Within-subject reproducibility of near-infrared spectroscopy signals in sensorimotor activation after 6 months

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Abstract. Near-infrared spectroscopy (NIRS) can measure the product of the optical path length and the concentration change in oxygenated hemoglobin ($\Delta C'_{oxy}$), deoxygenated hemoglobin ($\Delta C'_{deoxy}$), and their sum ($\Delta C'_{total}$) in the human cerebral cortex, and it has been used for noninvasive investigation of human brain functions. We evaluate the within-subject reproducibility of the NIRS signals by repeated measurement of the sensorimotor cortex in healthy adults taken over a period of about 6 months using near-infrared (NIR) topography. The maximum signal amplitudes and the location of activation centers are compared between two sessions for each subject. The signal amplitudes vary between sessions and no consistent tendency in the changes is found among subjects. However, the distance between the activation centers identified in two sessions is relatively small, within 20 mm on average across subjects, which is comparable to the smallest distance between measurement positions in the NIR topography (21 mm). Moreover, within-subject comparisons of signal time courses show high correlation coefficients (>0.8) between the two sessions. This result, demonstrating a high within-subject reproducibility of the temporal information in NIRS signals, particularly contributes to the development of a new application of NIRS. [DOI: 10.1117/1.2166632]

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

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1 Introduction

Near-infrared spectroscopy (NIRS) has been used for noninvasive measurement of cortical functions by monitoring cerebral oxygenation changes.[1–4] This technique provides the product of the concentration change and the effective optical path length for oxygenated hemoglobin ($\Delta C'_{oxy}$), deoxygenated hemoglobin ($\Delta C'_{deoxy}$), and their sum ($\Delta C'_{total}$) in the cerebral cortex to assess the cortical activity. Note that the absolute values of concentration changes in hemoglobin species (oxygenated hemoglobin, deoxygenated hemoglobin, and their sum, i.e., total hemoglobin) are not measured because an accurate estimation of the optical path length in the activation area is almost impossible with the current technique. 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,[5–7] it is inappropriate to use the mean path length as an alternative to the effective path length in the activation region.[8]

Near-infrared (NIR) topography was developed as a noninvasive modality for functional mapping with multiple measurement positions.[9–12] NIR topography has been widely used[13–21] because it is noninvasive, and measurements can be taken with far fewer constraints imposed on the subject than with other modalities, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These advantages are particularly useful for clinical applications[18,21,22] and for measuring infants and children.[13,14,19,23]

Brain activity can also be investigated noninvasively by using blood-oxygenation-level-dependent (BOLD) fMRI, which exploits the difference between diamagnetic oxygenated hemoglobin and paramagnetic deoxygenated hemoglo-

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bin, and NIR topography is a useful supplementary tool not only for functional studies but also for physiological studies because it can measure $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$. We think the information provided by NIR topography is useful for noninvasive assessments of the cerebral circulation and metabolism and has clinical uses, such as monitoring the rehabilitation of stroke victims.

The quality of the NIRS signals ($\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$), however, has not been fully explained and should be clarified for finding appropriate applications of NIR topography. We have been trying to evaluate the fundamental characteristics of NIRS signals,[24] but our efforts have been incomplete until now. In this paper, we evaluate the reproducibility of NIRS signals with the aim of making NIR topography more useful in the clinical assessment of cerebral circulation and metabolism as well as in functional studies. Although we have found atypical signal patterns for about 10% of subjects during sensorimotor activation,[24] here, we focus on the typical activation patterns (positive $\Delta C'_{oxy}$, $\Delta C'_{total}$, and negative $\Delta C'_{deoxy}$), which have been observed in most subjects, because atypical patterns might depend on complex factors, and it is difficult to determine whether or not they are reproduced at this stage.

We examined within-subject reproducibility of NIRS signals due to sensorimotor activation during a finger-tapping task. Sensorimotor activation has been investigated in a number of studies using PET (Refs. 25 and 26), fMRI (Refs. 27 and 28), and NIRS (Refs. 12, 24, 29, and 30). Although the reproducibility of PET and fMRI sensorimotor-activation signals has already been examined,[31–33] there are few reports related to the within-subject reproducibility of NIRS signals measured at different times. In the work reported here, we used a simple task to limit the number of cognitive process that might affect the activation. To reduce the effects of habituation and learning, we let about 6 months elapse between each subject's first and second experimental session and did not make the subject perform the experimental task during the period between sessions. We also controlled other conditions for each subject (e.g., the same examiner and the same experiment place and time of day). A portion of this study has already been reported in abstract form.[34]

2 Materials and Methods

2.1 *Subjects*

Seven healthy adults (two men and five women between 28 and 44 years old; mean age=35) participated in the experiment. Each gave written informed consent after the nature of the experimental procedures was explained before the experiments. Six of the subjects showed right-handedness, and none reported a history of neurological disorder.

2.2 *NIR Topography Measurement*

A multichannel NIR topography system (ETG-100: Hitachi Medical Corporation, Japan), which can take measurements at 24 positions, was used. The system delivers light beams with 780- and 830-nm wavelengths through an optical fiber to the same position simultaneously. The scattered light was detected every 100 ms using an avalanche photodiode (APD) 30 mm from the incident position through optical fibers. We regarded the midpoint of the source-detector distance as the measurement position because that is where the NIR topography system is most sensitive to changes in chromophore concentration.[35–37] Optical fibers carried the light from the sources to the subject's head and carried the scattered light from the subject's head to the APD. The average power of each light source was 1.5 mW, and each source was modulated at a different frequency to encode irradiated positions and wavelengths. Ten irradiated positions and eight detection positions were arranged to make 24 measurement positions (Fig. 1).

