A study of the usefulness of near-infrared spectroscopy (NIRS) in patients with halitosis

口臭症患者における近赤外分光法（NIRS）の有用性の検討

日本大学大学院松戸歯学研究科歯学専攻

吉野　亜州香

（指導：小方　賴昌　教授）

A Study of the Usefulness of Near-infrared Spectroscopy (NIRS) in Patients with Halitosis

Nihon University Graduate School of Dentistry at Matsudo, Oral Diagnostics, Matsudo, Chiba 271-8587, Japan

Keywords :

psychological halitosis, NIRS, depressive tendency, volatile sulfur compounds, psychological test

Correspondence to : Asuka Yoshino

E-mail : maas17015@g.nihon-u.ac.jp

Abstract

Objectives: Despite having low concentrations of volatile sulfur compounds (VSC), some patients are concerned with halitosis. This symptom is referred to as "psychological halitosis". The patients with psychological halitosis often show depressive tendencies, as it interferes with their interpersonal and social lives. Assessment of depressive tendencies only with psychological testing can yield ambiguous results. Thus, this study aimed to investigate whether near-infrared spectroscopy (NIRS) can be used as one of the diagnostic criteria to objectively identify the psychological characteristics of halitosis patients.

Methods: The study included 16 patients complaining the halitosis and 16 healthy individuals without halitosis as a control. All participants underwent VSC concentrations and NIRS evaluation. The patient group has done psychological testing to assess depression and anxiety.

Results: No significant difference was observed with the VSC. Psychological tests indicated a tendency toward depression and anxiety. The integral values on the NIRS corresponding to the left dorsolateral prefrontal cortex were significantly lower in the patient group, indicating a waveform pattern was consistent with depressive states. Patients without depression based on psychological tests showed waveform patterns consistent with depressive states on the NIRS.

Conclusion: This study showed that NIRS could serve as an objective diagnostic criterion for psychological halitosis.

Introduction

In general, halitosis is classified into the following categories: physiological halitosis, caused by tongue coating and other factors without any underlying disease-causing halitosis; and pathologic halitosis, caused by oral or systemic diseases or psychological causes (1). Pathologic halitosis is further divided into physical halitosis of systemic origin due to sinusitis, diabetes, etc., and psychological halitosis derived from mental stress and anxiety (2).

Recently, there has been more interest in psychological halitosis than physical halitosis (3, 4). In general, the extraction and analysis of information about the patient's personality, mental state, and lifestyle habits are important when diagnosing halitosis. Such information is usually collected by questionnaires and psychological tests (5). Also, the treatment process for halitosis includes measurement of volatile sulfur compound (VSC) concentrations in the oral cavity and inform the objective value to the patient (6).

However, some patients concern halitosis regardless of the objective VSC concentration test results. Even after explaining the test results, long communication periods are consumed for these patients to convince the absence of halitosis. Some of these patients had the idea of reference that they have an odor based on their reaction to their surroundings (7, 8). Some reports that the patients tend to be depressed because halitosis interferes with interpersonal relationships and social life (9, 10), and such patients need mental care (11, 12)

in addition to usual care.

Some patients have been are unable to resolve their anxiety and concerns despite negative objective halitosis results. Such patients need an objective understanding of the psychological state and physiological changes. Questionnaires and psychological tests can be used to determine the patient's psychological state. However, since the questionnaire is answered by the patients themselves, false response and social-desirability bias can exist (13). Some psychological tests consider false responses and lie scores and scales are included in the questions. These tests are guaranteed reliable and valid, but the results should be considered along with other results and are single reference findings (14).

Therefore, it was considered that necessary to use psychophysiological tests instead of questionnaires and psychological tests to objectively assess the patient's condition. Psychophysiological tests use various physiological indicators, such as electrocardiogram, electroencephalogram or event-related potentials, and cerebral blood flow. Positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy (NIRS) are some of the methods used to measure cerebral blood flow.

It was examined the characteristics of each cerebral blood flow measuring system. Of the three, NIRS was relatively easiest to use. NIRS has a weak signal-to-noise ratio, but it is highly correlated with fMRI measurements (15). NIRS can be used as an alternative to PET in detecting changes in cerebral blood flow (16). Hence, NIRS was focused on attention.

