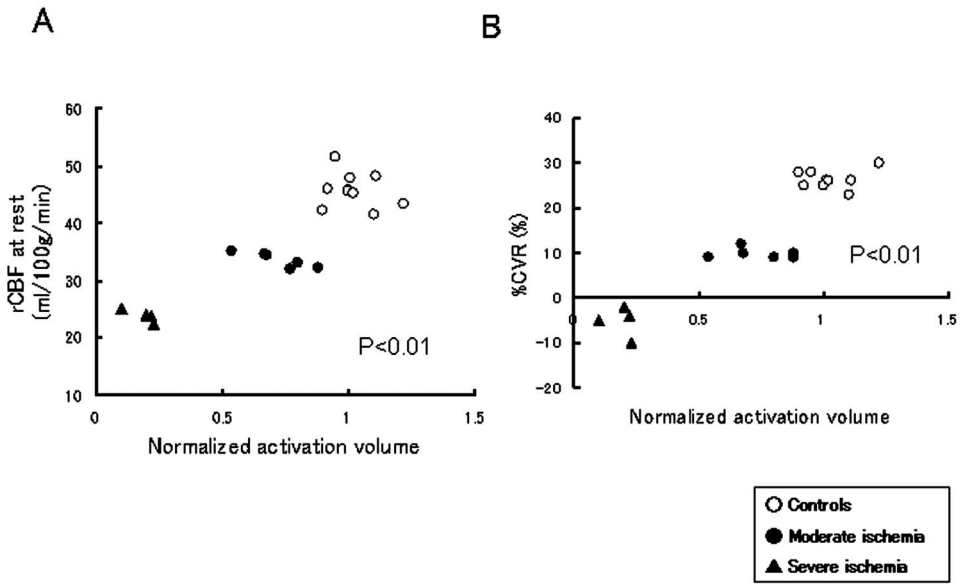

Fig. 3 Correlations between the normalized activation volume of BOLD-fMRI and the rCBF at rest (a) and %CVR (b) (Ref. 23). Significant positive correlations were observed for both the rCBF at rest ($p<0.01$) and %CVR ($p<0.01$).

demonstrated a decrease of deoxy-Hb. In contrast, the BOLD signal did not increase consistently during the tasks in the PSMC on the lesion side, where BOLD-fMRI did not identify neuronal activation, but NIRS revealed increases of deoxy-Hb (Fig. 4). The BOLD signal did not change in some areas of the PSMC, while it tended to decrease in other areas during the tasks.

It should be emphasized that cerebral ischemia, particularly misery perfusion, affects the evoked CBO response pattern and impairs BOLD imaging in stroke patients. BOLD-fMRI should therefore be performed on stroke patients while giving consideration to the baseline cerebral circulatory status at the time of examination. Otherwise, the results of the BOLD-fMRI in stroke patients could be open to misinterpretation.

4 Comparison of NIRS and BOLD-fMRI in Brain Tumors

Although BOLD-fMRI has, in the past, been employed for the preoperative brain function mapping of brain tumors, doubts have recently been expressed concerning its accuracy.[7–11] For example, BOLD-fMRI indicated that patients with brain tumors in or adjacent to the 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.[8,9] In addition, the fMRI-defined central sulcus did not coincide with the central sulcus as defined by magnetoencephalography.[7] To clarify the underlying mechanisms of the false-negative activation of BOLD-fMRI, we compared the NIRS measured evoked CBO response in the PSMC and the activation maps of BOLD-fMRI in patients with brain tumors.[24]

NIRS demonstrated two different patterns of evoked CBO changes in the PSMC on the lesion side according to the changes of deoxy-Hb occurring during activation: namely, deoxy-decrease and deoxy-increase patterns, where the concentration of deoxy-Hb decreased and increased during activation, respectively. Figures 5(a) and 5(b) compare the evoked CBO changes in the deoxy-decrease and deoxy-increase patterns. It should be noted that the oxy-Hb and t-Hb were increased during the task in both patterns, indicating the occurrence of rCBF increases in response to neuronal activation.

