

Changes in cerebral blood oxygenation of the frontal lobe induced by direct electrical stimulation of thalamus and globus pallidus: a near infrared spectroscopy study

Kaoru Sakatani, Yoichi Katayama, Takamitsu Yamamoto, Susumu Suzuki

Abstract

Objective—Blood oxygenation level dependent (BOLD) contrast functional MRI images show activated cortical areas by detecting a reduced concentration of deoxyhaemoglobin (deoxy-Hb) during neuronal activity; however, near infrared spectroscopy (NIRS) has shown various patterns of cerebral blood oxygenation (CBO) changes in the frontal lobe during cognitive tasks. To determine if various patterns of CBO changes occur in the frontal lobe when the brain is directly stimulated, changes in CBO in the frontal lobe induced by deep brain stimulation in patients with implanted electrodes were evaluated.

Methods—Six patients were studied, including five with Parkinson's disease and one with essential tremor. To reduce tremor or rigidity, the electrodes were implanted at the thalamic nucleus ventralis intermedius (VIM: three Parkinson's disease and one essential tremor) or the globus pallidus internus (GPi: two Parkinson's disease). Using NIRS, changes of deoxy-Hb, oxyhaemoglobin (oxy-Hb) and total haemoglobin (total Hb) were measured in the bilateral frontal lobes during various stimulus conditions.

Results—High frequency (120 Hz) GPi stimulation consistently increased oxy-Hb and total Hb with a decrease of deoxy-Hb in an intensity and time dependent manner. Oxy-Hb and total Hb increased immediately after the onset of stimulation and then gradually decreased when stimulation was continued. By contrast, high frequency (120 Hz) VIM stimulation decreased oxy-Hb, deoxy Hb and total Hb in an intensity dependent manner. In the severe tremor patient with VIM stimulation, frequency response was examined by decreasing stimulus frequencies; deoxy-Hb increased at high frequencies (70-40 Hz), and then decreased below the control level at low frequencies (30-0 Hz), whereas oxy-Hb and total Hb increased consistently at high and low frequencies.

Conclusion—The electrical stimulation of GPi and VIM caused various CBO changes in the frontal lobe, which were similar to those found during cognitive tasks. Such a multiplicity of CBO changes in the frontal lobe may be caused by complex neuronal circuits in the frontal lobe

which has many neuronal connections to other cortical areas or the basal ganglia.

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Keywords: Blood oxygenation level dependent (BOLD) images; functional MRI; near infrared spectroscopy; Parkinson's disease

Blood oxygenation level dependent (BOLD) contrast functional MRI images activating cortical areas by detecting a reduced concentration of deoxyhaemoglobin (deoxy-Hb) during neuronal activity.¹ PET activation studies on visual² or somatosensory functions^{3,4} showed that brain activation causes a much greater increase in regional cerebral blood flow (rCBF) than O₂ consumption in the activating area, which leads to a decrease in deoxy-Hb. However, recent neuronal activation studies using near infrared spectroscopy (NIRS) have shown that, in addition to this cerebral blood oxygenation (CBO) change, cognitive tasks cause various patterns of changes in CBO in the frontal lobe.⁵⁻⁹

NIRS is an optical method to measure concentration changes of oxyhaemoglobin (oxy-Hb) and deoxy-Hb in cerebral vessels by means of the characteristic absorption spectra of haemoglobin in the near infrared range.¹⁰ NIRS activation studies have shown that neuronal activation generally causes increases in oxy-Hb and total haemoglobin (total Hb) with a decrease of deoxy-Hb at the activated cortical area⁵⁻¹¹; this change in CBO is consistent with that obtained by PET or functional MRI. In addition to this CBO change, NIRS activation studies have disclosed several patterns of changes in CBO in the frontal lobe during cognitive functions, such as decreases of oxy-Hb and total Hb or an increase of deoxy-Hb associated with increases of oxy-Hb and total Hb.⁵⁻⁹ However, it is not yet clear whether these CBO changes in the frontal lobe were specific to cognitive tasks. In addition, the relation between the CBO changes and stimulus conditions such as stimulus frequency and intensity has not been elucidated in the frontal lobe.

Recently, deep brain stimulation therapies, such as electrical stimulation of the thalamic nucleus ventralis intermedius (VIM) or the globus pallidus internus (GPi), have been applied for the treatment of movement disorders including tremor or rigidity.¹²⁻¹⁵ Studies with PET have shown that electrical stimulations of GPi or VIM change rCBF in various

Department of
Neurosurgery, Nihon
University School of
Medicine, Japan
K Sakatani
Y Katayama
T Yamamoto

Department of
Neurosurgery,
China-Japan
Friendship Hospital,
China
K Sakatani

Hamamatsu
Photonics, Japan
S Suzuki

Correspondence to:
Dr Kaoru Sakatani,
Department of
Neurosurgery, Nihon
University School of
Medicine, 30-1
Oyaguchi-Kamimachi,
Itabasi-Ku, Tokyo 173,
Japan.