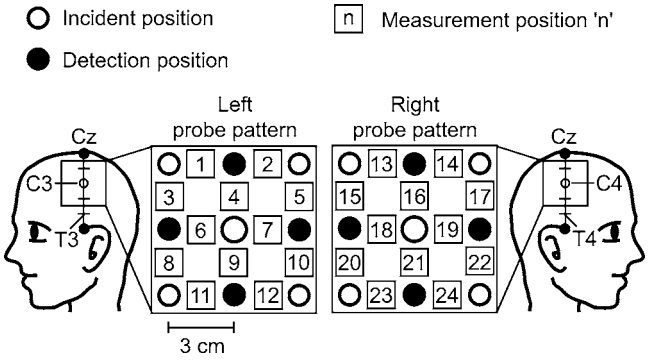

Fig. 1 Arrangement of measurement positions in probe patterns over left and right sensorimotor areas centered on locations C3 and C4, respectively.

The measurement positions were determined manually for each subject and were based on the international 10 to 20 system.[38] We measured 60- $\times$60-mm areas in the left and right parietal areas centered on C_3 and C_4 (Fig. 1). The 60- $\times$60-mm square was defined as the measurement area for each hemisphere based on the arrangement of optical fibers (irradiation and detection positions). The centers of the bilateral measurement areas were considered to correspond to each primary sensorimotor area based on previous studies examining the relation between the international 10 to 20 locations and the underlying cortical areas.[39–41]

2.3 *Task Paradigm*

The two experimental sessions for each subject were separated by about 6 months—167±11 days (mean±SD)—and two finger-tapping trials were conducted in each session (one with the left hand and one with the right hand) (Fig. 2). In each trial, the fingers of one hand were repeatedly placed on the tip of the thumb in the following 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 synchronized to the term "Finger tapping" blinking on a CRT monitor. Each task period lasted for 30 s and was followed by 30 s of rest (rest period). Each trial consisted of six rest periods and five task periods (Fig. 2).

2.4 *Data Analysis*

We divided each trial into five 55-s "blocks." A block consisted of 5 s of the rest period before a task (pretask rest period), the 30-s task period, and 20 s of the rest period after the task (posttask rest period), as illustrated in Fig. 3. The data collected for each block, i.e., the detected temporal attenua-

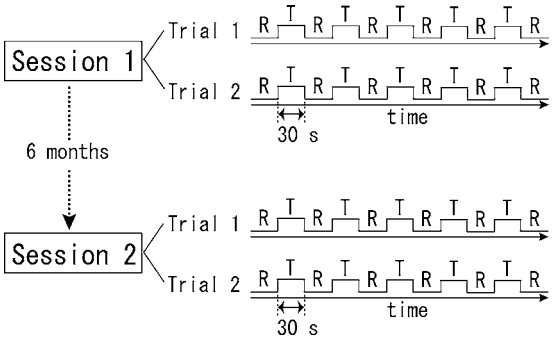

Fig. 2 Schematic diagram of measurement sequence (session and trial): R; rest period; T; task (finger-tapping) period. A finger-tapping task using either the left or right hand was conducted in each trial. The order of trials, right hand or left hand, was counterbalanced among subjects, and the order was fixed in the second session for each subject.

tion changes at each wavelength, were baseline-corrected using the data for the pre- and posttask rest periods. The products of the effective optical path length and the concentration changes of the independent hemoglobin ($\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$) were calculated by applying the modified Beer-Lambert law.[12]

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 (see Fig. 3). We used a within-subject averaged time course over the five blocks to select the 25-s activation period with the maximum absolute mean change for each hemoglobin signal. 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.

Using the mean changes in hemoglobin signals during the pretask period and those during the activation period for each block, we calculated the t value (paired t test) between the mean hemoglobin changes in the pretask rest periods of five blocks and those in the activation periods of the same five blocks.[24] We identified measurement positions with significant t values (two-tailed t test, $p<0.1$) as activation points by using the independent threshold ($p<0.1$) for each NIRS signal ($\Delta C'_{\text{oxy}}$, $\Delta C'_{\text{deoxy}}$, and $\Delta C'_{\text{total}}$). This statistical analysis was

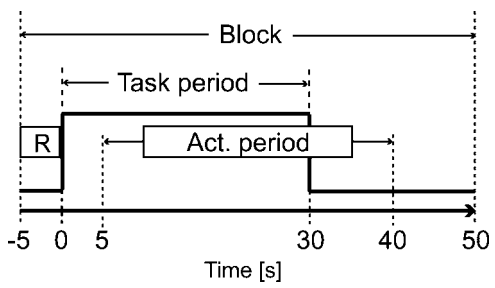

Fig. 3 Schematic diagram of analysis parameters for a block. Mean values during 5 s of rest period before task (R) and 25 s of activation period were used for statistical analysis. Note that activation period can shift from 5 s after task onset to 10 s after task completion, depending on the maximum absolute value for each case.

designed to determine the consistency (reproducibility within a session) of changes for the five activation periods. With this analysis, system noise is not detected as an activation because its 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[42] of 0.1 Hz. Moreover, a t test using the mean value in the pretask rest period (5 s) and that in the activation period (25 s) for each block reduces the effect of high-frequency system noise.

