Journal of Biomedical Optics

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Abstract. The reduction of trial-to-trial variability (TTV) in task-evoked functional near-infrared spectroscopy signals by considering the correlated low-frequency spontaneous fluctuations that account for the resting-state functional connectivity in the brain is investigated. A resting-state session followed by a task-state session of a right hand finger-tapping task has been performed on five subjects. Significant ipsilateral and bilateral resting-state functional connectivity has been detected at the subjects' motor cortex using the seed correlation method. The correlation coefficients obtained during the resting-state are used to reduce the TTV in the signals measured during the task sessions. The results suggest that correlated spontaneous low-frequency fluctuations contribute significantly to the TTV in the task evoked fNIRS signals. [DOI: 10.1117/1.JBO.18.1.017003]

Keywords: functional near-infrared spectroscopy; correlated spontaneous low-frequency hemodynamic fluctuations; resting-state functional connectivity; trial-to-trial variation.

Paper 12309 received May 17, 2012; revised manuscript received Nov. 6, 2012; accepted for publication Dec. 3, 2012; published online Jan. 4, 2013.

1 Introduction

Functional near-infrared spectroscopy (fNIRS) is an emerging optical brain imaging technique.[1] fNIRS measures the hemodynamic changes that effectively reflect brain activities occurring while people perform a wide range of mental tasks.[2–8] It can provide both topographic[4,7–10] and tomographic[6,11] brain images. Specifically, fNIRS monitors regional cerebral blood flow (rCBF) variations by measuring, through the skull, the absorption changes of near-infrared light at wavelengths between 700 and 1000 nm.[12] These changes are caused by the concentration variations of oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR), two primary absorbing chromophores in brain capillary blood.

fNIRS, compared with other prevalent brain imaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), offers a good trade-off between spatial and temporal resolutions. The utility and drawbacks of fNIRS compared with other neuroimaging methods were discussed and analyzed by Perrey.[13] Another comprehensive review[14] of the respective features of fNIRS and fMRI concluded that fNIRS has great potential for neurological and psychiatric applications due to its simplicity, portability, and insensitivity to motion artifacts. The EEG technique, meanwhile, is limited due to its poor spatial resolution and low signal-to-noise ratio (SNR) in many applications.[15,16] Overall, fNIRS provides comparatively better image quality.[17] In fact, fNIRS is being utilized by an increasing number of researchers for mental states decoding[18] and in brain-computer interface (BCI) development.[19]

The hemodynamic response is the collective expression of blood flow, volume, and oxygenation changes that accompany a neuronal activation in the brain. It forms the basis of several kinds of non-invasive brain imaging techniques including fMRI and fNIRS. It exhibits trial-to-trial variability (TTV), even when experimental tasks or stimuli are constant. Moreover, most previous fNIRS studies have paid insufficient attention to the TTV in the fNIRS signal, treating it implicitly as random noise. Understanding the TTV is crucial to obtaining better performance in fNIRS-based BCI and brain imaging applications. Although the sources of this variability remain poorly understood, two distinct candidates have been discussed.[20,21] The first plausible source is neuronal response differences (e.g., structural differences); the second is different states of the subject including subject variability (e.g., task involvement, experimental experience, different measurement time) and physiological noises.

Several previous studies have investigated the TTVs in both blood oxygen level dependent (BOLD) and fNIRS signals. Aguirre et al.[20] were the first to investigate the TTV in the BOLD signal. Using fMRI scanning with an event-related simple reaction-time task, they examined the TTV in the hemodynamic responses detected from the central sulcus. They concluded that subject differences and scanning time (within a day or on different days) had contributed to variations. Fox et al.[22,23] later suggested that the TTV in the event that evoked BOLD signal can be attributed largely to correlated low-frequency spontaneous fluctuation. More recently, Holper et al.[21] investigated the TTV in fNIRS signals measured in a virtual-reality

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0091-3286/2013/$25.00 © 2013 SPIE

grasping experiment involving 17 subjects. They found that the differences in signal amplitude and sign in different subjects contributed to the TTV in the fNIRS signals. Moreover, the TTV itself also was sensitive to the task modality.

Spontaneous low-frequency hemodynamic fluctuations in distant regions in a human brain exhibit some correlation even in the absence of tasks or stimuli.[24,25] This phenomenon (easily observable by fMRI) is often termed the resting-state functional connectivity (RSFC). Moreover, such correlation exists also under task conditions. The RSFC is believed to reflect neural interactions among distant brain regions, thereby providing information on the default brain network. The RSFC has thus become a powerful measure for the study of brain integration, brain working network, and brain diseases. Notably, researchers recently have reported that the RSFC can be detected using fNIRS:[26,27] its validity, further, has been confirmed.[28]

In the present study, we first investigate the TTV in relation to spontaneous fluctuations in the fNIRS signal in the resting state. Referencing the correlated spontaneous fluctuation detected in the right motor cortex, we reduce the TTV in the fNIRS signal detected in the left motor cortex during the task period.