BOLD-fMRI clearly demonstrated activation areas in the PSMC on the lesion side in the deoxy-decrease group [Fig. 5(c)]. However, in the deoxy-increase group, BOLD-fMRI revealed only small or no activation areas [Fig. 5(d)]. The normalized activated volumes in the deoxy-increase group were significantly smaller than those in the deoxy-decrease group ($p<0.0001$). Intraoperative brain mapping, which was performed in the patients with glioma, identified the primary motor cortex that could not be detected by BOLD-fMRI (Fig. 6), indicating that BOLD-fMRI failed to detect the activation areas in this patient.

These findings indicate that the atypical evoked CBO changes in activation areas of the brain that have been observed with cerebral ischemia also occur with brain tumors, and that, using BOLD-fMRI, the activation areas in such cases are imaged as being much smaller than they really are.

5 Relationship between NIRS Parameters and BOLD Signal During Activation

BOLD-fMRI disclosed significantly small activation volumes in the PSMC on the lesion side in stroke and brain tumors. We suggest that a failure of BOLD imaging might be caused by the atypical evoked CBO response (i.e., increases of both deoxy-Hb and t-Hb), which would have opposite effects on the BOLD signal change. That is to say, an increase of t-Hb (=CBV) increases the water fraction around the deoxy-Hb molecules in a given voxel leading to an increase of BOLD signal, while an increase of the paramagnetic deoxy-Hb concentration tends to decrease the BOLD signal.[19,20,42,43] Such

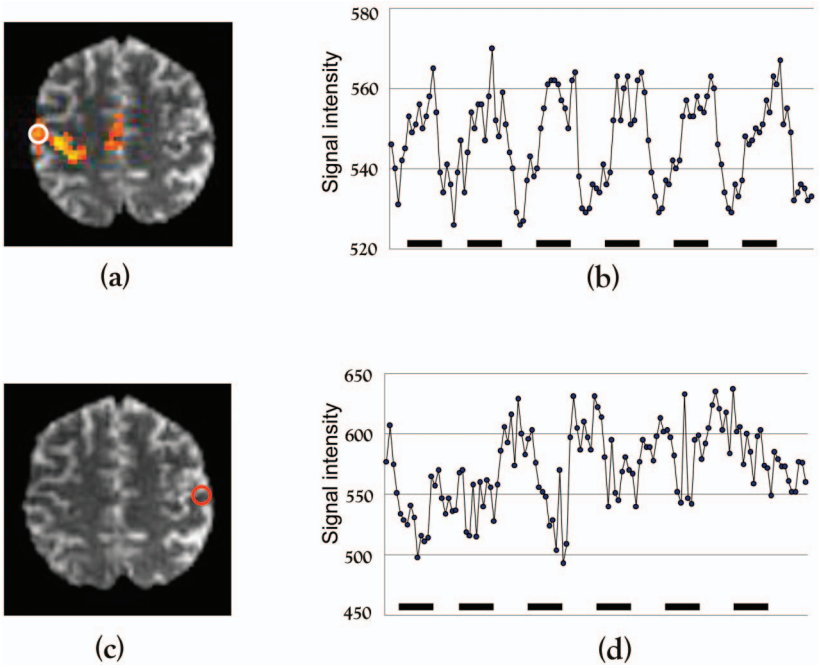

Fig. 4 Comparison of BOLD signal changes in the PSMC on the nonlesion side and lesion side in severe cerebral ischemia (Ref. 23). (a), (b) Activation maps for the left grasping task [nonlesion side (a)] and time courses of the BOLD signal changes in the PSMC on the nonlesion side [(b) corresponds to the white circle in (a)]. (c), (d) Activation maps for the right grasping task [lesion side (c)] and time courses of the BOLD signal changes in the PSMC on the lesion side [(d) corresponds to the red circle in (c)]. Thick bars indicate the task period (40 sec).

