Intersubject variability of near-infrared spectroscopy signals during sensorimotor cortex activation

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Abstract. We investigate the intersubject signal variability of near-infrared spectroscopy (NIRS), which is commonly used for noninvasive measurement of the product of the optical path length and the concentration change in oxygenated hemoglobin ($\Delta C'_{oxy}$) and deoxygenated hemoglobin ($\Delta C'_{deoxy}$) and their sum ($\Delta C'_{total}$) related to human cortical activation. We do this by measuring sensorimotor cortex activation in 31 healthy adults using 24-measurement-position near-infrared (NIR) topography. A finger-tapping task is used to activate the sensorimotor cortex, and significant changes in the hemisphere contralateral to the tapping hand are assessed as being due to the activation. Of the possible patterns of signal changes, 90% include a positive $\Delta C'_{oxy}$, 76% included a negative $\Delta C'_{deoxy}$, and 73% included a positive $\Delta C'_{total}$. The $\Delta C'_{deoxy}$ and $\Delta C'_{total}$ are less consistent because of a large intersubject variability in $\Delta C'_{deoxy}$; in some cases there is a positive $\Delta C'_{deoxy}$. In the cases with no positive $\Delta C'_{oxy}$ in the contralateral hemisphere, there are cases of other possible changes for either or both hemispheres and no cases of no change in any hemoglobin species in either hemisphere. These results suggest that NIR topography is useful for observing brain activity in most cases, although intersubject signal variability still needs to be resolved. [DOI: 10.1117/1.1960907]

Keywords: near-infrared spectroscopy; hemoglobin; sensorimotor cortex; intersubject variability; finger tapping.

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1 Introduction

Near-infrared spectroscopy (NIRS) was first developed for noninvasive monitoring of cerebral oxygenation.[1,2] Later, its ability to measure the secondary metabolic signals accompanying neural activities was demonstrated.[3–7] Cortical activation can be assessed by calculating the product of the concentration change and the effective optical path length for oxygenated hemoglobin ($\Delta C'_{oxy}$) and deoxygenated hemoglobin ($\Delta C'_{deoxy}$) and their sum ($\Delta C'_{total}$) in the cerebral cortex. A near-infrared (NIR) topography with multiple measurement positions was developed from the NIRS technique as a noninvasive modality for functional mapping.[8–11] It has been gaining wide acceptance[12–22] due to its noninvasiveness, handiness, and measurability without subject constraint. These advantages even make it possible to measure brain functions in healthy infants.[12,13,20,23]

While methods to obtain absolute concentration changes multiplied by the mean optical path length (which can be estimated using time-resolved measurement) have been suggested,[24–26] it is inappropriate to use the mean path length as an alternative to the effective path length in the activation region.[27,28] We therefore use the product of the effective optical path length and the concentration change in the hemoglobin species ($\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$) as the NIRS signals. The ability of NIRS to measure $\Delta C'_{oxy}$ and $\Delta C'_{deoxy}$ individually is an important advantage compared with one representative imaging method—blood oxygenation level-dependent functional magnetic resonance imaging (BOLD fMRI), which

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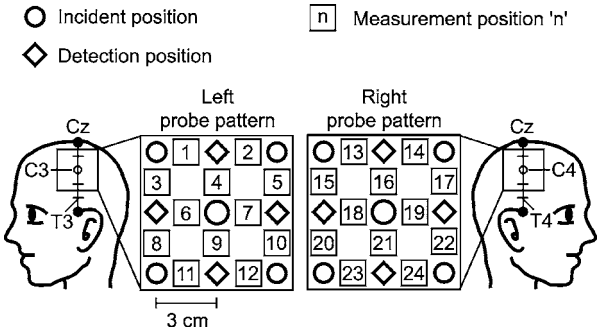

Fig. 1 Arrangement of measurement positions in probe patterns over left and right sensorimotor areas centered on locations C3 and C4, respectively.

measures the relative changes in only the paramagnetic deoxygenated hemoglobin that accompany oxygenation changes in the blood. NIRS is thus useful for examining the circulatory basis of brain activation.

The relationship between neural activity and hemodynamic changes, which cause changes in both the BOLD signal and NIRS signals, is an important issue in neuroscience. In general, the intensity of the BOLD signal increases with functional activation, which corresponds to a negative $\Delta C'_{\text{deoxy}}$,[29,30] and NIRS techniques have usually detected a positive $\Delta C'_{\text{oxy}}$ and a negative $\Delta C'_{\text{deoxy}}$ during a variety of stimulus paradigms.[3,5,11,21,30–32] However, contrary to the general understanding, a drop in the BOLD signal in fMRI studies[33,34] and a negative $\Delta C'_{\text{oxy}}$, together with a positive $\Delta C'_{\text{deoxy}}$ in NIRS studies,[5,30,35] have been reported. In addition, increases in all hemoglobin species have been observed in some NIRS studies.[6,22,36,37] Moreover, Seiyama et al. had conducted simultaneous fMRI and NIRS measurements and used NIRS function to explain the variability in the BOLD signal (increase, decrease, or no change) during cortical activation.[35] Although there are various patterns in the physiological changes caused by brain activation, they have not been classified, and their occurrence probabilities are still unknown, as are the pattern mechanisms.