The advantage of NIRS is that it is lightweight and allows measurements to be recorded in a natural, unrestricted position and with minimal strain on the patient. In recent years, NIRS has been used as a diagnostic aid in psychiatric disorders, and by using verbal fluency tasks, which are brain activation tasks, it can be used to investigate depression and other disorders (17). Therefore, further development is expected.

NIRS emits near-infrared light from sensors placed on the frontal scalp. It non-invasively measures changes in the concentration of oxidized hemoglobin (oxy-Hb) and deoxidized hemoglobin (deoxy-Hb) on the brain surface in real-time. NIRS measurements have shown that depressed individuals have lower cerebral blood flow and lower function of the left dorsolateral prefrontal cortex, which is associated with cognition, judgment, and decision making (18, 19), than healthy individuals (20-22).

The present study examined whether NIRS can serve as an objective complementary indicator of psychological testing for the diagnosis of halitosis in patients with negative VSCs.

Materials and Methods

1. Participants

This study included 32 participants. The patient group comprised 16 patients with suspected psychological halitosis (6 males and 10 females; mean age, 45.6 ± 14.7 years) who

presented to the Department of General Practice at Nihon University School of Dentistry at Matsudo Hospital with a chief complaint of halitosis between July 2019 and January 2020.

The control group consisted of 16 people (5 males and 11 females; mean age, 48.8 ± 16.6 years), without any complaint of halitosis, who were physically and mentally healthy. The control group was matched to the extent possible to the patient group for age and gender.

The inclusion criterion for all participants was that their native language was Japanese and they were right-handed, and the exclusion criterion was that they were not taking psychotropic drugs.

2. Methods

1) Volatile sulfur compounds measurement

The concentrations of the VSCs, such as hydrogen sulfide (H_2S), methyl mercaptan (CH_4S), and dimethyl sulfide (C_2H_6S), were measured for all participants using an Oral Chroma® CHM-2 (FIS Incorporated, Hyogo). Participants were asked to refrain from consuming breakfast, drinking water, and brushing their teeth after waking up on the day of the inspection to maintain the strongest early morning breath odor of the day with high reproducibility until the time of the inspection (23). They were instructed the day before inspection to avoid eating strong-smelling foods such as onions and garlic, which could affect their breath.

Measurements were performed at 9:00 a.m. The measurement method involved inserting a disposable syringe into the mouth and breathing through the nose with the lips closed. After 30 s, the oral gas was aspirated by pulling back the syringe piston. The piston was then pushed again, and the oral gas was suctioned one last time. Finally, 1.0 mL of oral gas was collected and used for evaluation.

The reference values for the VSCs were fixed in accordance with previous studies (24): 112 ppb for H_2S, 26 ppb for CH_4S, and 8 ppb for C_2H_6S.

2) Psychological test

Zung's self-rating depression scale (SDS) and the state-trait anxiety inventory (STAI) was used in the patient group to assess depression and anxiety, respectively (25, 26).

The SDS is a self-rating scale devised by Zung WW for depressive symptoms (25). The participants were asked to select one of four response levels to rate the "frequency of occurrence of depressive symptoms" in this self-administered, 20-item questionnaire. It can be answered in a relatively short period, and it allows for screening for depression by quantifying the level of depression (lowest score 20; highest score 80) (27). Higher scores indicate a higher level of depression. In line with previous studies (28), a score <40 was considered normal indicating no depressive symptom, and a score of ≥40 was considered high, indicating a depressive symptom.

The STAI is divided into STAI-1 for assessing state anxiety and STAI-2 for trait anxiety (lowest score 20; highest score 80, respectively) (29). State anxiety describes how anxious the person is currently, while trait anxiety describes how anxious the person usually is (26). In line with previous studies (28), STAI-1 and 2 scores <42 and 45, respectively, were considered normal, indicating no absence of anxiety symptoms, and scores of ≥42 and 45 were considered high, indicating anxiety symptoms.