2 Materials and Methods

2.1 *Data Acquisition*

The data were acquired with a continuous-wave NIRS imaging system (DYNOT: DYnamic Near-infrared Optical Tomography; NIRx Medical Technologies, Brooklyn, New York) at a sampling rate of 1.8 Hz. The NIRS system emits laser light at different wavelengths (760 and 830 nm) from each source. Figure 1 shows the channel distribution and measurement locations. The distance between adjacent optodes is 2 cm. The source-detector pairs are positioned above the entire motor cortex (the Cz position, according to the International 10/20 system, was used as a reference).

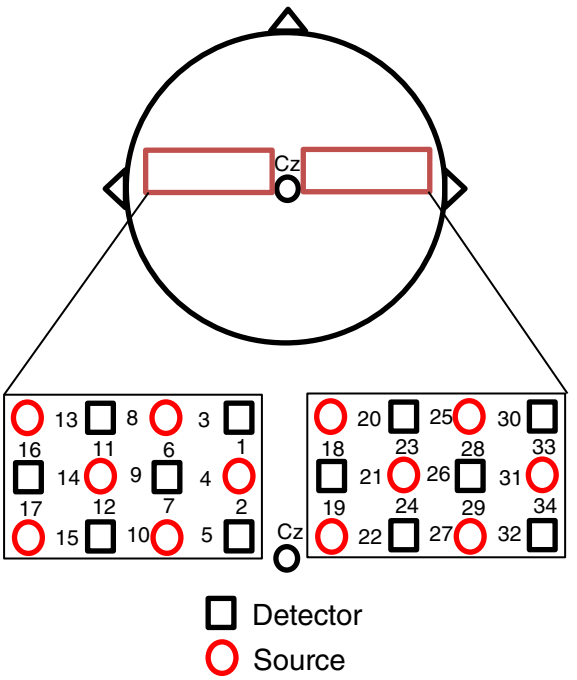

Fig. 1 Channel distribution and measurement locations on the head.

Five right-handed volunteers (all males, aged 24 to 31 years) participated in this experiment. None of the participants had a history of any neurological disorder. All of them provided written informed consent. In the experiment, the subjects were asked to complete two sessions. The first was a 480 s resting-state session, and the second, a 328 sec, right-hand finger-tapping session. There was a short break (20 s) between the two sessions. During Session 1, the subjects were asked to sit comfortably and remain motionless as much as possible. Session 2 consisted of seven task blocks and seven rest blocks. The length of a task block was 24 s, and the length of a rest block was 20 s.

2.2 *Data Analysis*

The entire data processing has been completed using Matlab 9.0 (Mathworks). We first applied a band-pass filter (0.01 to 0.08 Hz, Butterworth) to remove the long-term drift of the baseline as well as the physiological noises including cardiac and respiratory activities to the data measured during Sessions 1 and 2. The conventional seed correlation method[26,27] was then used to draw an RSFC map for each subject. Briefly, the data from Session 2 was processed using the conventional general linear model (GLM),[29] with the assumed gamma-type hemodynamic response function,[30] to identify the right-hand finger tapping task evoked brain activation map (t-map) as well as a seed region (covered by one channel) with the highest t-value on the map for each subject. Next, we calculated the correlation coefficients between the seed region and all the other non-seed regions to draw individual-level correlation maps showing the intra-hemisphere and inter-hemisphere correlation using the data measured during Session 1.

For each subject, the seed-pair region was identified as a non-seed region on the right hemisphere showing the highest correlation with the seed region according to the correlation maps. The regression coefficient β between the signal measured from the seed region on the left hemisphere and the seed-pair region on the right hemisphere was computed using the resting state time series. The β value was then used to generate the seed region time series with the scaled seed-pair region time series subtracted $f_L(t) - \beta \cdot f_R(t)$ with the data from Session 1. The seed region time series $f_L(t)$ and $f_L(t) - \beta \cdot f_R(t)$ were converted to a percentage change from an average baseline which was computed as the average of the first and last data points of all of the extracted time courses. Finally, the averaged hemodynamic response for task trials before and after scaled seed-pair region time series subtraction was calculated separately for both HbO and HbR signals. The averaged hemodynamic response for rest trials were also calculated as a reference of brain activation.

To quantify the effect of regressing out the spontaneous fluctuations measured at the seed-pair region from the task-evoked hemodynamic responses (HbO and HbR) measured for the seed region, we computed and compared the SNR for the seed region time series as well as the seed region time series with the seed-pair region time series subtracted. The signal power was computed as the mean squared deviation from the baseline of the average response across all the finger-tapping sessions. The noise power was computed as the mean squared deviation of the residual. Additionally, we compared the seed region t-values estimated by the GLM before and after the correlated spontaneous fluctuation subtraction to investigate the reduction of TTV.

3 Results

3.1 *Resting-State Functional Connectivity*

Figure 2 shows the individual-level right-hand finger tapping task evoked activation maps of the bilateral motor cortex. The HbO activation maps are on the left while the HbR activation maps are on the right. The *t*-threshold was 5. The right-hand finger tapping task evoked activation areas are generally consistent, and located on the left hemisphere, including the regions covered by Channels 1, 2, 9, 11, and 12. The right hemisphere activation maps are not consistent among different subjects, and the *t*-values are generally lower than the threshold.

Figure 3 plots two representative low-frequency spontaneous fluctuations from Subject 1 during the resting session. Figure 3(a) indicates the correlated spontaneous fluctuations from the measurement channels covering the homologous regions in the bilateral motor regions, and Fig. 3(b) shows the uncorrelated spontaneous fluctuations measured from those bilateral motor cortices.