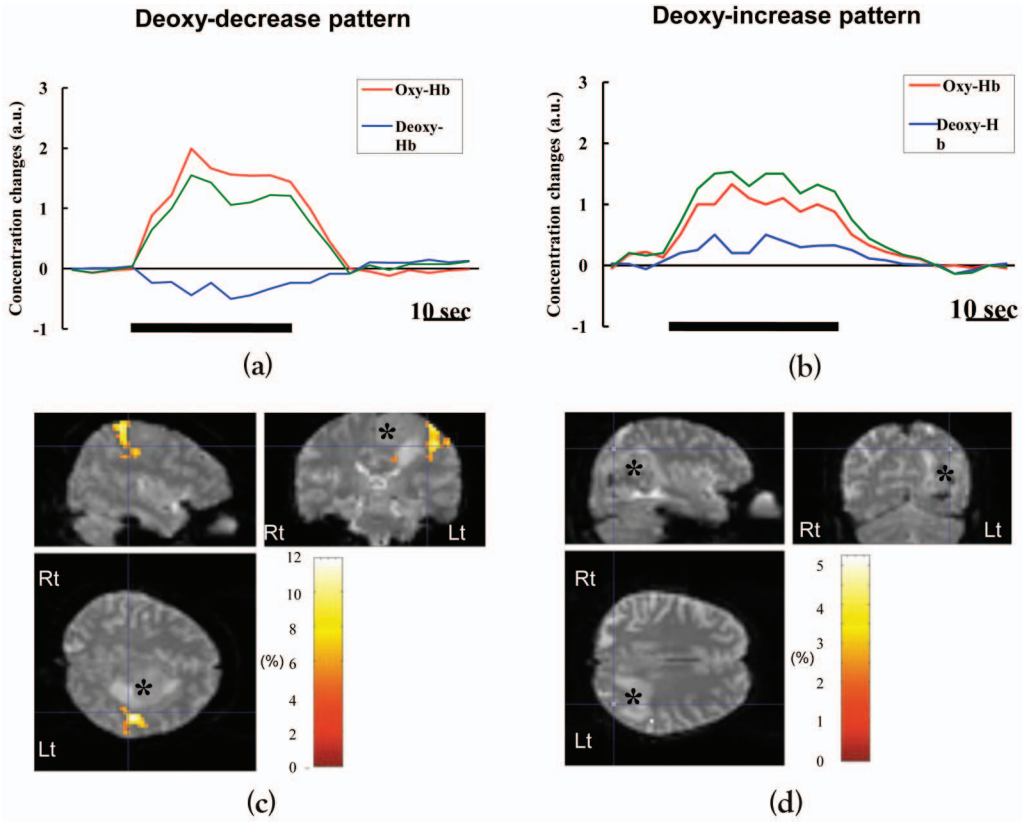

Fig. 5 Comparison of evoked CBO changes in the PSMC on the lesion side and activation maps of BOLD-fMRI between the deoxy-decrease and deoxy-increase patterns (Ref. 24). (a), (b) Evoked CBO changes in the PSMC on the lesion side in the deoxy-decrease (a) and deoxy-increase (b) patterns. (c), (d) Activation maps of BOLD-fMRI in the deoxy-decrease (c) and deoxy-increase (d) patterns. Asterisks indicate the tumors.