3) Near-infrared spectroscopy measurement

All participants were subjected to NIRS measurements using the Spectratech OEG-16 (Spectratech Inc., Tokyo, Japan). Twelve probes were placed in the frontal area of the head, and 16 channels were measured in total (Fig. 1). The anatomical landmarks of the probe setting position were determined according to the International 10-20 system, and the centerline of the head was determined by calculating Cz (vartex) from Iz (inion), Nz (nasion), LPA (pre-auricular point of the left), and RPA (pre-auricular point of the right). The lower end of the probes was placed in the area from F7 on the left side of the frontal lobe to F8 on the right side of the frontal lobe, following previous studies using the same device (30). The distance from the emitting probe to the receiving probe was 3 cm, and the near-infrared absorption bands of deoxy-Hb and oxy-Hb were approximately 770 nm and 840 nm, respectively. The temporal resolution (sampling interval) was 0.65 s, and the measurement

depth was 3 cm from the cortex. The channels 13, 14, and 16 that correspond to the left dorsolateral prefrontal cortex (Brodmann area 46), were analyzed in this study (20, 30-32).

The test used was the verbal fluency task (VFT), which is used as an activation task in clinical settings and experiments using NIRS (33). This task requires the participant to say as many words as possible, beginning with a given initial letter.

The participants were asked to follow the instruction “Start, A [ʌ], I [iː], U [u], E [e], O [ɔ]” and say “A [ʌ], I [iː], U [u], E [e], O [ɔ]” repeatedly for 30 s. This was the baseline. The repetition of meaningless sounds provides data that excludes the effect of brain activation by vocalization.

Next, they were asked to respond orally with as many words as possible, beginning with the initial letter of "a", "ka", and "shi" in 20 s each. Changing the acronym, every 20 s ensured that the responses were uninterrupted and sustained the activation by making it harder to abandon thinking. Finally, they were asked to follow the instruction “Stop, A [ʌ], I [iː], U [u], E [e], O [ɔ]” and say “A [ʌ], I [iː], U [u], E [e], O [ɔ]” repeatedly for 70 s. This was set as one protocol, and it was repeated five times for evaluation (Fig. 2) (34, 35).

The measured data included physiological artifacts and noise, such as respiration, masticatory muscle activity, and heart rate (Hz＜0.01, 0.1＜Hz) (36). Bandpass filters were used to reduce artifacts, and the analysis was performed between 0.005 and 0.08 Hz. The baseline correction was performed as per previous studies (35, 37) using the last 10 s of the

pre-task as the baseline and assuming that the elevated cerebral blood flow changed during the task period. These were attenuated during the first 50 s post-task, which then returned to the baseline in the next 5 s. BRain Analyzer (BRSystems Incorporated, Kanagawa) is a data processing tool used for this process.

Oxy-Hb was used for the analysis, as it is highly correlated with changes in cerebral blood flow and is thought to reflect brain activity (38). For comparison, three parameters were automatically calculated for 13, 14, and 16 channels in the control and patient groups: integral value, centroid value, and initial activation over the 60 s task period (37). The criteria for each parameter during task execution were described as follows: As for the integral values, the waveform patterns in healthy individuals are relatively larger than in depressed individuals, but the critical values cannot be determined (39). The centroid values are ≤54 in both healthy individuals and patients (40), and initial activation is rapid and low value in all cases (41). The centroid values and initial activation are not different between healthy individuals and patients. These values are displayed as unitless. The three channels' waveforms were investigated based on a previous study (42) (Fig. 3) and then compared with the psychological test results.

3. Statistical analysis

The VSC concentrations were analyzed by type. The NIRS data were analyzed using

the Mann-Whitney U test for integral value, centroid value, and initial activation for each channel. Statistical analysis was performed using Statistical Package for the Social Sciences version 25 (IBM SPSS Japan, Tokyo, Japan), and statistically significant differences were considered at <5% risk.

4. Ethical considerations

The purpose of this study was explained to all the participants, and informed consent was obtained. This study was conducted with the approval of the Ethics Review Committee of the Nihon University School of Dentistry at Matsudo (approval number: EC19-006).

Results

1. Volatile sulfur compound concentrations

Figure 4 shows the VSC concentrations. The median of VSC concentrations of all three VSCs were higher in the control group than in the patient group, and there were some patients who exceeded the reference value. Especially for dimethyl sulfide, most of the patients in the control group exceeded the reference value. However, no patients in the patient group exceeded the reference values, and there was no significant difference between the two groups.