Figure 4 provides the individual-level RSFC maps (correlation maps) for the seed regions: the left two columns and right two columns show correlation maps for the spontaneous HbO and HbR fluctuations, respectively. The regions that have a significant correlation with the left seed region are shown in red. The correlation threshold was set to 0.7. All of the subjects' RSFC maps generally showed a similar pattern. Significant correlations were found within and between the left and right hemispheres, respectively. The strongest correlations appeared mainly at Channels 1, 2, 9, 11, 12, 16, and 17 (Channels 16 and 17 for only 3 subjects) covering the left motor region, and at Channels 19, 21, 26, and 34 covering the right motor region. Moreover, the correlations within the ipsilateral motor regions were stronger than those between the bilateral motor regions.

3.2 *Reduction of TTV in Task Session*

The seed channels and seed-pair channels for different subjects (seed channel—seed pair channel) are: Subject 1, Channel 9–34 for HbO and HbR; Subject 2, Channel 9–34 for HbO and HbR; Subject 3, Channel 9–26 for HbO and HbR; Subject 4, Channel 9–26 for HbO and Channel 12–26 for HbR; Subject 5, Channel 9–34 for HbO and HbR.

Figures 5 and 6, respectively, show the individual-level averaged HbO and HbR responses (7 trials for each subject) during the rest and task trials, and the reduction of the TTV before and after subtraction of the correlated spontaneous fluctuation from the opposite hemisphere. The standard deviation indicating the TTV generally reduced after subtraction of the correlated spontaneous fluctuation from the seed-pair region for both HbO and HbR signals. Table 1 shows the intra-subject and inter-subject SNR of the signals measured during the finger-tapping trials before and after TTV reduction. The intra-subject SNR for both HbO and HbR signals generally increased (HbO: 9% to 275% and HbR: 8% to 84%) after removing the effect of spontaneous fluctuation, while the inter-subject SNR increased 102% for HbO signal and 44% for HbR signal.