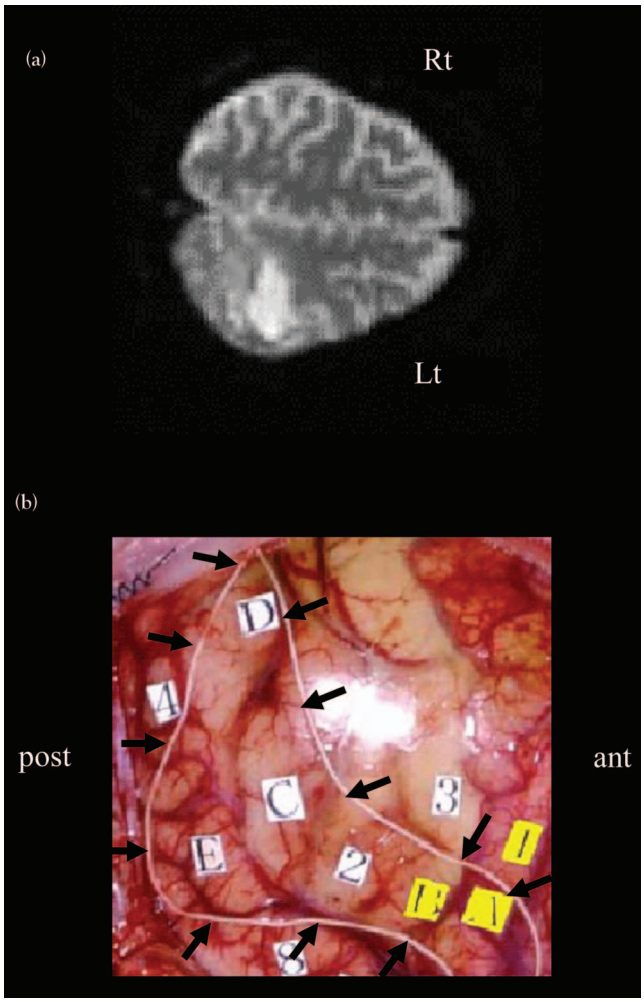

Fig. 6 Activation maps of BOLD-fMRI for the right grasping task (a) and cortical mapping (b) of the left motor cortex in glioma (Ref. 24). The activation maps of BOLD-fMRI demonstrated only limited areas, but the cortical mapping detected the motor cortex (arrows) during surgery.

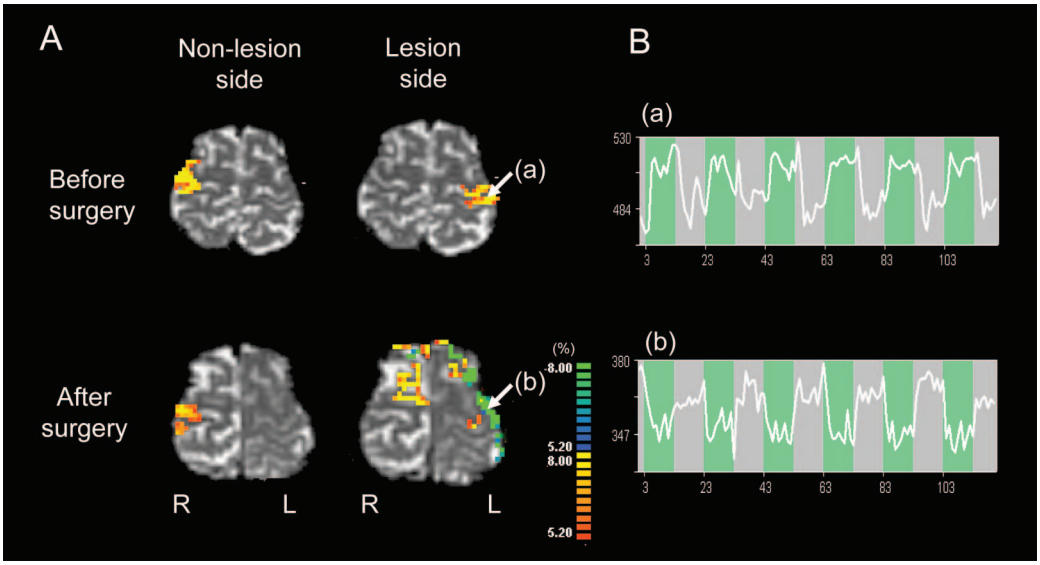

Fig. 7 (a) Activation maps of BOLD-fMRI for the right grasping task (lesion side) and the left grasping task (nonlesion side) before and after resection of glioma, which was located in the right frontal lobe (Ref. 25). Postoperative fMRI demonstrated negative BOLD signal changes in the motor cortex on the lesion side. (b) Time course of the BOLD signal changes. White arrows in (a) indicate the region of interest: (a) positive signal changes and (b) negative signal changes.