2. Psychological tests

1) Self-rating depression scale

Table 1 shows the psychological test scores. Eleven of the 16 patients had depressive symptoms, while the others did not. Depressive symptoms were not always present.

2) State-trait anxiety inventory

Twelve of the 16 patients tended to be anxious on both STAI-1 and STAI-2. There was one patient who showed only STAI-2 (Table 1).

3. Near-infrared spectroscopy measurement

1) Comparison of waveforms in 13, 14, and 16 channels

Figure 5 shows an example of the waveforms of a patient and control. The patient showed a smaller overall activation and less change in oxy-Hb compared to the control. On the other hand, the control showed a larger and clearer overall activation, and the oxy-Hb was highly variable. The waveforms of some patients are shown in Figure 6. Although there were individual differences in the height of the waveforms in channels 13, 14, and 16, the patient group tended to have less oxy-Hb activation and less change than the control group.

2) Comparison of integral values, centroid values, and initial activations

In channels 13 and 14, the integral value was significantly lower in the patients than in the controls. There were no significant differences in the centroid value and initial activation between the two groups (Fig. 7). These values of channel 14 varied a similar distribution to those of channel 13, and the significant differences were also similar (Fig. 8).

In channel 16, integral and initial activation values were significantly lower in the patients than in the controls. There was no significant difference in the centroid value between the two groups (Fig. 9).

Discussion

This study aimed to investigate whether near-infrared spectroscopy (NIRS) can be used as one of the diagnostic criteria to objectively identify the psychological characteristics of halitosis patients. As a result, no significant difference was observed with the VSC. The psychological tests showed that patients with halitosis tended to be depressed and anxious. The integral values on the NIRS were significantly lower in the patient group, indicating a waveform pattern was consistent with depressive states. The NIRS data showed that patients had depressive states even when no depressive symptoms were shown on psychological testing.

The patients' VSC concentrations were lower than the median for all three types (Fig. 4). The results revealed that the VSCs were not almost the cause of the halitosis.

Patients with halitosis are so concerned about their halitosis that they cannot communicate well with others, and their social activities are reduced, thus affecting their interpersonal relationships (43). Although the significant intergroup differences were not evident, the controls showed larger VSC values than patients. Many patients may have been actively brushing their teeth and cleaning their tongues to control their halitosis (44).

Anxiety associated with psychological halitosis is difficult to relieve without a psychological approach (11). It was believed that patients with halitosis suffer from their problems and are easily tensed and introverted (43), making them feel anxious; these psychological factors may lead to depressive symptoms. Depression and anxiety are reported to be significantly associated with halitosis (4). The findings of the previous study and the psychological test results of the present study are mostly consistent. However, two patients had both SDS and STAI below reference values (Patient 9, 10 in Table 1). Patients who do not show depressive or anxiety tendencies on psychological testing cannot be diagnosed objectively. Therefore, it was examined whether the application of NIRS in the diagnosis of halitosis patients and the results would help us understand the psychological characteristics of the patients, moreover, provide objective diagnosis.

The parameters used in the NIRS measurements were described as follows: The integral value is the area in the task that indicates the amount of brain activity response. The centroid value indicates the timing of brain activation. The initial activation is the slope of the

waveform in the first 5 s of the task and indicates the response speed (45).

Integral values were significantly lower in the patient group for channels 13, 14, and 16 in the present study. Psychological tests have shown that patients with halitosis tend to have depressive states. In addition, because depressed patients generally show impaired left dorsolateral prefrontal cortex function (39), it was considered that the function of this region of the brain was significantly lower in patients than in controls.

The initial activation was significantly different for channel 16. Patients tended to have both slightly slower slope and speed of response as compared to controls. Functional brain imaging findings in individuals with depressive tendencies have consistently reported dysfunction of the brain's prefrontal region, which consists of the dorsolateral prefrontal cortex, orbitofrontal cortex, and medial prefrontal cortex (46). These effects may be partly responsible for the differences between patients and controls. The patients are suspected prone to anxiety and live with various stresses in their interpersonal and social lives, and this effect may be reflected in the prefrontal cortex (47).