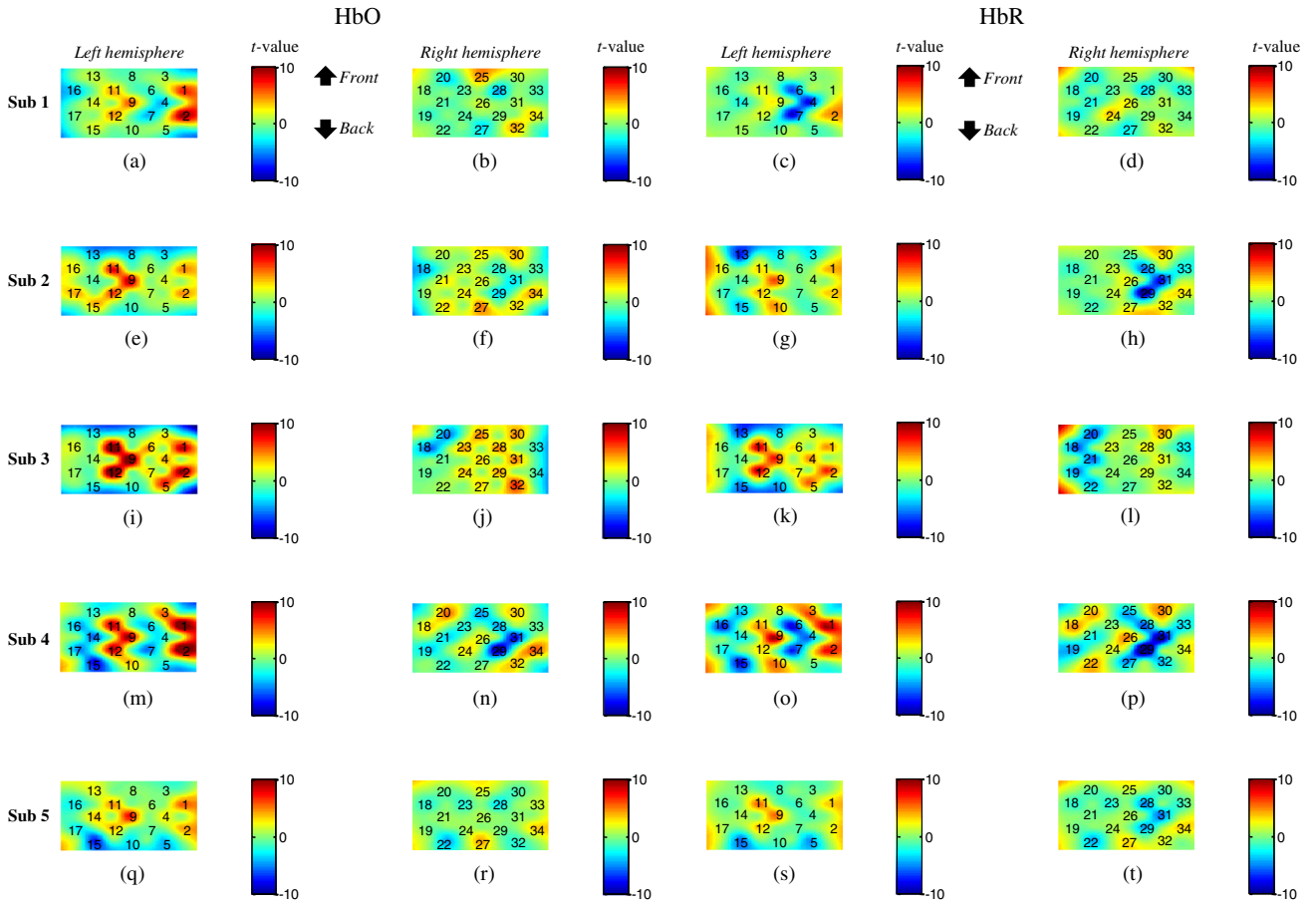

Fig. 2 Brain activation maps of the right-hand finger tapping task: HbO and HbR signals.

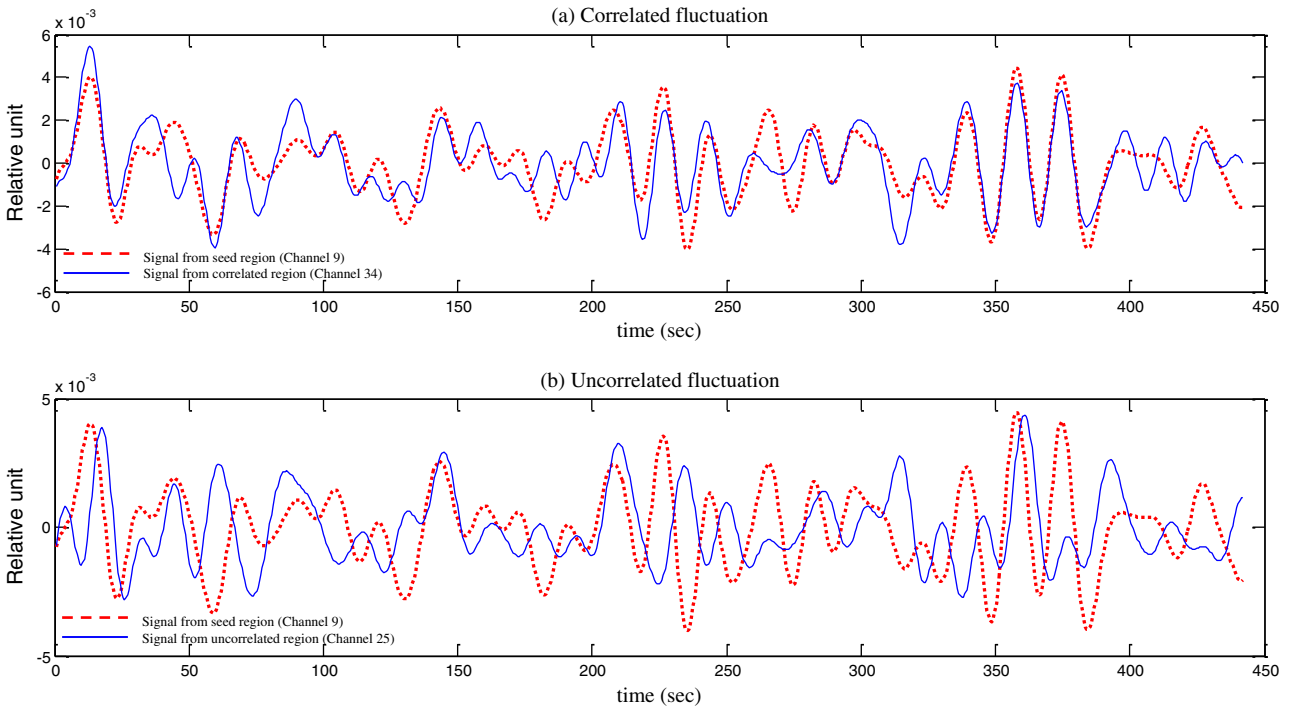

Fig. 3 Spontaneous low-frequency fluctuations from bilateral motor regions: (a) correlated versus (b) uncorrelated.