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Clinical profile of the patients

Patient No	Age	Sex	Disease	Main symptoms	Location of electrodes	Minimum stimulation to suppress symptoms	UPDRS (total score) (before/after stimulation)
1	46	F	Parkinson's disease	Rigidity	L GPi	2.5 V, 120 Hz	17/5
2	58	F	Parkinson's disease	Tremor	L VIM	3.0 V, 100 Hz	39/14
3	66	F	Parkinson's disease	Tremor	R VIM	1.0 V, 120 Hz	24/7
4	53	M	Parkinson's disease	Tremor, rigidity	R VIM	2.0 V, 120 Hz	39/23
5	51	M	Parkinson's disease	Akinesia, rigidity	Bil GPi	1.0 V, 120 Hz	43/24
6	63	M	Essential tremor	Tremor	L VIM	1.3 V, 120 Hz	TRS 3/0

VIM=thalamic nucleus ventralis intermedius; GPi =globus pallidus internus; UPDRS=unified Parkinson's disease rating scale; TRS=tremor rating scale; L=left; R=right; Bil=bilateral. Stimulus duration was fixed at 200 μ s. The values in the table were obtained during NIRS measurements.

cortical areas including the frontal lobe.^{16 17} In these patients with implanted electrodes, the stimulus variables such as stimulus intensity or frequency can be changed.^{14 15} In the present study, using NIRS, we evaluated CBO changes in the frontal lobe induced by electrical stimulation at VIM and GPi in the patients with movement disorders under various stimulus conditions.

Patients and methods

We studied six patients (three men and three women, all right handed, ranging in age from 46 to 66 years) with movement disorders; five cases of Parkinson's disease, and one case of essential tremor. The electrodes were implanted at VIM (three cases of Parkinson's disease and one case of essential tremor) or GPi (two cases of Parkinson's disease). Stimulation of the GPi was employed mainly for controlling rigidity, whereas VIM stimulation was selected for

controlling tremor of the contralateral side of the body¹²⁻¹⁵; all of the six patients had shown satisfactory control of their clinical symptoms with intermittent chronic electrical stimulation of VIM or GPi; the clinical effects of the deep brain stimulation on Parkinson's disease and essential tremor were evaluated with the unified Parkinson's disease rating scale¹⁸ and tremor rating scale,¹⁹ respectively. The electrode was placed at the position where rigidity or tremor was suppressed most effectively; the stereotactic surgical procedure used has been described elsewhere.^{14 15} MRI did not show any lesion involving supraspinal structures in these patients. The table summarises the clinical profile of the patients. Informed consent to participate in the study was obtained from each subject.

We measured CBO changes in the bilateral frontal lobes during various stimulus conditions using NIRO-300 (Hamamatsu Photonics K.K.). The NIR light from four laser diodes

