

Research article

Cortico-cortical evoked hemodynamic responses in human language systems using intraoperative near-infrared spectroscopy during direct cortical stimulation



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HIGHLIGHTS

- We evaluated language system cortico-cortical networks with intraoperative NIRS.
- Broca's area was stimulated and recordings were made around Wernicke's area.
- 50 Hz stimulation elicited hemodynamic changes in the superior temporal gyrus.
- This technique can aid intraoperative monitoring of the cortico-cortical networks.

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ABSTRACT

Background: Understanding of cortico-cortical activity in eloquent areas intraoperatively is crucial for neurosurgical procedures. Here, we used intraoperative near-infrared spectroscopy (iNIRS) during direct cortical stimulation as a robust tool to better understand the cortico-cortical connectivity in language systems.

Methods: We applied iNIRS to 3 patients who underwent epilepsy surgery due to lesions (cavernous angioma, epidermoid cyst, and low-grade glioma) located in language areas. Using iNIRS, we measured the blood concentration changes of oxyhemoglobin (HbO₂) and deoxyhemoglobin (HbR) in the lateral temporal cortex during direct cortical stimulation (50 Hz) at the inferior frontal area where Broca's area was probabilistically located.

Results: In all patients, 50 Hz stimulation elicited hemodynamic changes in the superior temporal gyrus (STG). During 0.8–4.8 s after stimulation, HbO₂ increased and HbR decreased in the posterior part of the STG (Wernicke's area). Similar responses were observed in the anterior part of the STG 1.3–8.0 s after stimulation. Finally, these changes were disappeared in the middle temporal gyrus.

Conclusions: Our results suggest that cortical stimulation of Broca's area elicits hemodynamic responses in Wernicke's area via cortico-cortical connectivity. We demonstrated cortico-cortical evoked responses in language systems using iNIRS during direct cortical stimulation. Our iNIRS data will provide useful information about cortico-cortical networks underlying human brain functions intraoperatively and will contribute to neurosurgical treatment in eloquent areas.

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Abbreviations: CCEPs, cortico-cortical evoked potentials; HbO₂, oxyhemoglobin; HbR, deoxyhemoglobin; IFG, inferior frontal gyrus; iNIRS, intraoperative near-infrared spectroscopy; STG, superior temporal gyrus.

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1. Introduction

Understanding the eloquent language networks is critical to minimize the risk of postoperative irreversible deficits. The major aspects of language functions are achieved via cortico-cortical networks between anterior and posterior language areas, which are connected to each other by subcortical fibers [1–3]. Recently, advanced tools such as functional magnetic resonance imaging, magnetoencephalography, diffusion tensor imaging, and navigated

transcranial magnetic stimulation have enabled researchers to identify functional areas of the cortex and anatomical pathways of the subcortical fibers in language networks [4–13]. These techniques may not only be useful for pre-surgical planning but also intraoperative mapping [4–13]. There are some intraoperative problems caused by brain shift and other factors when using neuronavigation systems [14]. As the gold standard technique, direct cortical stimulation during awake surgery can compensate for problems caused by brain shift due to the possibility of repeated measurements and verification of the validity of preoperative data. [15–19]. However, even such methods may fail to identify language areas due to complicated and delicate technical problems, lack of patient cooperation, and interpretation of the results [20,21]. A recent study reported the efficacy of intraoperative language network monitoring by means of cortico-cortical evoked potentials (CCEPs) [22]. This CCEPs monitoring could successfully delineate language networks even under general anesthesia.