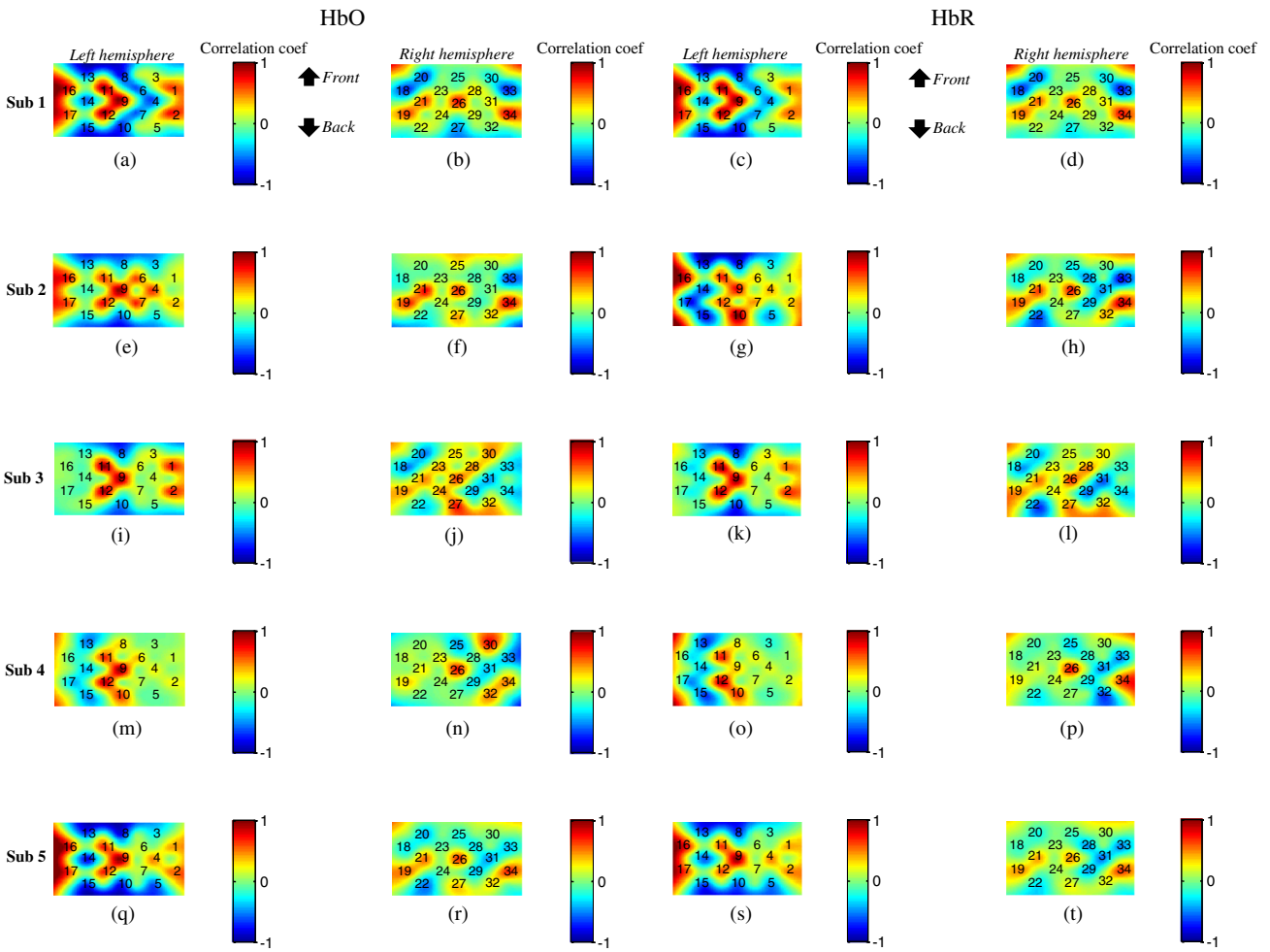

Fig. 4 Individual-level RSFC maps (correlation maps) for HbO and HbR signals.