In the present study, we examined how activation patterns, measured using NIRS, in the same cortical area vary among healthy adults with the aim of validating NIR topography for functional mapping and for explaining the circulation mechanisms in brain activation. The NIRS signals ($\Delta C'_{\text{oxy}}$, $\Delta C'_{\text{deoxy}}$, and $\Delta C'_{\text{total}}$) may be affected by anatomical variability such as thicknesses of skull and cerebrospinal fluid (CSF) layers as suggested by previous studies,[27,28] and the wavelength dependence of sensitivity may cause a cross talk effect between $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$.[38–40] However, the NIRS technique cannot provide anatomical information and there is no technique that specifies optical property for each layer of head *in vivo*, thus it is not possible to estimate the exact cross talk effect in practice. Therefore, to improve the existing method, we first need to assess the consistency of NIRS activation signals among a larger number of subjects.

We measured the activity in the sensorimotor cortex of 31 adults performing a simple sensorimotor task and evaluated the NIRS signals using a statistical analysis method. Sensorimotor cortex activation has already been investigated by a number of functional studies using positron emission tomography (PET),[41,42] fMRI,[43,44] and NIRS.[11,32] This study aims to provide a useful database that can be used for application of the NIR topography in both clinical and research fields. A portion of this study has been reported in abstract form.[45]

2 Materials and Methods

2.1 *Subjects*

31 healthy adults (21 men, 10 women; mean age 34±8.9, range 23 to 56) gave written informed consent before the experiments. All the subjects showed right-handedness except one, and none reported a history of neurological disorders.

2.2 *NIRS Measurement*

An NIR topography system with 24 measurement positions (ETG-100, Hitachi Medical Corporation, Japan) was used. The system irradiates light at 780- and 830-nm wavelength through an optical fiber to the same measurement point simultaneously. The reflected light was detected every 100 ms using an avalanche photodiode (APD) located 30 mm from the incident position.

We regarded the midpoint of the source-detector distance as the measurement position because the sensitivity of NIRS to chromophore-concentration changes is highest there.[46–48] Optical fibers were used for both the irradiating and detecting the lights. The average power of each light source was 1.5 mW, and each source was modulated at a distinctive frequency (1.0 to 10 kHz) to enable separation using a lock-in amplifier after detection. Ten irradiated positions and eight detection positions were configured to measure the 24 positions (Fig. 1).

The measurement area was determined for each subject based on the international 10–20 system.[49] We measured an area of 6×6 cm in the left and right parietal areas centered on C_3 and C_4, respectively (Fig. 1). The 6×6-cm square was defined as the measurement area for each hemisphere based on the arrangement of optical fibers (irradiation and detection positions). The probe patterns were positioned parallel to the line connecting Cz to T3 (left hemisphere) or T4 (right hemisphere). The centers of the bilateral measurement areas were considered to correspond to each primary sensorimotor area based on previous studies examining the relationship between the international 10–20 locations and cortical area.[50–52] In particular, Okamoto et al. recently reported that the C_3 and C_4 locations correspond to the central fissure with a standard deviation of less than 10 mm among 17 Mongoloids,[50] the same race as our subjects.

2.3 *Task Paradigm*

The sensorimotor cortices were activated using a finger-tapping task. The fingers of one hand were placed on the tip of the thumb in serial order (forefinger, second finger, third finger, little finger, third finger, second finger, forefinger). The subjects were asked to repeat the tapping sequence at 3 Hz timed to the rate of the term "finger tapping" blinking on a CRT monitor for 30 s (activation) followed by 30 s of rest (baseline). There were a total of five activation/baseline cycles per session. Two sessions of finger tapping (one left-hand tapping and one right-hand tapping) were conducted per subject

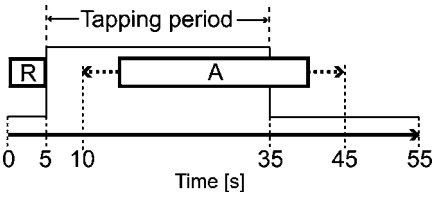

Fig. 2 Schematic diagram of analysis parameters for a task block. Mean value of 5 s for prestimulation (R) and mean value of 25 s for activation (A) were used for statistical analysis. Note that A could shift from 5 s after task onset to 10 s after task completion, depending on the maximum absolute value for each case.

in a counterbalanced order among subjects. During the measurements, the subject sat on a chair and was instructed to fix his or her gaze on the fixation point at the center of the screen and to concentrate on the task.