opposite effects of deoxy-Hb and t-Hb on the BOLD signal could lead to a marked reduction of activation volume.

The relation between the BOLD signal and evoked CBO responses in the pathological brain may differ from that in the normal brain. Hess et al. observed positive BOLD signals in the gerbil barrel cortex, where optical imaging demonstrated increases of deoxy-Hb and t-Hb during activation.[43] However, the BOLD signal did not increase consistently during the motor tasks in the PSMC on the lesion side in severe ischemia, where NIRS revealed increases of deoxy-Hb and t-Hb; the BOLD signal did not change in some areas, while it tended to decrease in other areas during the tasks (Fig. 4). Such a decrease of BOLD signal might be caused by an increase of paramagnetic deoxy-Hb in the activated cortical areas. We have observed a similar decrease of BOLD signals in the PSMC of a glioma patient after resection of the tumor; NIRS indicated increases of deoxy-Hb and t-Hb during activation (Fig. 7).[25] Such a paradoxical decrease of BOLD signal has also been noted in a stroke patient.[13] In addition, a fMRI study on rat stroke models has demonstrated that, compared to the normal cortex, the affected cortex revealed a lower covariance between activated voxels by BOLD and CBV-weighted fMRI during stroke recovery.[44]

6 Physiological Mechanism of Deoxy-Hb Increase During Activation

Although the physiological mechanism of the deoxy-Hb increase occurring during neuronal activity remains unclear, either a decrease of oxygen supply or an increase of oxygen consumption can cause a deoxy-Hb increase. In stroke patients, the reduced rCBF and impaired CVRC under resting conditions could elicit a lesser degree of rCBF rise during activation, resulting in a decrease in the driving force to wash out deoxy-Hb in the capillaries and veins. When such an impairment of the hemodynamic response is advanced, the oxygen extraction could increase to compensate for the decrease in oxygen delivery during activation. Quantitative models of the oxygen delivery during activation predict that disproportionately large increases of rCBF are required for small increases of the oxygen consumption.[45] Thus, a small decrease in the evoked rCBF response can give rise to oxygen deficiency during activation, leading to a lesser decrease or elevation of the deoxy-Hb concentrations in the vessels. Such alterations in the hemodynamic effects and oxygen metabolism might occur in patients with brain tumors, because compression by brain tumors or steeling of blood flow by neovascularization of tumors may cause cerebral ischemia around the tumors. A large increase of oxygen consumption during activation can also cause a deoxy-Hb rise. However, the oxygen metabolism during neuronal activity in brain disorders, including stroke and brain tumors, remains unclear because most examinations have been made on normal adults.[46–48] Further studies are needed to clarify in detail the oxygen metabolism and hemodynamics during neuronal activity in brain disorders.

7 Summary

Recent functional imaging studies have demonstrated that BOLD-fMRI does not image activation areas correctly in patients with stroke and brain tumors. We compared NIRS and BOLD-fMRI recording in the brain disorders and revealed that the false-negative activations in the BOLD-fMRI were associated an increase of deoxy-Hb during activation. Under such evoked CBO changes, BOLD signal may not increase consistently because an increase of the paramagnetic deoxy-Hb concentration tends to decrease the BOLD signal. The combined use of NIRS and BOLD-fMRI could facilitate the attainment of a higher level of accuracy in the brain functional imaging of diseased brains.

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