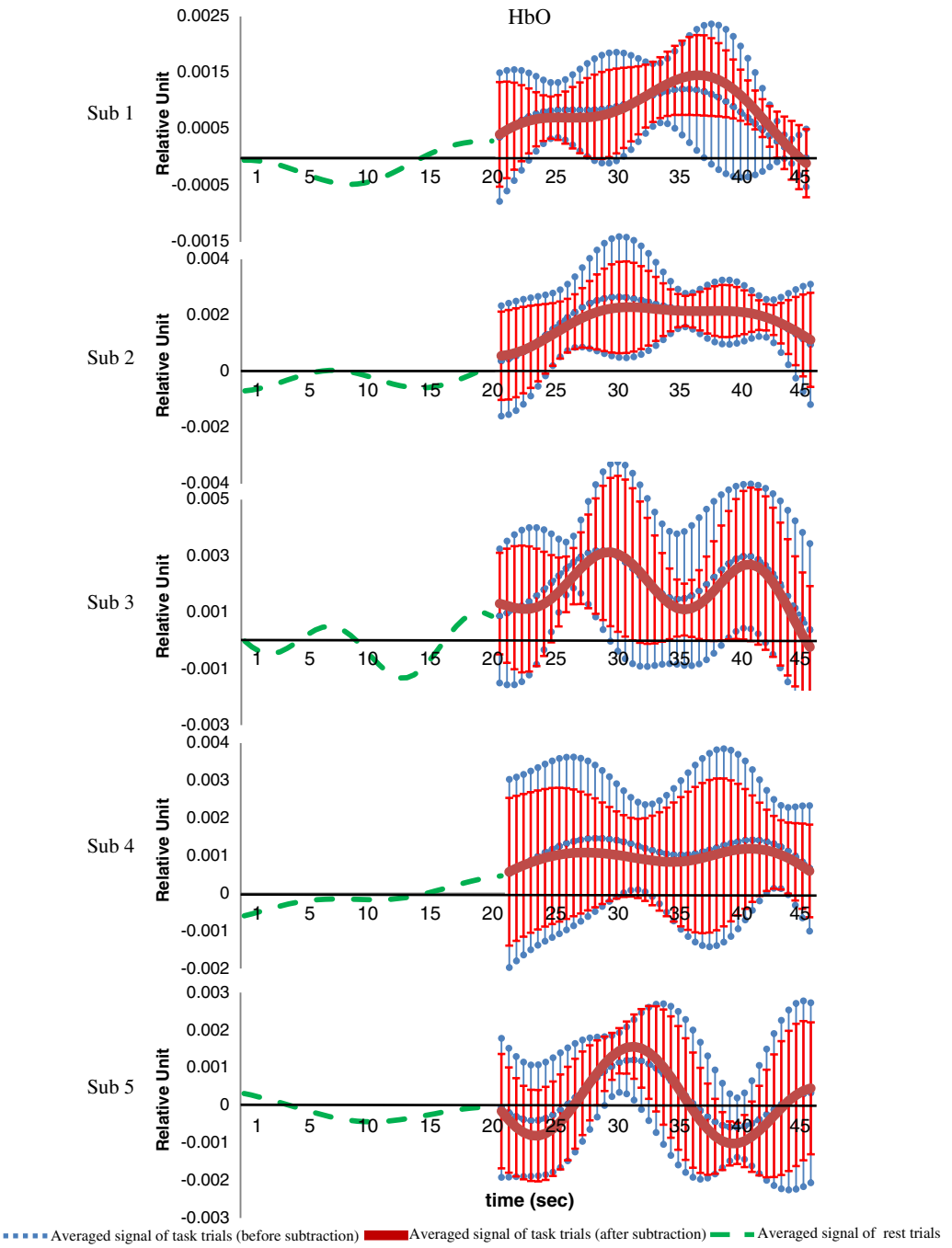

Fig. 5 Averaged HbO responses of rest and task trials: comparison of TTVs (standard deviation) before and after subtraction of correlated spontaneous fluctuation from the opposite hemisphere.

Table 2 compares the *t*-values of the seed channel estimated by the GLM before and after TTV reduction. The *t*-values for both HbO and HbR signals generally increased after TTV reduction.

4 Discussion

TTV is an important issue in brain imaging and BCI applications. Researchers have investigated various causes of TTV, including subject state as well as task modality in the BOLD and fNIRS signals.[21–23] In the present study, we investigated the relationship between the TTV and correlated low-frequency spontaneous fluctuations in the fNIRS signal. There were three noteworthy findings in the current experiment. First, the correlated low-frequency spontaneous fluctuation is a significant TTV source in fNIRS signals. Second, the TTV decreases after removing the effect of bilateral connectivity. Finally, we could replicate the meaningful RSFC revealed in the previous fNIRS studies.[26–28,31]

TTV exists in the fNIRS signal under constant task conditions. However, the sources of the TTV remained elusive. We found that after the subtraction of scaled correlated spontaneous fluctuation from the opposite hemisphere, the TTV between the task-evoked fNIRS trials was reduced, thus the SNR increased. These results suggest that spontaneous fluctuation accounts for