Near-infrared spectroscopy (NIRS) allows measurement of real-time concentration changes in oxyhemoglobin (HbO₂) and deoxyhemoglobin (HbR) during activation of various brain functions [23,24]. Recent studies have supported the utility of functional NIRS analysis to assess resting state functional connectivity in the human language system [25,26]. We have also reported that simultaneous NIRS and electroencephalography recordings provide useful information about neurovascular coupling in motor [27] and epileptic networks [28]. Considering that simultaneous NIRS and transcranial magnetic stimulation provide a reliable measure of regional cortical brain activation and connectivity [29], we successfully demonstrated that NIRS recordings during direct cortical stimulation could detect cortico-cortical hemodynamic responses between the superior temporal gyrus (STG) and the inferior frontal gyrus (IFG) [30]. In addition, we have recently developed intraoperative NIRS (iNIRS) to detect cortico-cortical hemodynamic responses elicited by direct cortical stimulation via epileptic networks in a patient with supplementary motor area seizures [31].

The aim of this study was to verify the effectiveness of our iNIRS during direct cortical stimulation in order to establish it as a powerful intraoperative technique to evaluate language networks. We performed iNIRS recordings in the posterior language areas during electrical stimulation to the anterior language areas in three patients who underwent temporal craniotomy due to epileptogenic lesions of the brain. We also attempted to evaluate the spatiotemporal changes of cortico-cortical hemodynamic activity using topographic imaging.

2. Methods

2.1. Patients

We performed iNIRS in 3 patients undergoing epilepsy surgery. The characteristics of all patients are shown in Table 1. Patient 1 and 2 had lesions in the left hemisphere (Patient 1, over the left hippocampal gyrus; Patient 2, from basal cistern to left temporal base), while Patient 3 had a lesion in the right hemisphere (from right hippocampus to uncus gyrus). The postsurgical neuropathology revealed cavernous angioma in Patient 1, epidermoid cyst in Patient 2, and ganglioglioma in Patient 3. Preoperatively, all

patients suffered from simple/complex partial seizures with secondary generalized seizures and had no neurological symptoms, including language dysfunction. The Wada test showed left hemispheric language dominance in Patient 1 and 2 and could not be performed in Patient 3 because of the patient's young age. Patient 1 and 2 were right-handed, and Patient 3 was left-handed. After surgery, Patient 1 and 2 had no neurological deficits and were completely seizure-free (20 months and 17 months), and Patient 3 had no neurological change and was seizure-free for 13 months. All patients provided informed consent before all examinations. This study was approved by the ethics committee of Niigata University Medical & Dental Hospital (IRB #1559). All patients provided informed consent before surgery.

2.2. Direct cortical stimulations

A strip electrode comprised of four contacts was set to cover the frontal cortex, including the IFG, using an intraoperative navigation system (BrainLab; Feldkirchen, Germany). One of the two neighboring contacts on the IFG corresponding to Broca's area was selected for direct cortical stimulation. Stimulations consisted of a constant current generator with a repetitive square wave pulse of 0.2 ms using Neuropac (Nihon Kodan Corporation; Tokyo, Japan). 50 Hz stimulations for 5 s were delivered to the IFG at the intensity of 8 mA in Patient 1 and 10 mA in Patient 2 and 3. Each session was repeated five times. No intraoperative seizures were observed in any of the sessions.

2.3. iNIRS recordings and data analysis

We have previously described the methods of iNIRS recordings using ETG-7100 (Hitachi Medical; Tokyo, Japan) in detail [31]. Emitting light intensity was adjusted to 1 mW (approximately one-fourth of scalp NIRS). A novel device comprising four recording probes spaced 1.5 cm apart from each other was fixed with a spatula retractor so that the tip of each probe gently attached to the lateral temporal cortex, including the posterior part of the STG corresponding to Wernicke's area. iNIRS signals were recorded at a sample rate of 10 Hz. The changes in HbO₂, HbR, and total hemoglobin concentration (HbO₂ + HbR) were measured in μM (mol/L). Each stimulation session consisted of a 60-s interval: a pre-stimulation block (10 s), a stimulation block (5 s), a post-stimulation block (25 s), and a resting block (20 s). The average baseline was calculated from a 5-s interval of the pre-stimulation block. In each patient, we averaged data from the 60-s intervals repeated five times under the same stimulus conditions and obtained topographic images from the average HbO₂ changes of the five measurements using ETG-7100 software. The raw HbO₂ and HbR data could be drawn from ETG-7100 as comma-separated values (CSV) file data. The data analysis was performed using Microsoft Excel.