2.4 *Data Analysis*

We defined a period of 55 s, consisting of a 5-s prestimulation resting period, a 30-s stimulation period in the finger-tapping state, and a 20-s poststimulation resting period as one (task) block. The detected temporal data for the attenuation change at each wavelength were separated into five blocks. Each block was baseline corrected using the data for the pre- and poststimulation periods; the products of the effective optical path length and the concentration changes of the independent hemoglobin species ($\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$) were calculated by applying the modified Beer-Lambert Law[11] as follows:

$$\Delta C'_{\text{oxy}} = L \cdot \Delta C_{\text{oxy}} = \frac{-\varepsilon_{\text{deoxy}(\lambda 2)} \cdot \Delta A_{(\lambda 1)} + \varepsilon_{\text{deoxy}(\lambda 1)} \cdot \Delta A_{(\lambda 2)}}{E}, \tag{1}$$

$$\Delta C'_{\text{deoxy}} = L \cdot \Delta C_{\text{deoxy}} = \frac{\varepsilon_{\text{oxy}(\lambda 2)} \cdot \Delta A_{(\lambda 1)} - \varepsilon_{\text{oxy}(\lambda 1)} \cdot \Delta A_{(\lambda 2)}}{E}, \tag{2}$$

where

$$E = \varepsilon_{\text{deoxy}(\lambda 1)} \cdot \varepsilon_{\text{oxy}(\lambda 2)} - \varepsilon_{\text{deoxy}(\lambda 2)} \cdot \varepsilon_{\text{oxy}(\lambda 1)}. \tag{3}$$

$\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$ are expressed as the indefinite effective optical path length in the activation region (L) multiplied by the concentration change (ΔC_{oxy} and ΔC_{deoxy}). The ΔA, ε_{oxy}, and $\varepsilon_{\text{deoxy}}$ indicate the logarithm of the intensity change in the detected light, the absorption coefficient of the oxygenated hemoglobin, and that of the deoxygenated hemoglobin, respectively, for two wavelengths ($\lambda 1, \lambda 2$). Note that we assume that the path length is equal for every wavelength because accurate estimation of L is almost impossible with the current technique.

The activation signals were statistically assessed. Assuming that the hemodynamic time courses induced by the task varied among the subjects, we defined a 25-s activation period for each subject. We used a within-subject averaged time course over the five blocks to select the one 25-s activation period with maximum absolute value of the mean change for each hemoglobin species. The 25-s activation period was allowed to shift from the initial 5 s after task onset to starting 15 s after task onset; the earliest period was from 5 s after task onset to task completion, and the latest period was from 15 s after task onset to 10 s after task completion (Fig. 2).

The mean changes in hemoglobin during the prestimulation period and those during the activation period were calculated for each block. We calculated the t value (paired t test) between the mean hemoglobin changes in the prestimulation periods of five blocks and those in the activation periods of the same five blocks, and identified measurement positions with significant t values (two-tailed t test, $p < 0.1$) as activation points.[14,36] We determined the threshold for each NIRS signal ($\Delta C'_{\text{oxy}}$, $\Delta C'_{\text{deoxy}}$, and $\Delta C'_{\text{total}}$). This statistical analysis was designed to determine the consistency (reproducibility) of changes for the five activation periods. With this analysis, causeless changes are not detected as activation because the statistical value does not reach the threshold unless similar changes arise in every (or almost every) activation period. In addition, using activation periods 25 s long reduces the possibility of misidentifying an increase or decrease due to spontaneous oscillations during a cycle of around 10 as activation.[53] Moreover, a t test using the variance of the mean value in the resting period and that in the activation period across task blocks reduces the effect of high-frequency system noise. Note that although the determination of the activation period based on the peak timing differs from the analytical method we used in our previous report,[45] these differences in the results were negligible.

3 Results

3.1 *Occurrence Probability of Typical Activation Pattern*

We assessed the occurrence probability of the typical activation pattern (positive $\Delta C'_{\text{oxy}}$, negative $\Delta C'_{\text{deoxy}}$, and positive $\Delta C'_{\text{total}}$) for each measurement-position (Fig. 3). Positive $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{total}}$ in the hemisphere contralateral to the tapping hand were observed with high probability. In addition, the measurement positions with high probabilities were around the center of the measurement area (left hemisphere: positions 6 and 9; right hemisphere: position 16). Contrary to that, negative $\Delta C'_{\text{deoxy}}$ as a whole showed less probability, although the activation centers were almost the same as those for $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{total}}$ (left hemisphere: position 9; right hemisphere: position 16). The mean signal amplitudes for subjects who showed the typical activation pattern are given in Table 1. The mean amplitudes for $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{total}}$ were 0.109 and 0.104 mM·mm, respectively, while that for $\Delta C'_{\text{deoxy}}$ was about half (–0.048 mM·mm). The amplitudes sometimes varied widely among subjects, from small [Fig. 4(a)] to large [Fig. 4(b)].

The numbers of subjects who showed a significant $\Delta C'_{\text{oxy}}$, $\Delta C'_{\text{deoxy}}$, or $\Delta C'_{\text{total}}$ (either positive or negative) for the hemisphere contralateral to the tapping hand are shown in Table 2. The most common change was a positive $\Delta C'_{\text{oxy}}$ (90%; left hemisphere 28/31, right hemisphere 28/31). Moreover, in 91% of the subjects showing this change, at least one of the four measurement positions in the central area (left hemisphere: positions 4, 6, 7, and 9; right hemisphere: positions