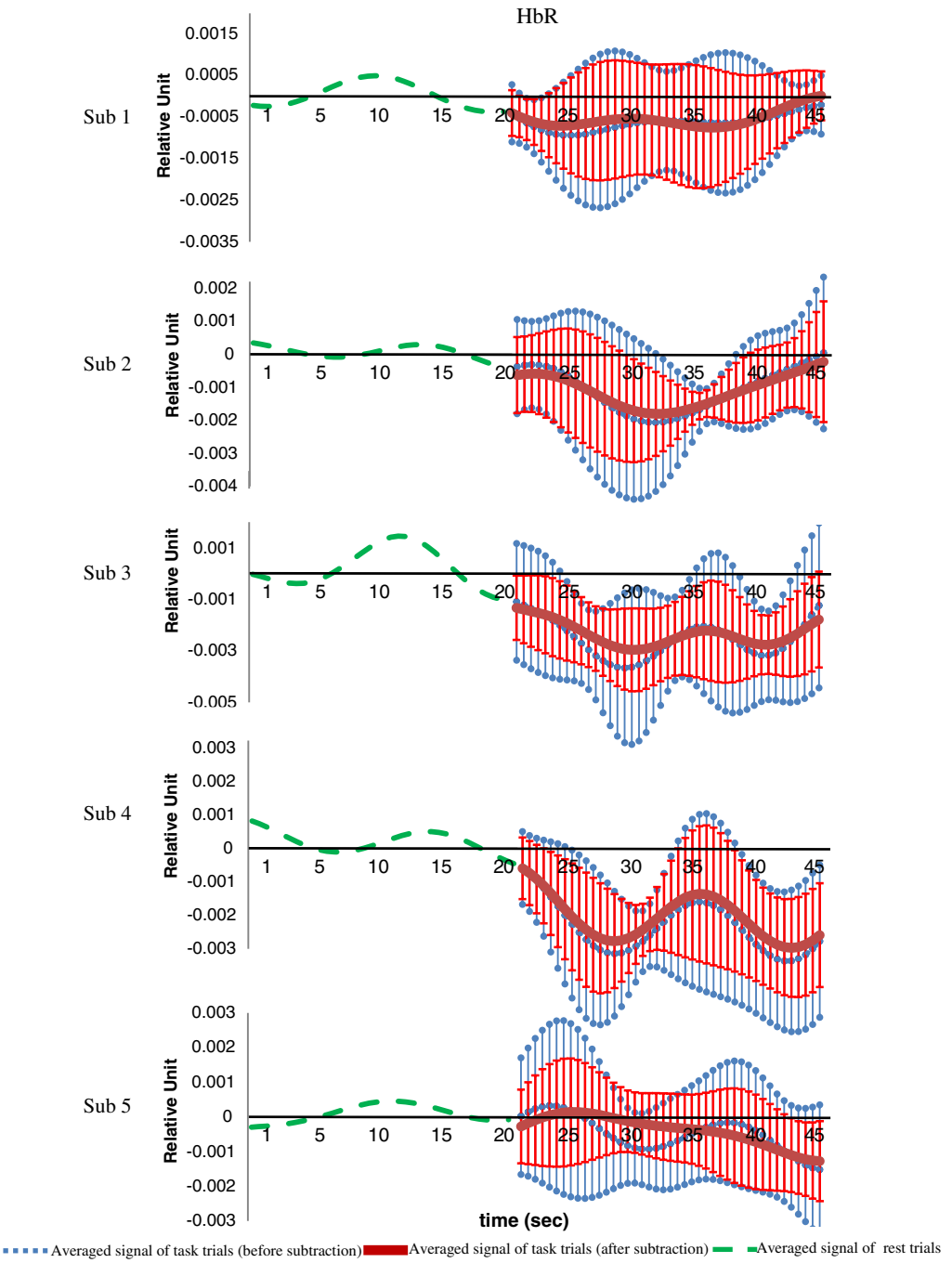

Fig. 6 Averaged HbR responses of rest and task trials: reduction of TTV is quite noticeable.

the TTV in the fNIRS signal. Holper et al.[21] considered subject performance states (i.e., higher or lower responses) as a source of TTV in the fNIRS signal. Further, they found that another source of TTV in the fNIRS signal is task modality (i.e., motor execution task and motor imagery during observation task). We assumed the spontaneous fluctuation as a part of the intrinsic subject state, because the spontaneous fluctuation patterns vary across subjects and experimental times. Among our findings, the TTV in the fNIRS signal measured from each subject was reduced by using his own spontaneous fluctuation. These results, moreover, are similar to those for fMRI signal reported by Fox et al.[22,23] Specifically, they found that the TTV could be explained by spontaneous fluctuation in the BOLD signal.

In our study, we investigated the SNR, signal power, and noise power (indicating TTV) at individual levels as well as group levels. As Table 1 shows, the SNR increased, while the TTV decreased for both HbO and HbR in all subjects after removing the effect of correlated spontaneous fluctuation. The group-level results also indicated SNR increase and TTV reduction. The SNR increase was lager in HbO signals than in HbR signals. These results suggest that spontaneous fluctuation might be proportionally higher in HbO signals than in HbR signals. Compared with the previous investigative results

Table 1 The intra-subject and inter-subject SNR during the finger-tapping session before and after subtraction of correlated spontaneous fluctuation from the opposite hemisphere (BS: before subtraction; AS: after subtraction).

	Subject no.			Signal-to-noise ratio	Signal power	Noise power
Intra subject	1	HbO	BS	1.17	1.65	1.40
			AS	3.02	2.14	0.71
		HbR	BS	0.44	0.54	1.24
			AS	0.81	0.76	0.94
	2	HbO	BS	0.31	2.21	7.07
			AS	0.34	1.45	4.30
		HbR	BS	0.12	2.44	20.40
			AS	0.13	1.30	10.05
	3	HbO	BS	0.23	5.30	23.40
			AS	0.28	4.07	14.30
		HbR	BS	0.08	1.30	16.25
			AS	0.09	3.34	37.00
	4	HbO	BS	0.70	6.87	9.78
			AS	0.80	4.62	5.79
		HbR	BS	0.16	5.65	35.10
			AS	0.18	3.42	19.30
	5	HbO	BS	0.24	1.51	6.26
			AS	0.90	2.32	2.57
		HbR	BS	0.08	1.31	16.60
			AS	0.11	0.88	8.04
Inter subject	—	HbO	BS	0.53	3.51	9.58
			AS	1.07	5.00	5.53
		HbR	BS	0.18	3.75	17.92
			AS	0.26	1.94	15.07

regarding the relationship between TTV and spontaneous fluctuation in the BOLD signal,[22,23] the TTV reduction in the fNIRS signal (HbO and HbR) in the present study was lower than that in the BOLD signal. Moreover, the signal power changing level was similar compared with the TTV reduction level. The reason might be that the fNIRS signal is noisier than the BOLD signal. Additionally, we investigated the effect of TTV reduction by examining the *t*-values of the seed channel estimated by the GLM. As Table 2 shows, the seed channel *t*-value for both HbO and HbR increased after removing the effect of bilateral connectivity removing, indicating that the signal quality improvement is a benefit of TTV reduction.

Table 2 The *t*-values of the seed channel estimated by GLM before and after TTV reduction (BS: before subtraction; AS: after subtraction).