3. Results

50 Hz Stimulation resulted in positive stimulation-related hemodynamic changes, specifically in the STG. In the posterior part of the left STG in Patient 1 (Fig. 1A, CH4), HbO₂ started to increase

Table 1
Characteristics of analyzed patients.

Patient	Gender	Age (years)	Lesion location	Pathology	WADA test	Hand dominancy	Postsurgical outcome
1	F	13	Left hippocampal gyrus	Cavernous angioma	Lt	Rt	Seizure free for 20 Months
2	F	28	Basal cistern – left temporal base	Epidermoid cyst	Lt	Rt	Seizure free for 17 Months
3	M	6	Right hippocampus – uncus gyrus	Ganglioglioma	None	Lt	Seizure free for 13 Months

F = female, Lt. = left, M = male; Rt. = right.

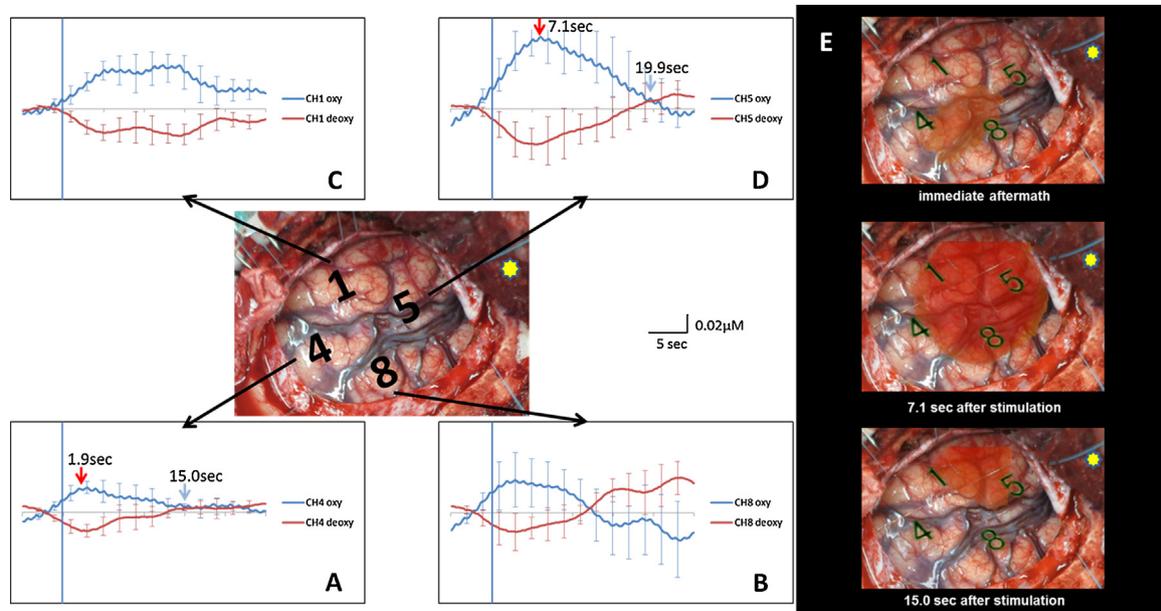


Fig. 1. (A, B, C, and D) Result of intraoperative NIRS during 50 Hz stimulations in Patient 1. Numbers show the positions of each channel, and the yellow mark indicates the stimulation site at the IFG. The red and blue arrows show the peak of HbO₂ increase and the return of HbO₂ to baseline, respectively. HbO₂ started to increase in the posterior part of the STG (CH 4 and 8, A and B) and subsequently in the anterior part of the STG (CH 1 and 5, C and D). HbR showed the opposite reaction to HbO₂. Between the posterior part of the STG and the anterior part of the STG, there were stimulation-related hemodynamic changes. The peak time (from stimulus onset) of HbO₂ changes showed a significant difference ($P=0.029$, paired t -test), and the bottom time (from stimulus onset) of HbR changes showed an almost significant difference ($P=0.081$, paired t -test). (E) Sequential changes in the topographic maps of HbO₂ in Patient 1. The yellow mark shows the stimulation site of IFG. Immediately after the 50 Hz stimulation, HbO₂ increased in the posterior part of the left STG. Subsequently, the HbO₂ increase peaked in the anterior part of the left STG at 7.1 s after stimulation. The topographic image at 15.0 s after stimulation shows that the HbO₂ increase was gradually disappeared in the middle temporal gyrus. On the whole, similar hemodynamic changes were observed in Patient 2 and 3.