Using the data for the activation points, we examined the reproducibility of spatial information, signal amplitude, and temporal information between sessions for each subject. The spatial information was represented by that for the activation center of the activation area. The coordinates of the activation center (x_c, y_c) were defined as

$$x_c = \frac{\sum_i x_i a_i}{\sum_i a_i}, \quad y_c = \frac{\sum_i y_i a_i}{\sum_i a_i}, \tag{1}$$

where (x_i, y_i) denotes the coordinates of the i'th activation point, and a_i is the signal amplitude at the i'th activation point. Note that the measurement positions with no significant changes were not used in calculating the activation center. We examined the reproducibility of spatial information by using the distance between the activation centers identified in the two sessions. The mean signal changes during the activation periods and the time courses of the hemoglobin signals ($\Delta C'_{\text{oxy}}$, $\Delta C'_{\text{deoxy}}$, and $\Delta C'_{\text{total}}$) were used as the respective reproducibility indices for signal amplitude and temporal information.

3 Results

3.1 *General Aspects of Reproducibility*

In the first session, every subject showed a positive $\Delta C'_{\text{oxy}}$, a negative $\Delta C'_{\text{deoxy}}$, and a positive $\Delta C'_{\text{total}}$ in the hemisphere contralateral to the tapping hand. Although the same patterns in $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$ were reproduced in the second session for every subject, for three subjects the $\Delta C'_{\text{total}}$ changes in one hemisphere were not significant in the second session. In these three cases, we could not derive the indices for the activation center and so on because no activation point was found there. Reproducibility was therefore further examined using 14 data sets (two hemispheres $\times$ 7 subjects) for $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$, and 11 data sets (14 minus the three exception cases) for $\Delta C'_{\text{total}}$.

3.2 *Reproducibility of Spatial Information*

Figure 4 shows representative activation maps for the left-hand finger tapping for the two sessions of a subject. For both sessions, similar patterns of activation (positive $\Delta C'_{\text{oxy}}$, negative $\Delta C'_{\text{deoxy}}$, and positive $\Delta C'_{\text{total}}$) were observed in the hemisphere contralateral to the tapping hand. By comparing the activation locations between the two sessions, we found that the activation center was reproduced within 16.0 ($\Delta C'_{\text{oxy}}$), 18.6 ($\Delta C'_{\text{deoxy}}$), and 16.0 mm ($\Delta C'_{\text{total}}$) on average (Table 1). A one-way analysis of variance (ANOVA) for hemoglobin

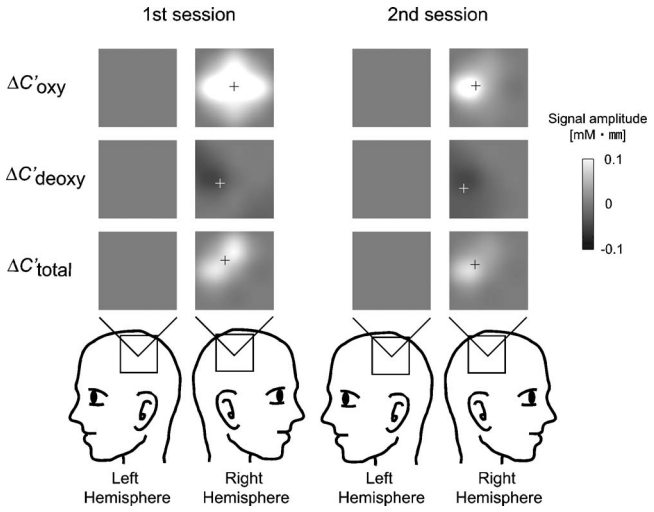

Fig. 4 Representative activation maps in two sessions during the left-hand finger-tapping period. Limited positions with significant changes (activation points) are shown in color with linear interpolation, and other measurement positions with no significant change are equally zeroed. Note that the activation centers ("+") were calculated using the raw coordinates of activation points weighted by the signal amplitude (distance between measurement positions >21 mm).

species was conducted using the between-sessions distances of the activation centers. It showed no significant effect of hemoglobin species on the activation center distances between sessions [$F(2,36)=0.24$, $p=0.79$], which indicates that the hemoglobin species does not affect spatial reproducibility.

3.3 *Reproducibility of Signal Amplitude*

The mean absolute values of $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$ in the activation periods were used as the signal amplitude for each hemoglobin species. Averaged across subjects, they were 0.095 ± 0.045 (mean±SD) mM mm for $\Delta C'_{oxy}$, 0.044 ± 0.018 mM mm for $\Delta C'_{deoxy}$, and 0.067 ± 0.031 mM mm for $\Delta C'_{total}$. We found a main effect of hemoglobin species on the signal amplitude [$F(2,78)=17.13$, $p<0.0001$] by one-way ANOVA. A *post hoc* test [Fisher's protected least-squares difference (PLSD)] revealed significant differences in every comparison (between $\Delta C'_{oxy}$ and $\Delta C'_{deoxy}$, $p<0.0001$; between $\Delta C'_{oxy}$ and $\Delta C'_{total}$, $p<0.005$; and between $\Delta C'_{deoxy}$ and $\Delta C'_{total}$, $p<0.05$).

Table 1 Mean distance of activation centers between two sessions.

	$\Delta C'_{oxy}$	$\Delta C'_{deoxy}$	$\Delta C'_{total}$
Mean distance±SD (mm)	16.0±12.1	18.6±12.0	16.0±9.1

SD is standard deviation.