Previous psychological testing results have shown that depressive and anxiety tendencies are not always present in all patients. A comparison of psychological test results and NIRS measurements showed that five of the 16 patients with a score <40, who were not considered depressed by the psychological test results (patients 4, 6, 7, 9, and 10 in table 1), showed attenuated activation and small changes in oxy-Hb. If the waveforms of these 5

patients were evaluated based on the pattern classification, they would have shown depressive states (patients 4 and 10 in Fig. 6). If the psychological test results are reflected in NIRS, they would have shown the same pattern of clear activation and large changes in oxy-Hb as that of the controls. However, the NIRS investigation indicated that these 5 patients had depressive states, which the psychological test results did not reflect the same.

These findings suggest that NIRS can provide a highly objective diagnosis that complements the results of psychological testing.

Although the NIRS parameters significantly differed between the patient and control groups, in the control group, individual variations that included those in the patient group were noted (Figs. 7-9). In order to establish diagnostic criteria, it is necessary to increase the number of participants as well as investigate the relationships between channels and analyze more channels. By doing so, it hopes to further increase objectivity.

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Conflicts of Interest

The author have no conflicts of interest to declare.

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Figure legends

Fig. 1. Position of the NIRS channel

The number indicates the channel. In this study, it was focused on that the 13, 14 and 16 channels shown in white letters.

Fig. 2. Schematic diagram of the verbal fluency task

Repeat this process five times.

The top figure shows the task's schema, and the bottom figure shows the NIRS waveform for the task.

Fig. 3. Frontal lobe function in psychiatric disorders as captured by NIRS (schematic diagram)

This figure was cited from the following reference; Ohtani T, Takahashi K, et al. Near-infrared spectroscopy as an auxiliary tool for differential diagnosis of mental disorder. Current Review of Clinical Pathology, 151: 95-102, 2014. (Reference number 42)

Fig. 4. Scatterplot of VSC concentrations

n=16 for both controls and patients. Mann-Whitney U; no significant

difference.

Bold lines indicate a reference value.

Fig. 5. An example of a patient's and control's waveform in channels 13, 14 and 16.

The patient number is shown in Table 1.

Fig. 6. NIRS waveform patterns in three patients. Patients 4 and 10 had no depressive symptoms in the psychological test results, and patient 11 had depressive symptoms.

Patient number is shown in Table 1.

Fig. 7. Scatterplot of the integral value, centroid value, and initial activation in channel 13

n=16 for both controls and patients. Mann-Whitney U *$p < 0.05$

Fig. 8. Scatterplot of the integral value, centroid value, and initial activation in channel 14

n=16 for both controls and patients. Mann-Whitney U *$p < 0.05$

Fig. 9. Scatterplot of the integral value, centroid value, and initial activation in channel 16

n=16 for both controls and patients. Mann-Whitney U *$p < 0.05$

Table and Figure

Table 1. Psychological test results

Patient	SDS (points)	STAI-1 (points)	STAI-2 (points)
1	42 ↑	48 ↑	63 ↑
2	50 ↑	57 ↑	63 ↑
3	56 ↑	60 ↑	58 ↑
4	31	60 ↑	52 ↑
5	51 ↑	64 ↑	54 ↑
6	38	61 ↑	53 ↑
7	31	58 ↑	48 ↑
8	44 ↑	40	62 ↑
9	31	36	38
10	38	38	41
11	45 ↑	61 ↑	50 ↑
12	40 ↑	40	40
13	57 ↑	67 ↑	62 ↑
14	50 ↑	51 ↑	53 ↑
15	40 ↑	45 ↑	46 ↑
16	43 ↑	49 ↑	46 ↑
Reference value	40	42	45

All of them were judged to be depressed or anxious if they were above the reference values.
The up arrow indicates a value higher than the reference value.