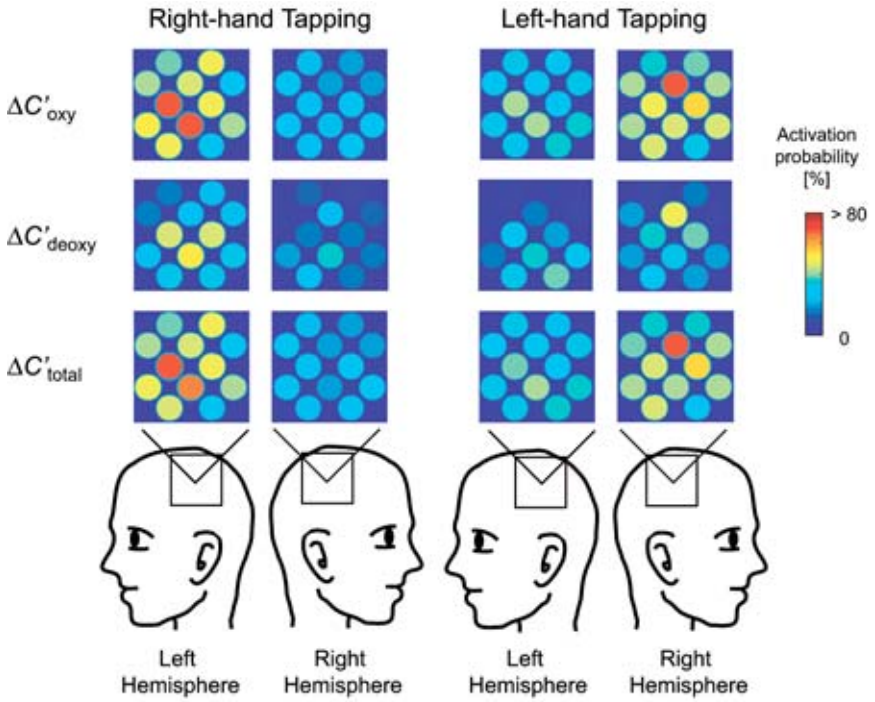

Fig. 3 Color maps of occurrence probabilities of typical activation pattern (positive $\Delta C'_{oxy}$, negative $\Delta C'_{deoxy}$, and positive $\Delta C'_{total}$) for each measurement position.

16, 18, 19, and 21) was included. A negative $\Delta C'_{deoxy}$ and a positive $\Delta C'_{total}$ were less frequently observed ($\Delta C'_{deoxy}$: 76%, left hemisphere 24/31, right hemisphere 23/31; $\Delta C'_{total}$: 73%, left hemisphere 23/31, right hemisphere 22/31). In 91% of the subjects showing a negative $\Delta C'_{deoxy}$ and in 89% of the ones showing a positive $\Delta C'_{total}$, at least one of the four measurement positions in the central area was included. Although $\Delta C'_{deoxy}$ was generally negative, 16% of the subjects showed a positive $\Delta C'_{deoxy}$. A negative $\Delta C'_{oxy}$ was observed for only one subject for the hemisphere contralateral to the tapping hand.

3.2 *Variability of Activation Pattern*

To determine the relationships among $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$ in detail, we classified the various patterns of combination. The patterns and appearance frequencies are shown in Table 3. Note that a significance threshold was set for each NIRS signal, so a significant change in one signal ($\Delta C'_{oxy}$ or $\Delta C'_{deoxy}$) will not result in a significant change in $\Delta C'_{total}$ (sum of $\Delta C'_{oxy}$ and $\Delta C'_{deoxy}$) due to a subthreshold change (noise) in the other signal.

The most common pattern (positive $\Delta C'_{oxy}$, negative $\Delta C'_{deoxy}$, positive $\Delta C'_{total}$; ↑↓↑ in Table 3) was shown in 18 and 17 subjects (total 56%) for the left and right hemispheres, respectively. Similar to the most common pattern, the patterns in which $\Delta C'_{oxy}$ was positive and $\Delta C'_{deoxy}$ was negative without a positive $\Delta C'_{total}$ (↑↓↓ and ↑↓-) were seen in four and five subjects (total 15%) for the left and right hemispheres, respectively. In addition, positive $\Delta C'_{oxy}$ and $\Delta C'_{total}$ with subthreshold $\Delta C'_{deoxy}$ (↑-↑) and a positive $\Delta C'_{oxy}$ with subthreshold $\Delta C'_{deoxy}$ and $\Delta C'_{total}$ (↑--) were observed in four and one subjects (total 6%) for the left and right hemispheres, respectively.

Another frequent pattern was the all-positive pattern (↑↑↑ in Table 3), which was observed in three and five subjects (total 13%) for the left and right hemispheres, respectively. There were mainly two types of changes in this pattern; a general type showed a strong positive $\Delta C'_{oxy}$ and $\Delta C'_{total}$ with a positive $\Delta C'_{deoxy}$ [Fig. 4(c)], and a singular type that showed a strong positive $\Delta C'_{oxy}$ and $\Delta C'_{deoxy}$, resulting in a stronger positive $\Delta C'_{total}$ [Fig. 4(d)].

A significant characteristic of all these patterns was a positive $\Delta C'_{oxy}$, which was observed in 90% of the cases.

The 10% that did not show a positive $\Delta C'_{oxy}$ were grouped into three patterns; the first is the pattern with a negative

Table 1 Mean signal amplitude of each hemoglobin species among subjects who showed typical activation pattern (positive $\Delta C'_{oxy}$, negative $\Delta C'_{deoxy}$, positive $\Delta C'_{total}$). An activation position with the highest signal amplitude within the contralateral hemisphere to the tapping hand for each subject was used.