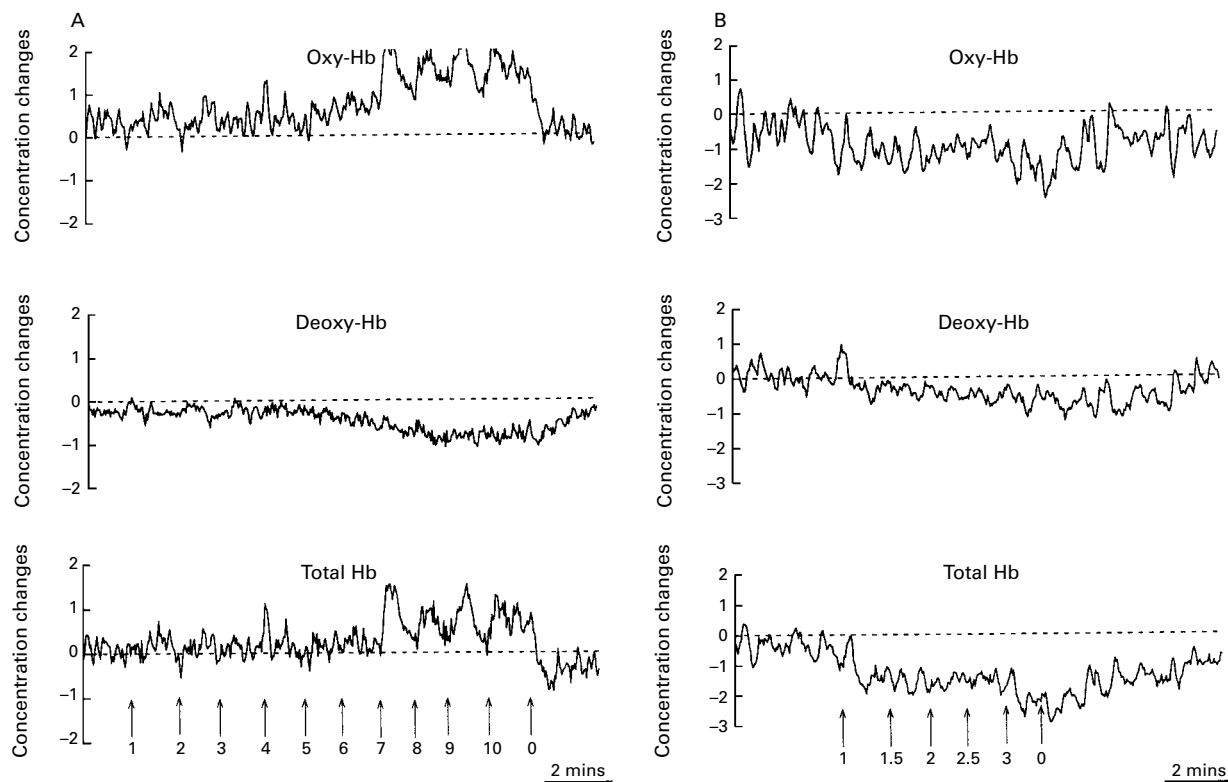


Figure 1 (A) Changes in CBO in the left frontal lobe during left GPi stimulation under different stimulus conditions; stimulus intensity was changed stepwise by 1 V from 0 V to 10 V. (B) Changes in CBO in the left frontal lobe during left VIM stimulation under different stimulus conditions; stimulus intensity was increased stepwise by 0.5–1 V from 0 V to 3 V. In A and B, stimulus frequency and duration were fixed at 120 Hz and 200 μ s, respectively. The numbers below arrows indicate the stimulus intensity in V. The ordinates indicate concentration changes of oxy-Hb, deoxy-Hb, and total Hb in arbitrary units. Horizontal thick bars indicate time scale of 2 minutes.