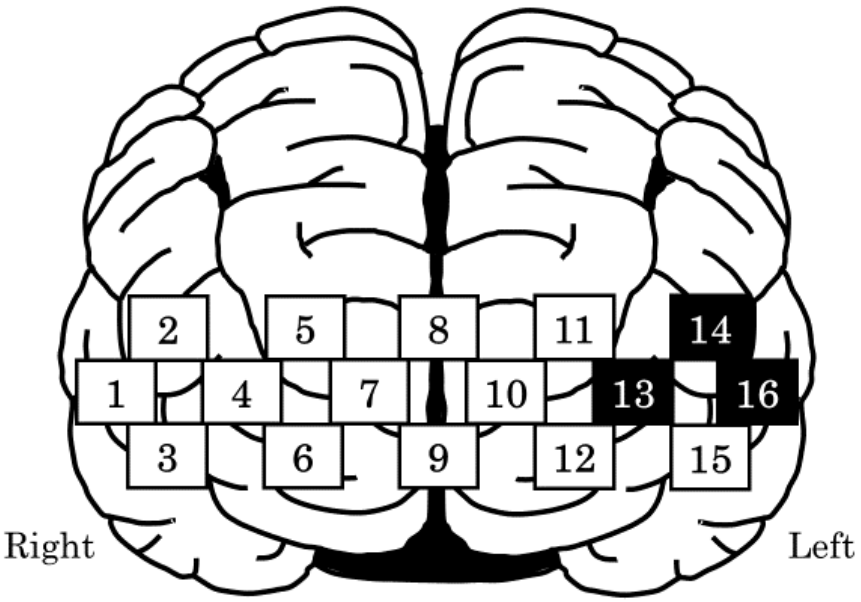


Fig. 1

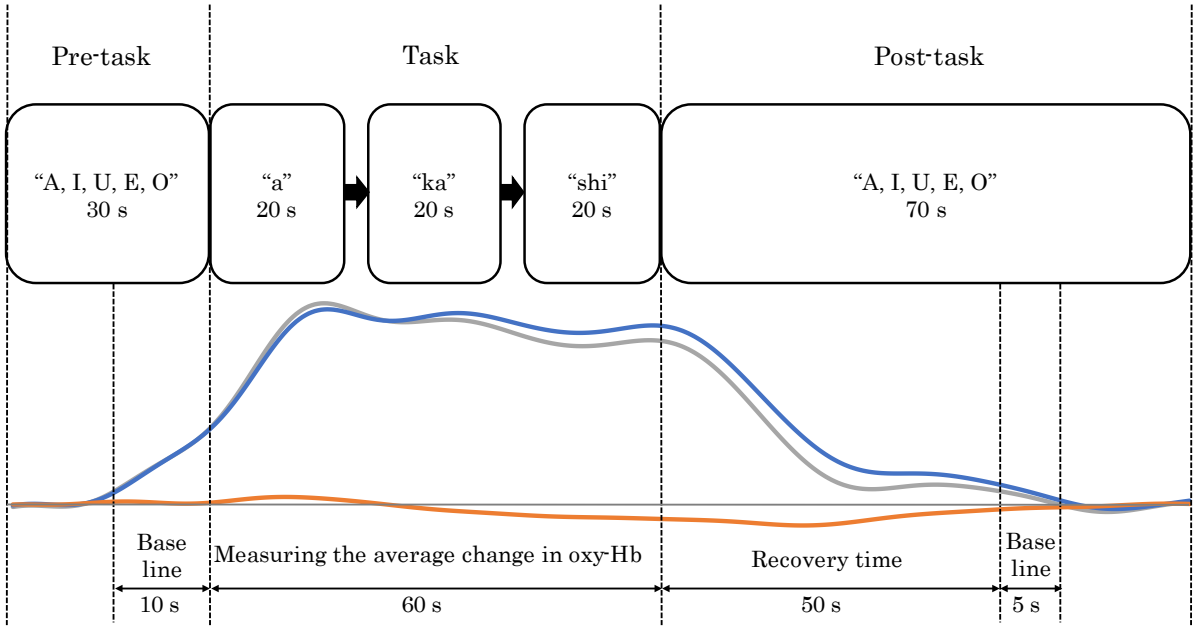

Pre-task
Task
Post-task
“A, I, U, E, O”
30 s
“a”
20 s
“ka”
20 s
“shi”
20 s
“A, I, U, E, O”
70 s
Base line
10 s
Measuring the average change in oxy-Hb
60 s
Recovery time
50 s
Base line
5 s