	$\Delta C'_{oxy}$	$\Delta C'_{deoxy}$	$\Delta C'_{total}$
Mean signal amplitude ±SD (mM·mm)	0.109±0.063	−0.047±0.026	0.104±0.056

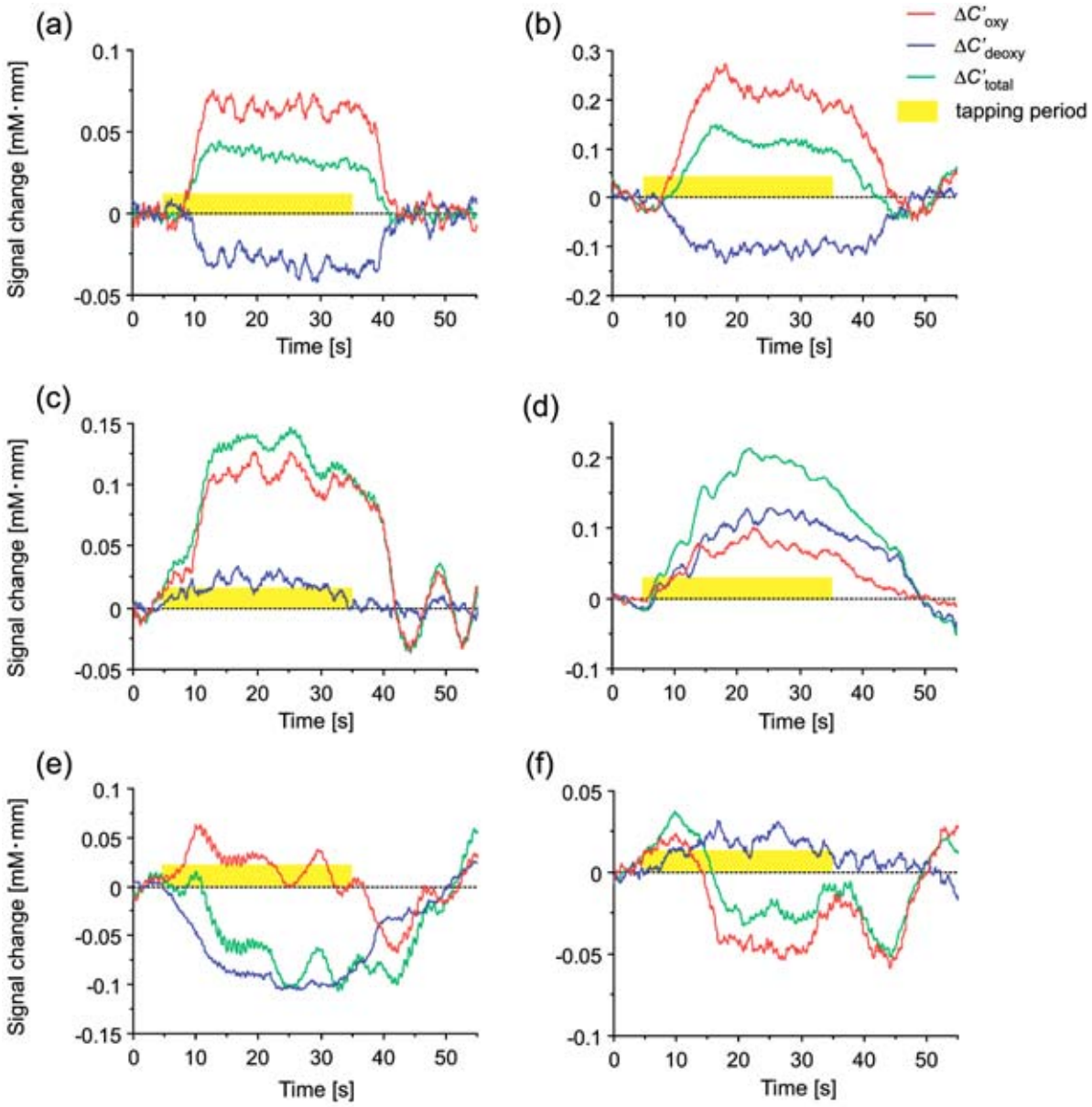

Fig. 4 Representative time courses of $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$. Typical pattern (positive $\Delta C'_{oxy}$, negative $\Delta C'_{deoxy}$, and positive $\Delta C'_{total}$) is shown in (a) and (b); changes in (b) are larger than those in (a). An all-positive pattern (positive $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$) is shown in (c) and (d). Pattern in (d) was a rare case—$\Delta C'_{deoxy}$ was positive similar to $\Delta C'_{oxy}$. Two exceptional patterns are shown in (e) and (f). The pattern with only a negative $\Delta C'_{deoxy}$, (e), was observed in only two subjects. The pattern with a negative $\Delta C'_{oxy}$ and a positive $\Delta C'_{deoxy}$, (f), was observed in only one subject.