immediately after stimulation, peaked 1.9 s after stimulation (red arrow in Fig. 1A), and returned to baseline 15.0 s after stimulation (blue arrow in Fig. 1A). Meanwhile, HbR started to decrease 1.0 s after stimulation, bottomed out 2.0 s after stimulation, and returned to baseline 16.2 s after stimulation. Subsequently, in the anterior part of the left STG (Fig. 1D, CH5), HbO₂ started to increase 1.7 s after stimulation, peaked 7.1 s after stimulation (red arrow in Fig. 1D), and returned to baseline 19.9 s after stimulation (blue arrow in Fig. 1D). HbR started to decrease 1.3 s after stimulation, bottomed out 6.4 s after stimulation, and returned to baseline 19.7 s after stimulation. Finally, these changes were disappeared in the middle temporal gyrus (Fig. 1C, CH1). Furthermore, the topographic

maps of HbO₂ allowed us to visually understand spatiotemporal hemodynamics in the lateral temporal cortex (Fig. 1E). Similar hemodynamic changes were observed during 50 Hz stimulation in Patient 2 and 3, albeit the degree of changes varied among the three patients. The time of onset, peak/bottom, return to baseline, and the amplitude for HbO₂/HbR changes during 50 Hz stimulation in each patient are shown in Table 2 (posterior part of STG and anterior part of STG). Between the posterior part of the STG and the anterior part of the STG, the peak time (from stimulus onset) of HbO₂ changes showed a significant difference (posterior part; 6.0 ± 3.6 s, anterior part; 10.2 ± 3.6 s, $n=3$, $P=0.029$, $t(2)=4.0$, paired t -test). The bottom time (from stimulus onset) of HbR changes also showed

Table 2

Time & amplitude data of HbO₂ and HbR during 50 Hz stimulation in each patient (posterior part of STG & anterior part of STG).

Patient	Hb changes	Time from stimulation (sec)			Amplitude (μ M)	
		Onset	Peak/Bottom	Returning to baseline	HbO ₂ increase	HbR decrease
1: posterior part of STG	HbO ₂ increase	0.8	1.9	15.0	0.019	0.013
	HbR decrease	1.0	2.0	16.2		
1: anterior part of STG	HbO ₂ increase	1.7	7.1	19.9	0.079	0.051
	HbR decrease	1.3	6.4	19.7		
2: posterior part of STG	HbO ₂ increase	3.0	8.7	14.2	0.024	0.016
	HbR decrease	4.0	8.5	13.9		
2: anterior part of STG	HbO ₂ increase	7.2	14.1	20.7	0.040	0.021
	HbR decrease	8.0	14.4	19.6		
3: posterior part of STG	HbO ₂ increase	4.4	7.3	13.6	0.0061	0.0015
	HbR decrease	4.8	9.8	15.2		
3: anterior part of STG	HbO ₂ increase	5.4	9.4	14.9	0.0089	0.0057
	HbR decrease	5.5	10.2	16.1		
Mean \pm SD:	HbO ₂ increase	2.7 \pm 1.8	6.0 \pm 3.6	14.3 \pm 0.7	0.017 \pm 0.0093	0.010 \pm 0.0077
posterior part of STG	HbR decrease	3.3 \pm 2.0	6.8 \pm 4.2	15.1 \pm 1.2		
Mean \pm SD:	HbO ₂ increase	4.8 \pm 2.8	10.2 \pm 3.6	18.5 \pm 3.1	0.043 \pm 0.035	0.026 \pm 0.0023
anterior part of STG	HbR decrease	4.9 \pm 3.4	10.3 \pm 4.0	18.5 \pm 2.1		