Fig. 2

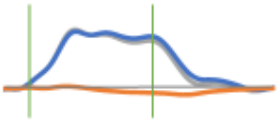
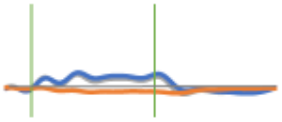
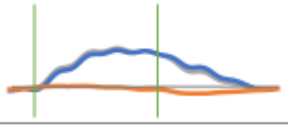
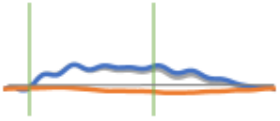
	NIRS waveforms	Activation reactive
Healthy subject		Clarity
Depression		Decay
Bipolar disorder		Delay
Schizophrenia		Inefficiency

Fig. 3

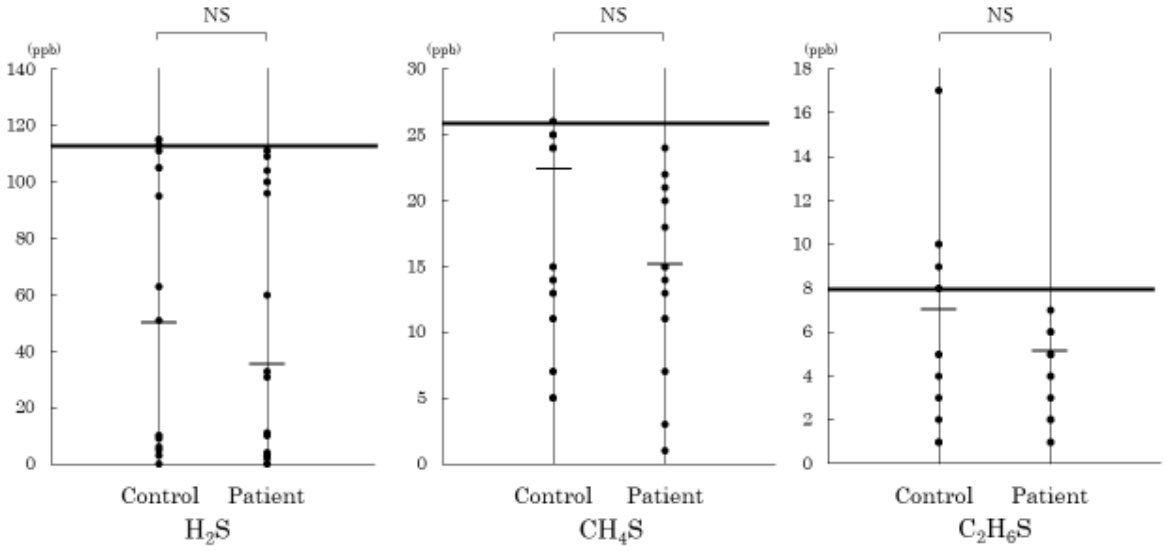

NS
(ppb)
140
120
100
80
60
40
20
0
Control
Patient
H_2S
NS
(ppb)
30
25
20
15
10
5
0
Control
Patient
CH_4S
NS
(ppb)
18
16
14
12
10
8
6
4
2
0
Control
Patient
C_2H_6S