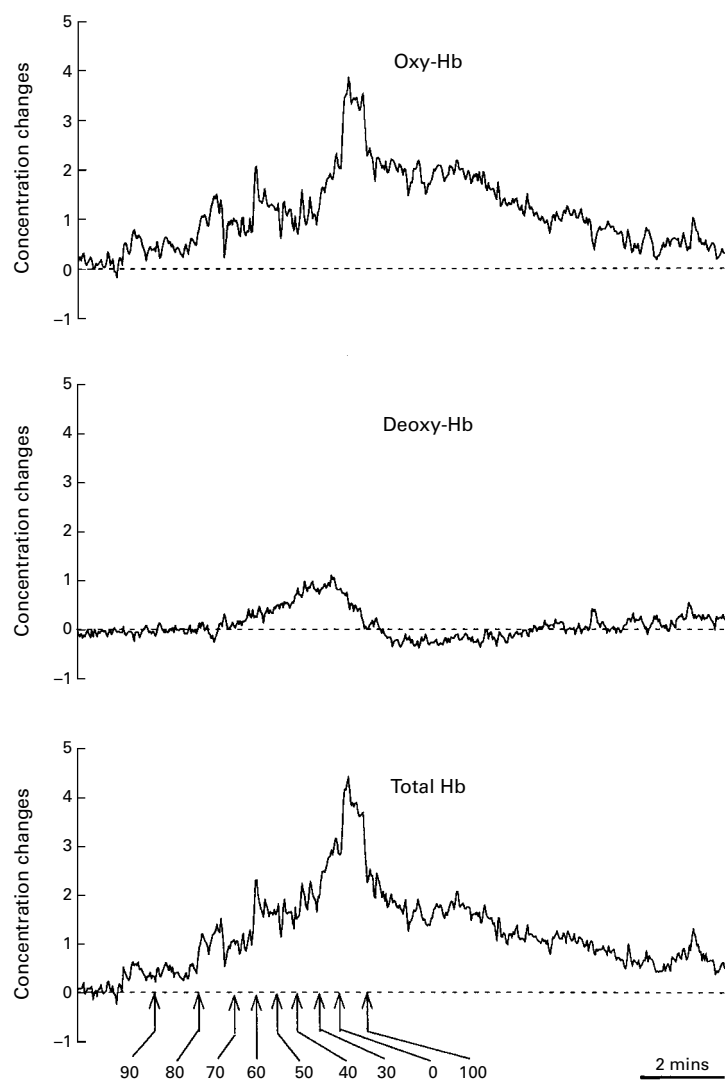


Figure 2 Changes in CBO in the left frontal lobe during decrease of left VIM stimulation. Stimulus frequency was decreased stepwise by 10 Hz from 100 Hz to 0 Hz under the same stimulus intensity (3 V). The numbers below arrows indicate the stimulus frequency in Hz. The ordinates indicate concentration changes of oxy-Hb, deoxy-Hb, and total Hb in arbitrary units. Horizontal thick bar indicates a time scale of 2 minutes

was directed at the head through a fiberoptic bundle, and reflected light was transmitted to a multisegment photodiode detector array.²⁰ Absolute concentration changes of oxy-Hb, deoxy-Hb, and total Hb were continuously analysed, and were expressed in arbitrary units²¹; if the differential path length factor of the adult head is assumed to be 5.9, one arbitrary unit equals 1 μM .²² Changes in total Hb indicate blood volume changes and correlate with CBF changes under conditions with constant packed cell volume and perfusion pressure.^{23–25} The centre between the emitter and detector was identical to the Fp2 position of the international EEG 10–20 system; in the previous study, MRI showed that the emitter-detector was placed over the frontal lobe, mainly the prefrontal cortex.⁸

In the present study, we mainly analysed the changes of oxy-Hb, deoxy-Hb, and total Hb by qualitative pattern analysis, which was used in our previous study⁸; we classified several common patterns according to the changes of the

NIRS variables during stimulations. We also evaluated the changes of the NIRS variables by subtracting mean baseline values from mean stimulation values; we performed *t* tests to compare the baseline values and stimulation values.

Results

Electrical stimulation of GPi increased oxy-Hb and total Hb with a decrease of deoxy-Hb in the frontal lobes. Figure 1A shows an example of the CBO changes in the left frontal lobe during the left GPi stimulation of 0–10 V at 120 Hz; stimulus intensity was increased stepwise by 1 V from 0 V to 10 V. GPi stimulation under 6 V did not cause detectable changes of oxy-Hb, deoxy-Hb, or total Hb; however, stimulation over 7 V increased oxy-Hb and total Hb with a decrease of deoxy-Hb. At 7 V stimulation, mean oxy-Hb and total Hb increased by 1.6 (SD 0.2) ($p < 0.01$) and 1.3 (SD 0.2) ($p < 0.01$), respectively, and deoxy-Hb decreased by -0.4 (SD 0.1) ($p < 0.01$). Interestingly, oxy-Hb and total Hb increased immediately after the onset of GPi stimulation and then gradually decreased when stimulation was continued. After the cessation of GPi stimulation, the NIRS variables quickly returned to the control level. The increases in oxy-Hb and Total Hb were induced in the frontal lobes of both sides, although a larger increase was found in the ipsilateral frontal lobe in one of the three patients examined. The clinical symptoms of the patients with GPi stimulation were suppressed by the stimulus conditions that evoked no detectable CBO changes in the frontal lobe.

Figure 1B shows an example of the CBO changes in the left frontal lobe during the left VIM stimulation of 0–3 V at 120 Hz; stimulus intensity was increased stepwise by 0.5–1 V from 0 V to 3 V. Stimulation of VIM with low intensities (< 1 V) did not cause detectable changes in the NIRS variables. By contrast with GPi stimulation, oxy-Hb, deoxy-Hb, and Total Hb tended to decrease when intensity was increased to a level which abolished tremor (> 1.5 V). At 1.5 V stimulation, mean oxy-Hb, deoxy-Hb, and total Hb decreased by -1.0 (SD 1.0) ($p < 0.01$), -0.4 (SD 0.3) ($p < 0.01$), and -1.4 (SD 0.6) ($p < 0.01$), respectively. No further decrease in the NIRS variables was induced by increasing intensity above this level. The decreases in the NIRS variables tended to continue during stimulation. After the cessation of VIM stimulation, the NIRS variables quickly returned to the control levels. The decreases in the NIRS variables were induced in the frontal lobes of both sides; however, a larger change was seen in the ipsilateral frontal lobe in one of the three patients examined.