HbO₂ = oxyhemoglobin; HbR = deoxyhemoglobin; STG = superior temporal gyrus.

an almost significant difference (posterior part; 6.8 ± 4.2 s, anterior part; 10.3 ± 4.0 s, $n=3$, $P=0.081$, $t(2)=2.2$, paired *t*-test). On the other hand, the amplitude of the HbO2 increase showed no significant difference (posterior part; 0.017 ± 0.0093 μ M, anterior part; 0.043 ± 0.035 μ M, $n=3$, $P=0.14$, $t(2)=1.5$, paired *t*-test). Similarly, the amplitude of the HbR decrease showed no significant difference (posterior part; 0.010 ± 0.0077 μ M, anterior part; 0.026 ± 0.0023 μ M, $n=3$, $P=0.14$, $t(2)=1.4$, paired *t*-test). In this study, we assigned these *p*-values using a one tailed *t*-test, and in addition due to the low number of subjects, these statistical tests provide us only with some preliminary indication about the temporal dynamics of the activation of the anterior/posterior STG.

4. Discussion

Here, we have demonstrated cortico-cortical hemodynamic responses in language systems using iNIRS during direct cortical stimulation in epilepsy surgery. We revealed that 1) 50 Hz stimulation of the IFG elicited hemodynamic changes in the STG during the period 0.8–8.0 s after stimulation; 2) these hemodynamic changes in the STG were characterized by an increase in HbO2 and a decrease in HbR; 3) these hemodynamic changes began in the posterior part of the STG and shifted into the anterior part of the STG; and, 4) such widespread hemodynamic changes may represent distributions of the arcuate fasciculus in Wernicke's area, which project from Broca's area. We provided the first report, to the best of our knowledge, of intraoperative language networks detection using iNIRS during direct cortical stimulation.

In the present study, the maximum increase of HbO2 in the STG occurred about 7 s after stimulation in the IFG. This reaction was consistent with the results of our previous study using simultaneous NIRS and electrocorticography recordings, although the sides of the stimulation and the recording were reversed [27]. Another of our studies also found that the hemodynamic responses to language tasks typically peak approximately 6–11 s after task stimuli [27]. These findings suggest the existence of a bidirectional connection between Broca's and Wernicke's areas through the cortico-cortical pathways, and the stimulation of one of these areas can elicit hemodynamic responses in the other area. Utilizing the same phenomena, recent studies revealed that intraoperative CCEP monitoring might be useful for delineating language networks [22,32]. The latency of CCEPs was much shorter than that of hemodynamic responses in our study. This discrepancy might be because hemodynamic changes could be gradually induced by direct stimulation of cortical neurons, glia, pericytes, and so on in accordance with the mechanism underlying neurovascular coupling [33].