The signal amplitudes of each hemoglobin species were compared between sessions for each subject (Fig. 5). The signal amplitude was variable within each subject, and no consistent tendency was found across subjects. A one-way ANOVA indicated no significant differences between the two sessions ($\Delta C'_{oxy}$: $F(1,26)=1.75$, $p=0.19$; $\Delta C'_{deoxy}$: $F(1,26)=1.04$, $p=0.32$; $\Delta C'_{total}$: $F(1,23)=0.15$, $p=0.90$), although the amplitude of the $\Delta C'_{oxy}$ signal tended to be slightly lower in the second session (Fig. 5). In percentage terms, the signal amplitudes varied: on average, $-18\pm31\%$ (mean±SD) for $\Delta C'_{oxy}$, $-1\pm60\%$ for $\Delta C'_{deoxy}$, and $9\pm45\%$ for $\Delta C'_{total}$.

3.4 *Reproducibility of Temporal Information*

We examined the reproducibility of temporal information by comparing the time courses for the three activation signals between the two sessions. As shown in Fig. 6, the time courses for each signal were similar for each subject, with a high correlation coefficient. The mean between-sessions correlation coefficients for the activation point with the maximum signal amplitude are listed in Table 2.

4 Discussion

4.1 *General Aspects of Reproducibility*

The three cases that did not show significant $\Delta C'_{total}$ activation in the second session could have been due to a slight difference in the ratio of $\Delta C'_{oxy}$ to $\Delta C'_{deoxy}$. The ratio of $\Delta C'_{oxy}$ to

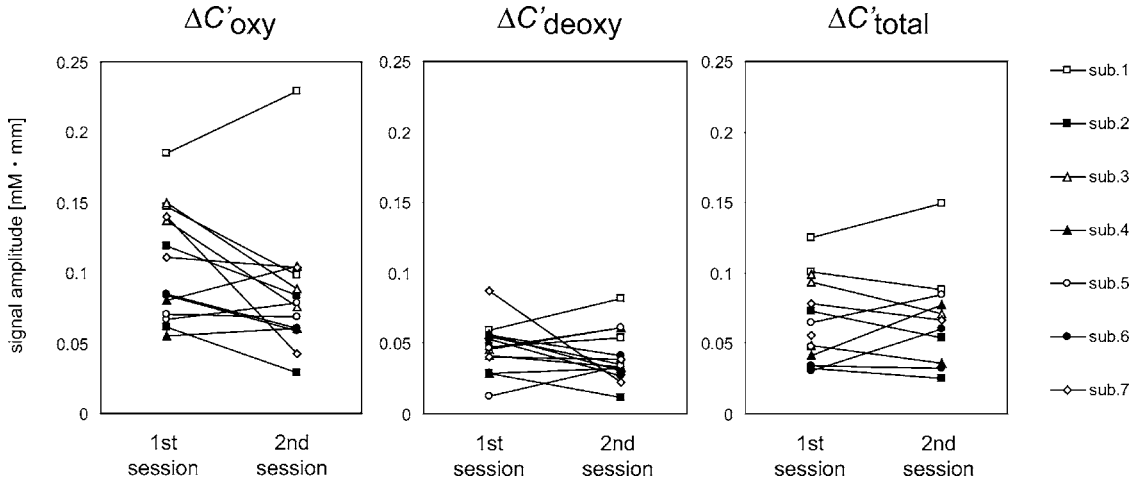

Fig. 5 Signal amplitudes of each hemoglobin signal ($\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$) for each subject in two sessions.