In the patient with severe tremor with VIM stimulation, frequency response was examined by decreasing stimulus frequencies; stimulus frequencies were decreased stepwise by 10 Hz from 100 Hz to 0 Hz under the same stimulus intensity (3 V). During decreases of the stimulus frequency, deoxy-Hb increased at high frequencies (70–40 Hz), and then decreased below the control level at low frequencies

(30–0 Hz); whereas oxy-Hb and total Hb increased consistently during the stimulation decrease (fig 2). The tremor of the patient increased gradually associated with the decrease of stimulus frequency.

Discussion

The present results showed that the electrical stimulation of GPi and VIM caused CBO changes in the frontal lobe. There was a considerable difference in characteristics of changes in CBO induced by GPi and VIM stimulation; GPi stimulation increased oxy-Hb and total Hb, whereas VIM stimulation decreased oxy-Hb and total Hb. These CBO changes suggest a possible functional interaction between the frontal lobe and GPi or VIM during deep brain stimulation.

Stimulation of the GPi increased oxy-Hb and total Hb with a decrease of deoxy-Hb in the frontal lobe (fig 1A). These changes are consistent with the reported changes in NIRS variables induced by various neuronal activations.^{5–11} The NIRS changes induced by GPi stimulation reflect an increase in rCBF at the measurement areas.^{5–11} These findings suggest that GPi stimulation has a functional effect on the frontal lobe, which leads to an increase of neuronal activity in the frontal lobe. However, until now, there has been no evidence of such connections. Studies with PET have shown that GPi stimulation causes an increase of the rCBF in the premotor cortex and the sensory-motor cortex, but not in the prefrontal cortex.¹⁷

In the present study, the CBO changes in the prefrontal cortex might be induced by relatively large stimulus intensities because the clinical symptoms of the most patients were suppressed by the stimulus conditions that evoked no detectable CBO changes. We do not know whether the CBO in the premotor cortex and the sensory-motor cortex changed during GPi stimulation. However, these results suggest that the GPi stimulation in the present study might activate a possible functional connection between the GPi and the prefrontal cortex, the threshold of which is higher than those of the connections between the GPi and the motor or premotor cortex. To clarify this possibility, further studies, such as simultaneous measurements of NIRS and PET or multichannel NIRS recording, are necessary.

By contrast with GPi stimulation, VIM stimulation decreased oxy-Hb and total Hb in the frontal lobe (fig 1B). This CBO change suggests that VIM stimulation has a suppressing effect on neuronal activity in the frontal lobe for the following reasons. Firstly, simultaneous measurements of NIRS and PET showed that the decreases in oxy-Hb and total Hb were associated with rCBF decrease at the NIRS recording region.^{5–7} Secondly, a PET activation study has shown that regional depressions of synaptic activity decreased rCBF.⁴ Finally, decreases in VIM stimulation caused increases of oxy-Hb and total Hb (fig 2), suggesting that VIM stimulation suppressed the neuronal activity in the frontal lobe. The present results suggest a presence of neuronal

connections between the VIM and the prefrontal cortex. However, a PET study on parkinsonian patients with tremor showed that the rCBF changes in the frontal lobe induced by VIM stimulation were restricted in the motor or premotor cortex.¹⁶ Simultaneous measurements of NIRS and PET may clarify this inconsistency between the PET findings and the present NIRS findings.

The present study using NIRS, which allows real time monitoring of CBO changes, showed changes in CBO which have not been detected by PET. Firstly, a “fatigue phenomenon” of CBO response; after the onset of GPi stimulation oxy-Hb and Total Hb increased initially, and then gradually decreased when stimulation was continued (fig 1A). Such a “fatigue phenomenon” of CBO response measured by NIRS was also found in the frontal lobe during cognitive tasks.^{5–9} The fatigue phenomenon of CBO response in the present study was not due to a decrease of stimulus input. This may be due to either a fatigue of neuronal activity in the neuronal network between the frontal lobe and GPi, or a fatigue of the coupling of neuronal activation and CBO. Secondly, a diphasic change of deoxy-Hb during decreases of the stimulus frequency; deoxy-Hb increased at high frequency, and then decreased towards the control level at low frequency. Changes of deoxy-Hb depend on the balance between O₂ delivery and O₂ consumption at the activation area^{8–26}; therefore, the diphasic change of deoxy-Hb suggests that the balance between O₂ delivery and O₂ consumption changed during the decrease of VIM stimulation.

In summary, the present NIRS study demonstrated dynamic changes of CBO in the frontal lobe during electrical stimulations of VIM and GPi. In addition, the variety of changes in CBO measured by NIRS in the frontal lobe was not specific to cognitive tasks. Complex neural circuits in the frontal lobe, which has many neuronal connections to other cortical areas or the basal ganglia, may cause such a multiplicity of CBO changes in the frontal lobe.

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