Most task-oriented NIRS studies have demonstrated that task-evoked hemodynamic changes typically show a pattern of increased HbO2 with decreased HbR, which would be a physiological functional pattern of hemodynamic changes [27,34]. Results from the present study showed the same pattern while our previous study of cortico-cortical language networks using NIRS during direct cortical stimulation showed a hemodynamic pattern characterized by increases in both HbO2 and HbR [27]. These two studies had technical differences between emitting light intensity and inter-probe distance. It was revealed that the contribution of larger blood vessels to the overall blood volume tends to be underestimated by diffuse optical measurements using NIRS [35]. Consequently, iNIRS might be more sensitive to more local hemodynamic changes. Furthermore, our recent study using iNIRS demonstrated that cortical stimulation of the seizure onset zone induced increases of both HbO2 and HbR in remote areas that had robust connections with epileptic networks [31]. We speculate that such strong neuronal activities via epileptic networks could lead to excessive oxygen consumption above its delivery and subse-

quent increases of both HbO2 and HbR. To clarify the mechanisms of such hemodynamic responses, we will tackle further studies of cortico-cortical activities using iNIRS in a variety of cases.

The arcuate fasciculus, especially the phonological loop, anatomo-functionally connects the posterior STG to Broca's area in the left hemisphere, which is particularly important during early language acquisition [36]. In the right hemisphere, the pathway connecting the STG to Broca's area is associated with prosodic processing [37], although the volume of its fibers is smaller than that of the left hemisphere [38]. Mainly through the pathways described above, stimulation of the IFG might evoke the early hemodynamic responses in the posterior part of the STG. The following hemodynamic responses in the anterior part of the STG might be related to the fact that the STG contains multi-interconnected acoustically functional areas [39]. The number of subjects is still low, so further studies are needed to validate these propositions.

A NIRS study in a patient with a left frontal glioma showed that when 50 Hz stimulation was applied to the left hand motor area, significant hemodynamic responses appeared at the stimulation site and in the areas associated with prominent muscle contractions of the right upper extremity. Conversely, 5 Hz stimulation demonstrated no significant hemodynamic changes [40]. These results suggest that the adequate frequency of stimulation to elicit neuronal activation is 50 Hz, not 5 Hz, which is consistent with our previous results [27]. 50 Hz stimulation has been also applied in language mapping to elicit language dysfunction involving Broca's area, Wernicke's area, and the basal temporal language area [41]. Duffau et al. demonstrated using neurophysiology that membrane depolarization of the neural cell had a robust relationship with the initial segment of myelinated axons, and that myelinated axons produce a single response for stimulation at 50–100 Hz [18]. Therefore, we propose that 50 Hz stimulation is suitable and adequate in iNIRS to provide both hemodynamic and functional cortico-cortical responses by producing neural excitations.

In this study, we tried to map Wernicke's area by confirming the hemodynamic responses caused by cortical stimulation of Broca's area, which may have remote and functional connections with Wernicke's area as part of language systems. We speculated that those responses reflected the subcortical language system's passage through the arcuate fasciculus. It may be possible to be able to preserve Wernicke's area, including the surrounding subcortical pathways, by using iNIRS, as well as CCEPs, by direct cortical stimulation under general anesthesia. Furthermore, iNIRS produces fewer artifacts than conventional transcranial NIRS because iNIRS can measure hemodynamic changes from the brain's surface directly.

At the present stage of our iNIRS technique, there were a number of limitations. First, the number of iNIRS probes was only four, which led to inadequate spatial resolution for highly precise measurements of hemodynamic activity. We will develop a new iNIRS device that is smaller and has more probes in the future. Second, we pre-measured hemodynamic changes only in the lateral temporal cortex. It will be also necessary to evaluate hemodynamic activity in the anterior language area during direct cortical stimulation of the posterior language area in order to validate a bidirectional connection between the two areas via cortico-cortical pathways. Finally, we used only a small number of patients. Future research investigating a larger number and different kinds of patients will be needed to assess the feasibility and applicability of iNIRS.

5. Conclusions

We demonstrated the clinical utility of iNIRS during direct cortical stimulation to better understand cortico-cortical connectivity in language systems. This technique might be usable for intraop-

erative monitoring of cortico-cortical activity in the eloquent areas while under general anesthesia. Further studies will provide new insight into the cortico-cortical networks underlying human brain functions.

Conflicts of interest

None declared.

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