	HbO		HbR	
Subject no.	BS	AS	BS	AS
1	9.5541	12.6740	4.1486	5.7782
2	9.0688	11.9839	4.7018	5.5671
3	10.3109	11.5989	6.9109	7.4896
4	9.0688	13.6831	9.4917	10.0540
5	4.0201	5.4211	6.0392	7.1375

The spontaneous fluctuations in the brain are known as human brain activities during the resting state mixed with physiological noises. Therefore, the TTV reduction effect in this paper might be due to the physiological noises removing. To investigate the true reason for TTV reduction, we used the time series from a channel that uncorrelated with the seed region as the seed-pair channel to test the TTV reduction effect (Subject 1: Channels 9–25 for HbO and HbR). For the purpose of comparison, we used the same scaling coefficient compared with that used for the correlated seed-pair channel subtraction. The results are presented in Fig. 7, for both HbO and HbR signals, the standard deviation indicating the TTV increased. Moreover, the changes in signal mean were larger than the case of using correlated seed-pair channel. These results support that the TTV reduction in this paper is mainly due to the removal of the correlated spontaneous fluctuations.

The utility of fNIRS for assessing the RSFC has been validated in several previous studies.[26–28,31] In this paper, a significant connectivity between ipsilateral and bilateral hemisphere has been found. We first drew individual-level brain activation maps to locate the seed regions for each subject. Right-hand finger tapping task evoked hemodynamic responses could be obviously found by comparing the averaged resting-state trials and task-state trials in Figs. 5 and 6, respectively. The individual-level RSFC maps were then calculated using the seed region identified before.

Finally, our study has some limitations. First, there are potential anomalies evoked by sensory activity and attention/anticipation. For example, global arousal might cause fluctuations in neuronal activity and peripheral hemodynamic response. This hemodynamic effect should be present in many regions of the brain, not localized to the motor cortex. Moreover, a hemodynamic response undershoot from the previous trial might persist, influencing the next trial, thus skewing our results. Second, there was found no direct proof that the correlation pattern during the rest period remains constant during the task period. Previous studies[23,24] have validated the functional connectivity in the resting state using the fNIRS technique, simply because it is difficult to identify functional connectivity directly during a task session. Our assumption was that the functional connectivity pattern remained constant across different periods. Finally, further to the assumption just noted, our results were not validated at different times. Rather, we should examine the TTV reduction effect at different times, for example, during the next day. Thus, the stability of spontaneous-fluctuation-subtraction-

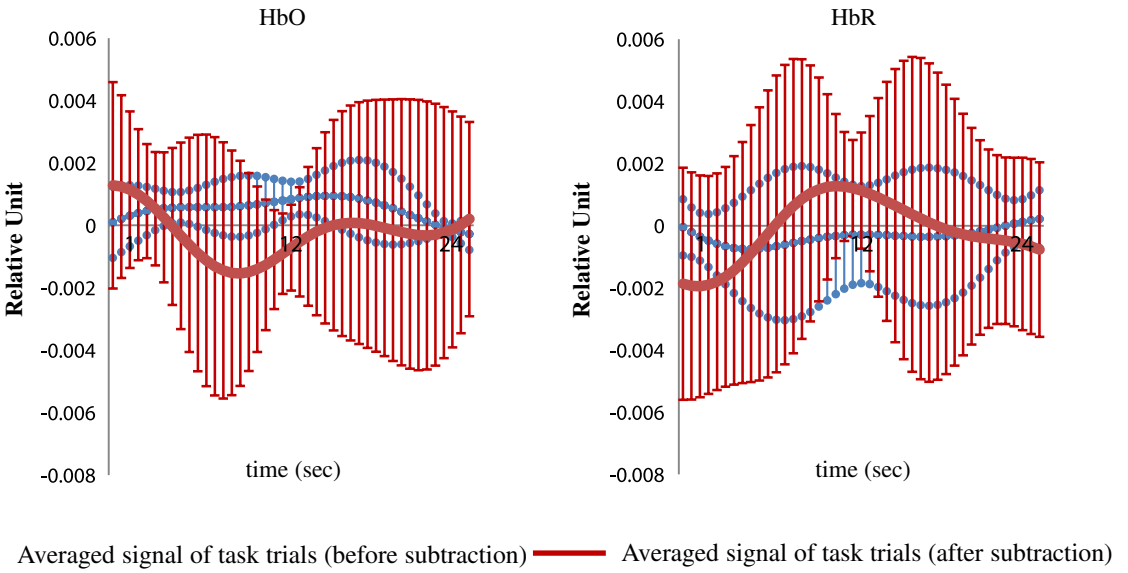

Fig. 7 TTV reduction is insignificant if uncorrelated spontaneous fluctuation from the right hemisphere is subtracted (between Channel 9 and Channel 34).

induced TTV reduction across different times (long intervals) should be investigated in a future study.

5 Conclusions

Holper et al.[21] emphasized the importance of investigating TTV in the fNIRS signal for the purposes of analyzing and quantifying a task-related brain activation. Our study, accordingly, investigated the relationship between spontaneous fluctuations and TTV in the fNIRS signal. Comparing the TTV before and after subtraction of the spontaneous fluctuation from the opposite hemisphere, we were able to demonstrate that: 1 the correlated low-frequency spontaneous fluctuation is a significant source of TTV in the fNIRS signal; 2. the TTV decreases after removing the effect of bilateral connectivity; and 3. the RSFC maps drawn in this study are similar to those produced in the literature.

Acknowledgments

This research was supported by the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology, Korea (No. MEST-2012-R1A2A2A01046411) and the World Class University Program (No. R31-20004).

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