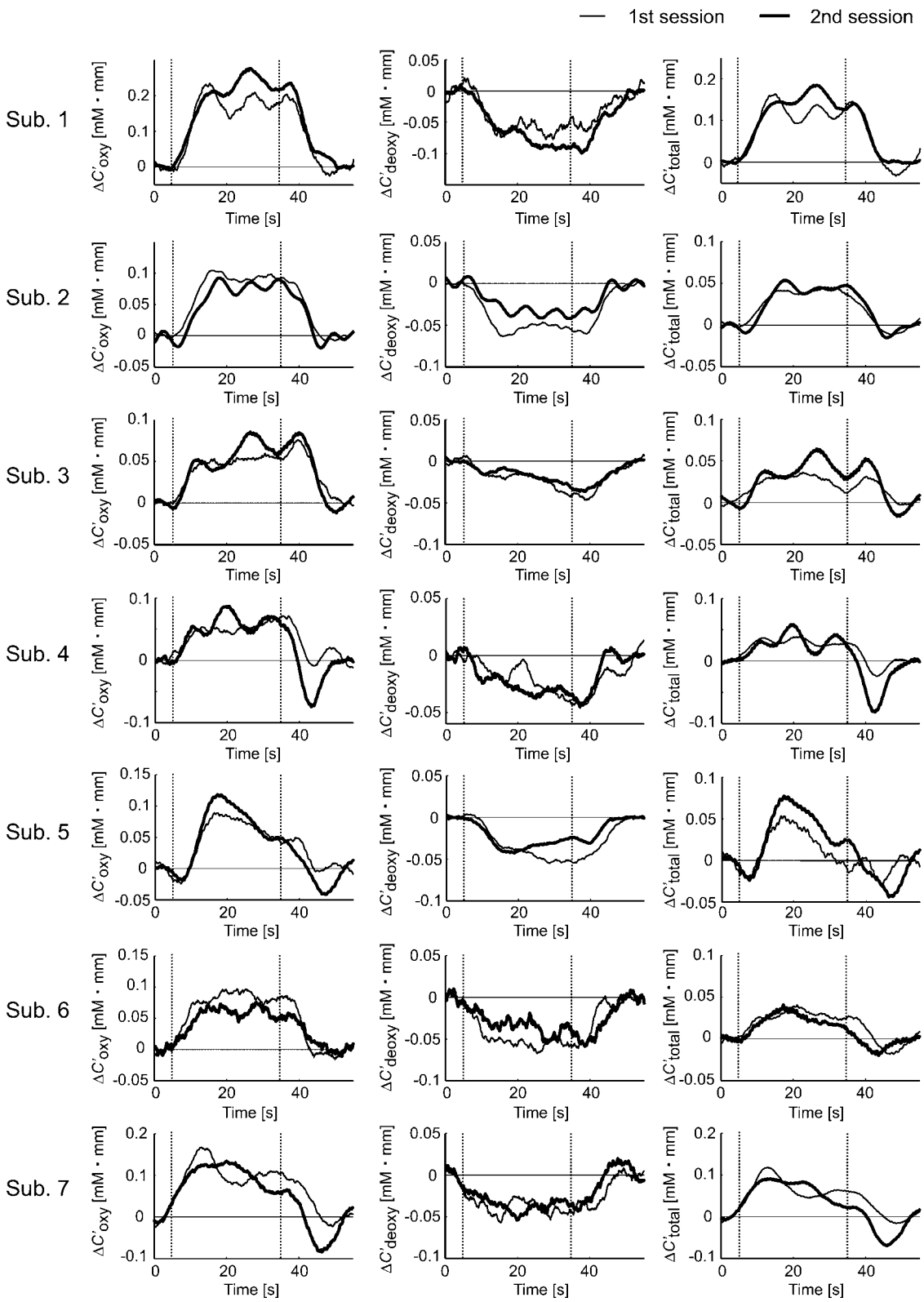

Fig. 6 Comparison of time courses in two sessions for either hemisphere of each subject. Time courses of $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$ are shown in left column, middle column, and right column, respectively. Measurement positions were 18 (first session)/18 (second session) (see Fig. 2) for subjects 1, 3, 6, and 7, and 19/19 for subject 2, in left-hand finger-tapping session. Measurement positions were 9/10 and 6/9 for subjects 4 and 5, respectively, in right-hand finger-tapping session. Correlation coefficients (Pearson's product-moment correlation coefficient) of time courses were as follows: 0.955 ($\Delta C'_{oxy}$), 0.911 ($\Delta C'_{deoxy}$), and 0.945 ($\Delta C'_{total}$) for subject 1; 0.975 ($\Delta C'_{oxy}$), 0.935 ($\Delta C'_{deoxy}$), and 0.966 ($\Delta C'_{total}$) for subject 2; 0.950 ($\Delta C'_{oxy}$), 0.956 ($\Delta C'_{deoxy}$), and 0.886 ($\Delta C'_{total}$) for subject 3; and 0.814 ($\Delta C'_{oxy}$), 0.740 ($\Delta C'_{deoxy}$), and 0.896 ($\Delta C'_{total}$) for subject 4; 0.939 ($\Delta C'_{oxy}$), 0.846 ($\Delta C'_{deoxy}$), and 0.880 ($\Delta C'_{total}$) for subject 5; 0.951 ($\Delta C'_{oxy}$), 0.785 ($\Delta C'_{deoxy}$), and 0.84 ($\Delta C'_{total}$) for subject 6; and 0.835 ($\Delta C'_{oxy}$), 0.812 ($\Delta C'_{deoxy}$), and 0.835 ($\Delta C'_{total}$) for subject 7.

Table 2 Mean correlation coefficients (Pearson's product-moment correlation coefficient) between time courses of two sessions.

	$\Delta C'_{oxy}$	$\Delta C'_{deoxy}$	$\Delta C'_{total}$
Mean correlation coefficient ±SD	0.877±0.135	0.843±0.074	0.844±0.125

$\Delta C'_{deoxy}$ was somewhat unstable between sessions even for the same subject, and this instability sometimes kept the rest-task differences from reaching the threshold of statistical significance. This result is consistent with our previous study[24] showing that, for measurements using 31 subjects, the probability of significant activation is less for $\Delta C'_{total}$ than for $\Delta C'_{oxy}$. These findings suggest that we must analyze the various relationships between $\Delta C'_{oxy}$ and $\Delta C'_{deoxy}$ before using $\Delta C'_{total}$ to evaluate the activation amplitudes.

4.2 *Reproducibility of Spatial Information*

Each subject showed similar activation-map spatial patterns between sessions. For each hemoglobin species, the activation center locations determined in the two experimental sessions were reproduced within 20 mm (Table 1), which is comparable to the minimum distance between measurement positions in NIR topography (21 mm). The high reproducibility of activation centers over time is consistent with the findings of a previous PET study[32] that showed consistent anatomical locations of motor activation after 6 months, and of an fMRI study[31] that also showed small distances between the activation centers determined in experimental sessions separated by 30, 49, and 60 days. Although these previous studies showed intersession gaps of millimeter order, their results are not comparable with our NIR topography results because of the difference in analytical methods and the spatial resolutions of those methods. For example, the previous fMRI study used $1.17 \times 1.17 \times 1$ mm voxels when identifying the coordinates of the maximum peak in the activation area as the activation center,[31] while the current NIR topography used measurement positions separated by 21 mm when identifying the activation center.