$\Delta C'_{oxy}$ and a positive $\Delta C'_{deoxy}$ in the right hemisphere during left tapping [Fig. 4(f); ↓↑- in Table 3]. In addition, the same subject showed only a negative $\Delta C'_{oxy}$ in the left hemisphere during right-hand tapping (↓--), but a similar pattern of a negative $\Delta C'_{oxy}$ and a positive $\Delta C'_{deoxy}$ was observed in the right (ipsilateral) hemisphere. We therefore classified the changes for this subject as the same pattern. Another is the pattern with a negative $\Delta C'_{deoxy}$ only [Fig. 4(e); -↓-]. This pattern was observed in two subjects (both hemispheres in one; one hemisphere in the other). The last is the pattern with a positive $\Delta C'_{deoxy}$ only in the right hemisphere (-↑-) while the subject showed all-positive pattern (↑↑↑) in the left (ipsilateral) hemisphere [Fig. 4(d)]. Note that in every case of these three patterns there was a hemoglobin change in at least one of the hemispheres.

4 Discussion

4.1 *Occurrence Probability of Typical Activation Pattern*

First, we examined the occurrence probability of the typical activation pattern (positive $\Delta C'_{oxy}$, negative $\Delta C'_{deoxy}$, and positive $\Delta C'_{total}$) in the hemisphere contralateral to the tapping hand. These physiological changes were consistent with the accepted theory[29,30] and previous NIRS studies.[11,32] The occurrence probabilities in a previous study[32] were nearly con-

sistent with our results for both $\Delta C'_{oxy}$ (about 89% in the previous study and 90% in ours) and $\Delta C'_{deoxy}$ (about 84% in the previous study and 76% in ours). Moreover, the combination of a positive $\Delta C'_{oxy}$ and a negative $\Delta C'_{deoxy}$ was observed in 73 and 71% of the cases for the previous and present study, respectively.

Our results showed that a negative $\Delta C'_{deoxy}$ was observed less frequently in the activation center than positive $\Delta C'_{oxy}$ and $\Delta C'_{total}$ (Fig. 3; left hemisphere: position 9; right hemisphere: position 16). This could be due to the smaller total number of $\Delta C'_{deoxy}$ activation positions compared to the other hemoglobin species for each subject, which is supported by our finding that the number of subjects with positive $\Delta C'_{deoxy}$ did not differ much from those with positive $\Delta C'_{total}$ (Table 2).

One possible reason for this is the effect of systemic changes on the responses of $\Delta C'_{oxy}$ and $\Delta C'_{total}$. It has been suggested that a finger-tapping task can lead to systemic changes in blood pressure and heart rate that affect measurements of $\Delta C'_{oxy}$ in particular.[54,55] Both $\Delta C'_{oxy}$ and $\Delta C'_{total}$ had a larger activation area, i.e., they were measured at more positions, while the activation area for $\Delta C'_{deoxy}$ was more focused. While monitoring the systemic effects and using an analytical method that subtracts the effects from the signals would be ideal,[54] a more practical approach may be to design a task paradigm that does not induce systemic variance between the rest period and task period.

Although it was difficult to distinguish the systemic effects from the cortical response in this study, the activation area for $\Delta C'_{deoxy}$ may actually have been smaller than those for $\Delta C'_{oxy}$ and $\Delta C'_{total}$ for most subjects. A previous study of simultaneous recordings of fMRI and NIRS signals suggests that $\Delta C'_{deoxy}$ provides more specific information for focal cerebral responses than $\Delta C'_{oxy}$.[56] Moreover, another study of simultaneous recordings showed that an activation map using $\Delta C'_{oxy}$ did not overlap maps using $\Delta C'_{deoxy}$ and BOLD signals.[35] Further study of the spatial and temporal diversities between the two signals ($\Delta C'_{oxy}$ and $\Delta C'_{deoxy}$) is thus important. Higher spatial resolution, however, will be needed before NIR topography can be used to analyze the activation centers accurately.

We also observed that the probable positions of highest activation differed between the left (position 9) and right hemisphere (position 16). Possible reasons for this longitudinal asymmetry of the highest activation positions are a methodological problem and an anatomical characteristic of the cerebral cortex. The methodological problem is possible inaccurate placement of the measurement probes, since we placed them by hand though we did determine the positions according to the international 10–20 system. We need to develop a better method for accurate positioning. The anatomical characteristic is possible asymmetry due to the anatomical asymmetry of the cerebral cortex. According to a previous study,[57] the parietal and temporal cortices of the left hemisphere are larger than those of the right hemisphere in most subjects. As a result, even though the probes are placed symmetrically on the head surface, they may actually be shifted upward in relation to the cerebral cortex. A placement error of only a few millimeters can mislead the peak activation position to the next measurement position when the investigated area is placed at the center of the measurement area surrounded by four measurement positions.[46]

Table 2 Number of subjects (out of 31) who showed a significant $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, or $\Delta C'_{total}$ (two-tailed t test, $p<0.1$). Numbers in ( ) show the number of subjects having a significant change at measurement positions in the central area (left hemisphere: positions 4, 6, 7, 9; right hemisphere: positions 16, 18, 19, 21).

		Left hemisphere (right-hand tapping)	Right hemisphere (left-hand tapping)
$\Delta C'_{oxy}$	Positive	28 (25)	28 (26)
	Negative	1(1)	1(0)
	Insignificant	2	2
$\Delta C'_{deoxy}$	Positive	3 (3)	7 (1)
	Negative	24 (21)	23 (22)
	Insignificant	4	1
$\Delta C'_{total}$	Positive	23 (22)	22 (18)
	Negative	4 (3)	3 (1)
	Insignificant	4	6

Even with this possible low spatial resolution, our finding that measurement positions with high activation probabilities were around the center of the measurement area (left hemisphere: positions 4, 6, 7, and 9; right hemisphere: positions 16, 18, 19, and 21) suggests that the 10–20 international system is useful in determining the measurement area for NIR topography.

Examination of the activation probabilities in detail (Table 2) shows that a negative $\Delta C'_{deoxy}$, which can cause the typical BOLD signal pattern, was not as consistently observed (negative 76%, positive 16%) as a positive $\Delta C'_{oxy}$ (positive 90%, negative 3%). This peculiar feature of $\Delta C'_{deoxy}$—the possibility of it being positive or negative—might be another reason for the less-focused activation in $\Delta C'_{deoxy}$. Our results suggest that the $\Delta C'_{deoxy}$ signal can occasionally vary not only in amplitude but also in direction, which conflicts with the common idea of BOLD fMRI.

The variable behavior of $\Delta C'_{deoxy}$ may be due to the variability of the cross talk effect[39,40] among subjects; however, it is not possible to estimate the actual cross talk effect for an individual. Although we used a wavelength pair of 780 and 830 nm, which is not an optimal wavelength pair (e.g., 690 and 830 nm) for reducing the cross talk effect, as suggested by some simulation studies,[38,58] we did previously determine that the primary shape of the activation signal (positive change or negative change) does not depend on the wavelength pair (either 692 and 830 nm or 782 and 830 nm).[45] We therefore think the variability of $\Delta C'_{deoxy}$ was not due solely to the wavelengths used.

Another possibility is that the variability in $\Delta C'_{deoxy}$ reflects some physiological phenomena relating to brain activation, since unusual behavior in the $\Delta C'_{deoxy}$ or the BOLD signal has been previously reported.[30,33] The variability of

Table 3 Patterns of hemoglobin changes and their occurrence rate among 31 subjects. [*1] ↑ increase, ↓ decrease, -subthreshold change. The changes were assessed using a two-tailed *t* test ($p<0.1$). When both changes appeared for one condition, the change for more measurement positions was used; when both changes appeared for the same number of measurement positions, the change with the maximum *t* value (absolute value) was used. [*2] A subject's change characterized by positive $\Delta C'_{deoxy}$ and negative $\Delta C'_{oxy}$ in the right hemisphere during both-hand tapping [Fig. 4(f)]. The subject showed only a negative $\Delta C'_{oxy}$ in the left hemisphere during right-hand taping (↓--), but a similar pattern of a negative $\Delta C'_{oxy}$ and a positive $\Delta C'_{deoxy}$ was observed in the right (ipsilateral) hemisphere. [*3] Three cases including both hemispheres of one subject. $\Delta C'_{deoxy}$ was consistently negative, though $\Delta C'_{oxy}$ tended to be noisy. [*4] The pattern with a positive $\Delta C'_{deoxy}$ only in the right hemisphere (-↑-), while the subject showed all-positive pattern (↑ ↑ ↑) in the left (ipsilateral) hemisphere.

Change pattern[*1]			Left Hemisphere (Right-hand tapping)	Right Hemisphere (Left-hand tapping)
$\Delta C'_{oxy}$	$\Delta C'_{deoxy}$	$\Delta C'_{total}$		
↑	↓	↑	18	17
↑	↓	↓	2	3
↑	↓	-	2	2
↑	↑	↑	3	5
↑	↑	↓	0	0
↑	↑	-	0	0
↑	-	↑	2	0
↑	-	↓	0	0
↑	-	-	1	1
↓	↓	↑	0	0
↓	↓	↓	0	0
↓	↓	-	0	0
↓	↑	↑	0	0
↓	↑	↓	0	0
↓	↑	-	0	1[*2]
↓	-	↑	0	0
↓	-	↓	0	0
↓	-	-	1[*2]	0
-	↓	↑	0	0
-	↓	↓	0	0
-	↓	-	2[*3]	1[*3]
-	↑	↑	0	0
-	↑	↓	0	0
-	↑	-	0	1[*4]
-	-	↑	0	0
-	-	↓	0	0
-	-	-	0	0
	Total		31	31

hemodynamic responses is normally considered to be dependent on several factors such as cerebral blood flow (CBF), cerebral blood volume (CBV), and oxygen consumption rate ($CMRO_2$).[35] One previous study showed positive, negative, and silent BOLD signals with a negative, positive, and subthreshold $\Delta C'_{deoxy}$, respectively, while $\Delta C'_{oxy}$ showed various behaviors by simultaneous measurement of fMRI and NIRS.[35] Another study demonstrated positive $\Delta C'_{oxy}$ and $\Delta C'_{deoxy}$ in the capillary area along with a negative $\Delta C'_{deoxy}$ and positive $\Delta C'_{oxy}$ in the large vein area.[37]