In addition, we should keep in mind that the spatial difference between sessions included unavoidable errors caused by the manual method for probe setting. The error in the manual setting was roughly estimated by 10-times repeated setting of the probe holder for one subject and marking of the measurement position each time. We found that the difference among the repeated settings was about 4.8±3.0 (mean±SD) mm. This small difference can result in a maximum shift of the activation center of 21 mm (the distance between measurement positions) depending on the relationship between the location of the activation area and the probe positions.[35,37] Consequently, we can say that the spatial reproducibility of the current NIR topography system is less than 20 mm after 6 months, including both physiological shifts and technical artifacts. A more accurate method to place the measurement probes, and a probe arrangement with higher density measurement positions[36,37] is necessary to distinguish the difference caused by a technical artifact from an actual physiological shift of the activation centers.

4.3 *Reproducibility of Signal Amplitude*

Our results showed that the mean $\Delta C'_{oxy}$ amplitude was approximately twice the mean $\Delta C'_{deoxy}$ amplitude, which is consistent with the results of our previous studies.[12,20]

The differences in the signal amplitudes between sessions within the same subject showed large variability (SD: 31, 60, and 45% for $\Delta C'_{oxy}$, $\Delta C'_{deoxy}$, and $\Delta C'_{total}$, respectively). In addition, we did not find significant consistency in the difference in signal amplitudes between the two sessions, indicating that habituation has little effect on tasks repeated after 6 months. These results suggest variability of the signal amplitude in the NIR topography measurement.

The variability could reflect physiological phenomena and/or technical artifacts. One possible physiological phenomenon is the effect of the baseline differences. The existence of spontaneous oscillation in the hemoglobin oxygenation state has been shown by NIRS studies of adults[42] and infants,[19] and a difference in the baseline state could affect the activation amplitude, as suggested in previous fMRI and PET studies.[43,44]

Technical artifacts may result from small differences in measurement positions. As already described, the measurement position can vary about 4.8 mm on average due to manual setting. The difference in measurement positions could affect the signal amplitude, since the current method has uneven spatial sensitivity due to the relationship between the activation area (location and size) and the probe positions.[37] Although the tendency of a lower $\Delta C'_{oxy}$ in the second session might indicate a habituation effect similar to the one shown in a previous fMRI study,[31] where habituation effects for sensorimotor activation were observed between two sessions separated by 5 h and by 1 or 2 months, it would be difficult to estimate the activation level by using the signal amplitude in current NIRS systems.

4.4 *Reproducibility of Temporal Information*

We found high correlation coefficients for the time courses in repeated sessions for the same subject (Fig. 6). Although we know of no other NIRS studies reporting such a similar time course reproduced after more than a few days, our findings could be important with regard to the development of new NIRS applications in the clinical area. The qualitative characteristics of the subject might be more clearly inferred from temporal information, such as the time course of the activation, than from spatial information and amplitude information, which vary with the experimental conditions. A recent study used the characteristics of the NIRS time course ($\Delta C'_{oxy}$) to assess patients exhibiting depression and schizophrenia.[22] Moreover, examining the shape of the time course in the same subject can be used to evaluate the subject's state, which

would help in longitudinal studies as well as in monitoring rehabilitation effects.

5 Conclusion

We used NIR topography to evaluate the within-subject reproducibility of sensorimotor-activation NIRS signals in healthy adults who were retested 6 months after their first session. For all subjects, the activations of positive $\Delta C'_{\text{oxy}}$ and negative $\Delta C'_{\text{deoxy}}$ were reproduced in the hemisphere contralateral to the tapping hand, but positive $\Delta C'_{\text{total}}$ was less reproducible and did not reach the statistical threshold that depended on the proportion of $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$. This suggests the necessity to examine the relationship between $\Delta C'_{\text{oxy}}$ and $\Delta C'_{\text{deoxy}}$ before using $\Delta C'_{\text{total}}$ as the activation index.

The activation center was reproduced within 20 mm on average across subjects, suggesting fair reproducibility comparable to the minimum distance between measurement positions (21 mm) in NIR topography. The location of an activation center, however, can shift depending on the activation area and probe locations. We thus must improve the accuracy of the method used to place the measurement probes and to develop a probe arrangement with higher density measurement positions so that we can distinguish the difference caused by technical artifacts from the actual physiological change of the activation area.

The signal amplitudes varied within subjects between sessions even though no consistent tendency in the changes was found. This was possibly due to physiological conditions and/or technical artifacts. A difference in the resting state due to oscillation might be one of the reasons for a physiological condition, and the small between-session differences in measurement positions could be due to the same technical artifact shifting the activation locations.

Finally, the signal time courses between sessions for each subject showed high correlation, which is our most significant finding. This time-course temporal information is particularly useful for examining the qualitative characteristics both within and across subjects and should enable the expansion of NIRS applications.

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References

1. A. Villringer, J. Planck, C. Hock, L. Schleinkofer, and U. Dirnagl, "Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults," *Neurosci. Lett.* **154**(1–2), 101–104 (1993).
2. T. Kato, A. Kamei, S. Takashima, and T. Ozaki, "Human visual cortical function during photic stimulation monitoring by means of near-infrared spectroscopy," *J. Cereb. Blood Flow Metab.* **13**(3), 516–520 (1993).
3. Y. Hoshi and M. Tamura, "Detection of dynamic changes in cerebral oxygenation coupled to neuronal function during mental work in man," *Neurosci. Lett.* **150**(1), 5–8 (1993).
4. B. Chance, Z. Zhuang, C. UnAh, C. Alter, and L. Lipton, "Cognition-activated low-frequency modulation of light absorption in human brain," *Proc. Natl. Acad. Sci. U.S.A.* **90**(8), 3770–3774 (1993).
5. J. S. Wyatt, M. Cope, D. T. Delpy, C. E. Richardson, A. D. Edwards, S. Wray, and E. O. Reynolds, "Quantitation of cerebral blood volume in human infants by near-infrared spectroscopy," *J. Appl. Physiol.* **68**(3), 1086–1091 (1990).
6. D. T. Delpy, S. R. Arridge, M. Cope, D. Edwards, E. O. Reynolds, C. E. Richardson, S. Wray, J. Wyatt, and P. van der Zee, "Quantitation of pathlength in optical spectroscopy," *Adv. Exp. Med. Biol.* **248**, 41–46 (1989).
7. D. T. Delpy, M. Cope, P. van der Zee, S. Arridge, S. Wray, and J. Wyatt, "Estimation of optical pathlength through tissue from direct time of flight measurement," *Phys. Med. Biol.* **33**(12), 1433–1442 (1988).
8. E. Okada and D. T. Delpy, "Near-infrared light propagation in an adult head model. II. Effect of superficial tissue thickness on the sensitivity of the near-infrared spectroscopy signal," *Appl. Opt.* **42**(16), 2915–2922 (2003).
9. H. Koizumi, Y. Yamashita, A. Maki, T. Yamamoto, Y. Ito, H. Itagaki, and R. P. Kennan, "Higher-order brain function analysis by transcranial dynamic near-infrared spectroscopy imaging," *J. Biomed. Opt.* **4**(4), 403–413 (1999).
10. Y. Yamashita, A. Maki, Y. Ito, E. Watanabe, H. Mayanagi, and H. Koizumi, "Noninvasive near-infrared topography of human brain activity using intensity modulation spectroscopy," *Opt. Eng.* **35**, 1046–1099 (1996).
11. A. Maki, Y. Yamashita, E. Watanabe, and H. Koizumi, "Visualizing human motor activity by using non-invasive optical topography," *Front Med. Biol. Eng.* **7**(4), 285–297 (1996).
12. A. Maki, Y. Yamashita, Y. Ito, E. Watanabe, Y. Mayanagi, and H. Koizumi, "Spatial and temporal analysis of human motor activity using noninvasive NIR topography," *Med. Phys.* **22**(12), 1997–2005 (1995).
13. G. Taga, K. Asakawa, A. Maki, Y. Konishi, and H. Koizumi, "Brain imaging in awake infants by near-infrared optical topography," *Proc. Natl. Acad. Sci. U.S.A.* **100**(19), 10722–10727 (2003).
14. M. Pena, A. Maki, D. Kovacic, G. Dehaene-Lambertz, H. Koizumi, F. Bouquet, and J. Mehler, "Sounds and silence: an optical topography study of language recognition at birth," *Proc. Natl. Acad. Sci. U.S.A.* **100**(20), 11702–11705 (2003).
15. A. Obata, K. Morimoto, H. Sato, A. Maki, and H. Koizumi, "Acute effects of alcohol on hemodynamic changes during visual stimulation assessed using 24-channel near-infrared spectroscopy," *Psychiatry Res.* **123**(2), 145–152 (2003).
16. Y. Noguchi, T. Takeuchi, and K. L. Sakai, "Lateralized activation in the inferior frontal cortex during syntactic processing: event-related optical topography study," *Hum. Brain Mapp* **17**(2), 89–99 (2002).
17. Y. Minagawa-Kawai, K. Mori, I. Furuya, R. Hayashi, and Y. Sato, "Assessing cerebral representations of short and long vowel categories by NIRS," *NeuroReport* **13**(5), 581–584 (2002).
18. E. Watanabe, A. Maki, F. Kawaguchi, Y. Yamashita, H. Koizumi, and Y. Mayanagi, "Noninvasive cerebral blood volume measurement during seizures using multichannel near infrared spectroscopic topography," *J. Biomed. Opt.* **5**(3), 287–290 (2000).
19. G. Taga, Y. Konishi, A. Maki, T. Tachibana, M. Fujiwara, and H. Koizumi, "Spontaneous oscillation of oxy- and deoxy-hemoglobin changes with a phase difference throughout the occipital cortex of newborn infants observed using non-invasive optical topography," *Neurosci. Lett.* **282**(1–2), 101–104 (2000).
20. H. Sato, T. Takeuchi, and K. L. Sakai, "Temporal cortex activation during speech recognition: an optical topography study," *Cognition* **73**(3), B55–66 (1999).
21. E. Watanabe, A. Maki, F. Kawaguchi, K. Takashiro, Y. Yamashita, H. Koizumi, and Y. Mayanagi, "Non-invasive assessment of language dominance with near-infrared spectroscopic mapping," *Neurosci. Lett.* **256**(1), 49–52 (1998).
22. T. Suto, M. Fukuda, M. Ito, T. Uehara, and M. Mikuni, "Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study," *Biol. Psychiatry* **55**(5), 501–511 (2004).
23. S. Tsujimoto, T. Yamamoto, H. Kawaguchi, H. Koizumi, and T. Sawaguchi, "Prefrontal cortical activation associated with working memory in adults and preschool children: an event-related optical topography study," *Cereb. Cortex* **14**(7), 703–712 (2004).
24. H. Sato, Y. Fuchino, M. Kiguchi, T. Katura, A. Maki, T. Yoro, and H. Koizumi, "Intersubject variability of near-infrared spectroscopy signals during sensorimotor cortex activation," *J. Biomed. Opt.* **10**,