4.2 *Variability of Activation Pattern*

Next, we examined the various patterns in more detail using classification analysis for the various combinations of hemoglobin changes (Table 3). We considered the patterns with a positive $\Delta C'_{oxy}$ and without a positive $\Delta C'_{deoxy}$ (↑ ↓ ↓, ↑ ↓-, and ↑-↑ in Table 3) to be the same as the most common pattern (↑ ↓ ↑) seen in this study. These patterns were observed in 25 and 23 subjects (77%) for the left and right hemispheres, respectively. As mentioned before, the variety of patterns for $\Delta C'_{deoxy}$ and $\Delta C'_{total}$ could depend on CBF, CBV, and $CMRO_2$[29,30,33] and on the proportions of the capillary and large vein areas in the measurement region.[37] Simulation studies in which the proportions of these factors were changed might be useful in determining the physiological mechanism leading to each pattern. In addition, the cross talk effect due to anatomical characteristics or different SNRs in the $\Delta C'_{deoxy}$ signal may have resulted in the pattern with subthreshold $\Delta C'_{deoxy}$ (↑-↑).

The all-positive pattern (↑↑↑ in Table 3), which was occasionally observed (13%), was also reported in a number of previous NIRS studies.[6,22,37] In one of the previous studies, this pattern occurred in capillary areas such as the inferior frontal gyrus (Broca's area), while the common pattern with a negative $\Delta C'_{deoxy}$ occurred in large vein areas such as the superior temporal area.[37] If the variability of the hemodynamics depends on the distribution of the vascular system, there could be a large variability in the distributive condition of vessels among subjects, even for the same cortical area.

Our observation on both the common pattern and the all-positive pattern in the same cortical area during the same activation paradigm suggests that the variation in hemoglobin changes depends on the subject's anatomical characteristics and condition rather than the characteristics of the measurement area or the paradigm.

The patterns described earlier showing a positive $\Delta C'_{oxy}$ were observed in 90% of the subjects. This suggests high reliability of $\Delta C'_{oxy}$ as an activation signal, whereas some previous studies used only $\Delta C'_{total}$ to identify cognitive-related activation.[13,16,17]

The other 10% are interpreted as follows: an atypical pattern with a positive $\Delta C'_{deoxy}$ [Fig. 4(f); ↓↑ - and - ↑ - in Table 3] was observed in one subject. The combination pattern, which is similar to the deactivation in fMRI[30,33–35] and PET,[59,60] possibly appears when $CMRO_2$ significantly increases during activation.[35] Another possibility for this pattern is that the signal pattern showed blood stealing or neural suppression due to neighboring activation, but the reason only deactivation could be observed remains unexplained. Another is the pattern with a negative $\Delta C'_{deoxy}$ only [Fig. 4(e); - ↓ - in Table 3], which was observed in two subjects (both hemispheres in one; one hemisphere in the other). This pattern might result from less sensitivity for $\Delta C'_{oxy}$. While the $\Delta C'_{oxy}$ signal tended to increase more, the level did not reach the statistical threshold for these subjects. This is possibly due to greater noise in the $\Delta C'_{oxy}$ signal than in the $\Delta C'_{deoxy}$ one. Physiological noise, such as low frequency oscillations[53] or systemic changes,[54,55] can have more effect on $\Delta C'_{oxy}$ than on $\Delta C'_{deoxy}$. Although it may be possible to subtract the systemic changes from NIRS signals by using simultaneously recorded data for the arterial saturation and heart rate,[54] simultaneous measurements of these physiological signals with NIRS is difficult.

Another pattern was a positive $\Delta C'_{deoxy}$ only in the right hemisphere (-↑-in Table 3) during left-hand tapping, while this subject showed an all-positive pattern (↑ ↑ ↑) in the ipsilateral (left) hemisphere as well as during contralateral right-hand tapping [Fig. 4(d)]. While activation in both hemispheres during unilateral finger movement has been reported,[61,62] predominant activation in the ipsilateral one rarely occurs in normal adults. Further examination with anatomical imaging will be necessary to explain this unusual lateralization.

5 Conclusion

We study the variability of NIRS signals induced by sensorimotor activation in 31 healthy subjects using NIR topography. Activation patterns with a positive $\Delta C'_{oxy}$ for the hemisphere contralateral to the tapping hand were observed with high probability (90%). Moreover, every other case showed other significant changes for either or both hemispheres, suggesting that NIR topography is useful for observing brain activity in most cases. In addition, our finding that activation positions tended to be around the center of the measurement area demonstrated the effectiveness of the 10–20 international system for determining the measurement positions.

Although this study evaluated NIRS signals that may have been affected by cross talk, intersubject anatomical variation, and systemic changes accompanying the task, we believe that it is important to evaluate the variability of NIRS signals in spite of these effects, because the NIRS technique has been widely used in its present state and improvements in the technique will come with its usage.

Relating the activation patterns to the anatomical characteristics of the subjects requires further examination of the anatomical variability among subjects and its effects on NIRS signals as well as the development of better techniques. In addition, further experiments under a wider variety of conditions for the measurement area, task paradigm, and subject group will be helpful for understanding the activation patterns. Moreover, invasive animal studies may be needed to generate a more sophisticated theory explaining the physiological mechanism of these various activation patterns.

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