044001 (2005).
25. S. T. Grafton, R. P. Woods, J. C. Mazziotta, and M. E. Phelps, "Somatotopic mapping of the primary motor cortex in humans: activation studies with cerebral blood flow and positron emission tomography," *J. Neurophysiol.* **66**(3), 735–743 (1991).
26. P. E. Roland, B. Larsen, N. A. Lassen, and E. Skinhoj, "Supplementary motor area and other cortical areas in organization of voluntary movements in man," *J. Neurophysiol.* **43**(1), 118–136 (1980).
27. S. G. Kim, J. Ashe, A. P. Georgopoulos, H. Merkle, J. M. Ellermann, R. S. Menon, S. Ogawa, and K. Ugurbil, "Functional imaging of human motor cortex at high magnetic field," *J. Neurophysiol.* **69**(1), 297–302 (1993).
28. S. M. Rao, J. R. Binder, P. A. Bandettini, T. A. Hammeke, F. Z. Yetkin, A. Jesmanowicz, L. M. Lisk, G. L. Morris, W. M. Mueller, and L. D. Estkowski, "Functional magnetic resonance imaging of complex human movements," *Neurology* **43**(11), 2311–2318 (1993).
29. H. Obrig, C. Hirth, J. G. Junge-Hulsing, C. Doge, T. Wolf, U. Dirnagl, and A. Villringer, "Cerebral oxygenation changes in response to motor stimulation," *J. Appl. Physiol.* **81**(3), 1174–1183 (1996).
30. M. A. Franceschini, S. Fantini, J. H. Thompson, J. P. Culver, and D. A. Boas, "Hemodynamic evoked response of the sensorimotor cortex measured noninvasively with near-infrared optical imaging," *Psychophysiology* **40**(4), 548–560 (2003).
31. I. Loubinoux, C. Carel, F. Alary, K. Boulanouar, G. Viallard, C. Manelfe, O. Rascol, P. Celsis, and F. Chollet, "Within-session and between-session reproducibility of cerebral sensorimotor activation: a test–retest effect evidenced with functional magnetic resonance imaging," *J. Cereb. Blood Flow Metab.* **21**(5), 592–607 (2001).
32. L. M. Carey, D. F. Abbott, G. F. Egan, H. J. Tochon-Danguy, and G. A. Donnan, "The functional neuroanatomy and long-term reproducibility of brain activation associated with a simple finger tapping task in older healthy volunteers: a serial PET study," *Neuroimage* **11**(2), 124–144 (2000).
33. C. Carel, I. Loubinoux, K. Boulanouar, C. Manelfe, O. Rascol, P. Celsis, and F. Chollet, "Neural substrate for the effects of passive training on sensorimotor cortical representation: a study with functional magnetic resonance imaging in healthy subjects," *J. Cereb. Blood Flow Metab.* **20**(3), 478–484 (2000).
34. H. Sato, M. Kiguchi, Y. Fuchino, T. Katsura, A. Maki, T. Yoro, and H. Koizumi, "Reproducibility of NIRS signal in sensorimotor cortex activation after six months," paper presented at the Society for Neuroscience, Washington, DC (2004).
35. T. Yamamoto, A. Maki, Y. Yamashita, Y. Tanikawa, Y. Yamada, and H. Koizumi "Noninvasive brain function measurement system: optical topography," *Proc. SPIE* **4250**, 339–350 (2001).
36. T. Yamamoto, A. Maki, T. Kadoya, Y. Tanikawa, Y. Yamada, E. Okada, and H. Koizumi, "Arranging optical fibres for the spatial resolution improvement of topographical images," *Phys. Med. Biol.* **47**(18), 3429–3440 (2002).
37. T. Yamamoto, E. Okada, F. Kawaguchi, A. Maki, Y. Yamada, and H. Koizumi, "Optical fiber arrangement of optical topography for spatial resolution improvement," *Proc. SPIE* **4955**, 487–496 (2003).
38. G. H. Klem, H. O. Luders, H. H. Jasper, and C. Elger, "The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology," *Electroencephalogr Clin. Neurophysiol. Suppl.* **52**, 3–6 (1999).
39. M. Okamoto, H. Dan, K. Sakamoto, K. Takeo, K. Shimizu, S. Kohno, I. Oda, S. Isobe, T. Suzuki, K. Kohyama, and I. Dan, "Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping," *Neuroimage* **21**(1), 99–111 (2004).
40. H. Steinmetz, G. Furst, and B. U. Meyer, "Craniocerebral topography within the international 10–20 system," *Electroencephalogr. Clin. Neurophysiol.* **72**(6), 499–506 (1989).
41. V. L. Towle, J. Bolanos, D. Suarez, K. Tan, R. Grzeszczuk, D. N. Levin, R. Cakmur, S. A. Frank, and J. P. Spire, "The spatial location of EEG electrodes: locating the best-fitting sphere relative to cortical anatomy," *Electroencephalogr. Clin. Neurophysiol.* **86**(1), 1–6 (1993).
42. H. Obrig, M. Neufang, R. Wenzel, M. Kohl, J. Steinbrink, K. Einhaupl, and A. Villringer, "Spontaneous low frequency oscillations of cerebral hemodynamics and metabolism in human adults," *Neuroimage* **12**(6), 623–639 (2000).
43. M. E. Raichle, A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman, "A default mode of brain function," *Proc. Natl. Acad. Sci. U.S.A.* **98**(2), 676–682 (2001).
44. C. E. Stark and L. R. Squire, "When zero is not zero: the problem of ambiguous baseline conditions in fMRI," *Proc. Natl. Acad. Sci. U.S.A.* **98**(22), 12760–12766 (2001).