Fig. 4

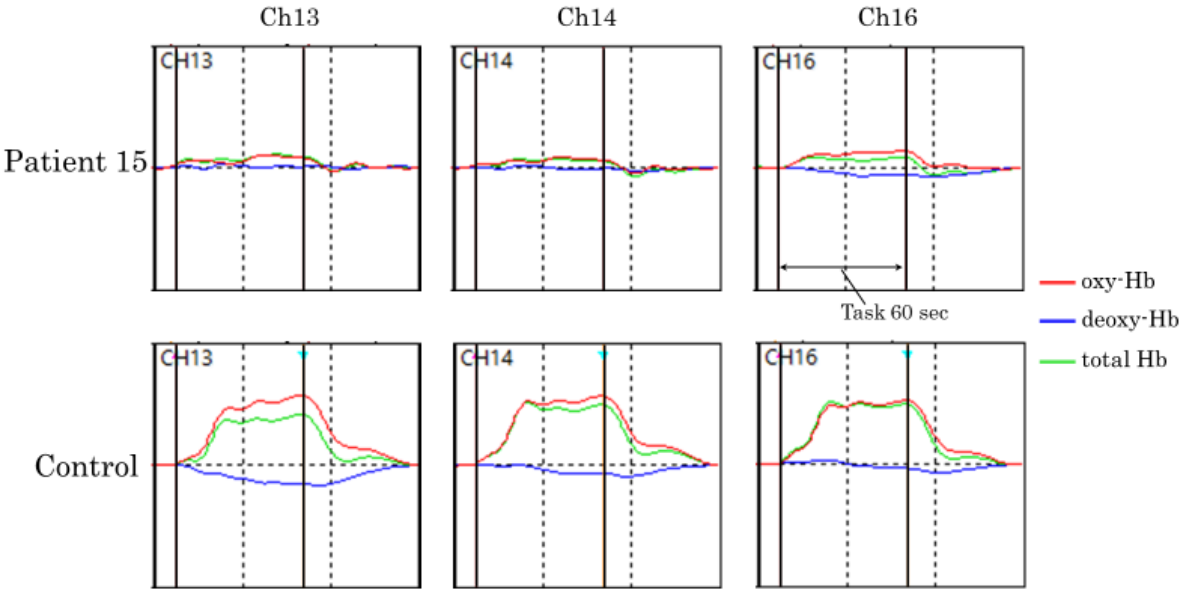

Ch13
Ch14
Ch16
Patient 15
Control
CH13
CH14
CH16
Task 60 sec
oxy-Hb
deoxy-Hb
total Hb

Fig. 5

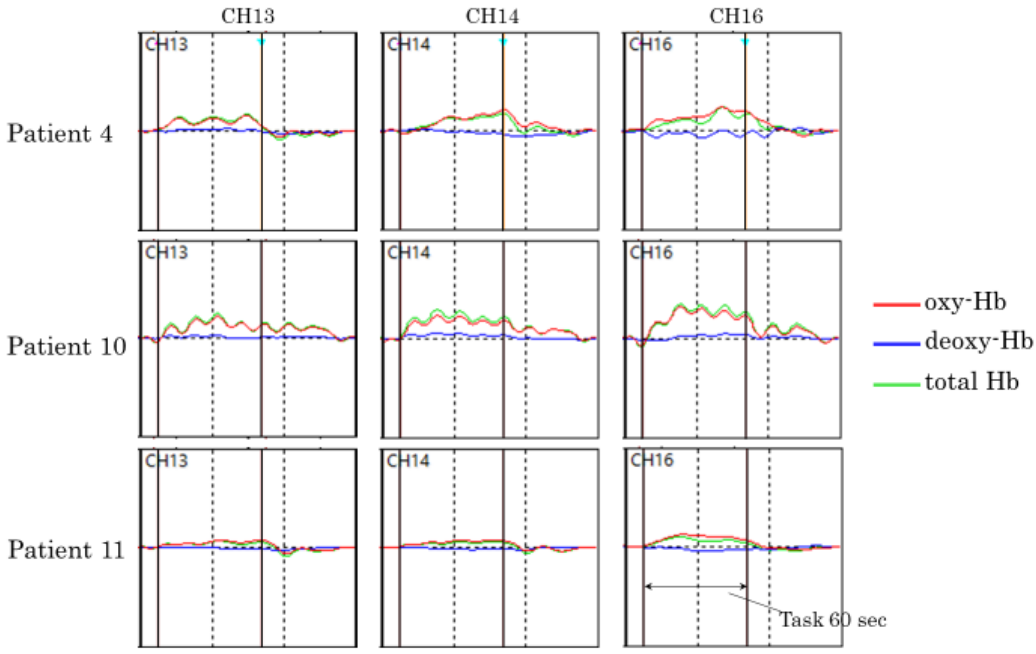

CH13
CH14
CH16
Patient 4
Patient 10
Patient 11
oxy-Hb
deoxy-Hb
total Hb
Task 60 sec

Fig. 6

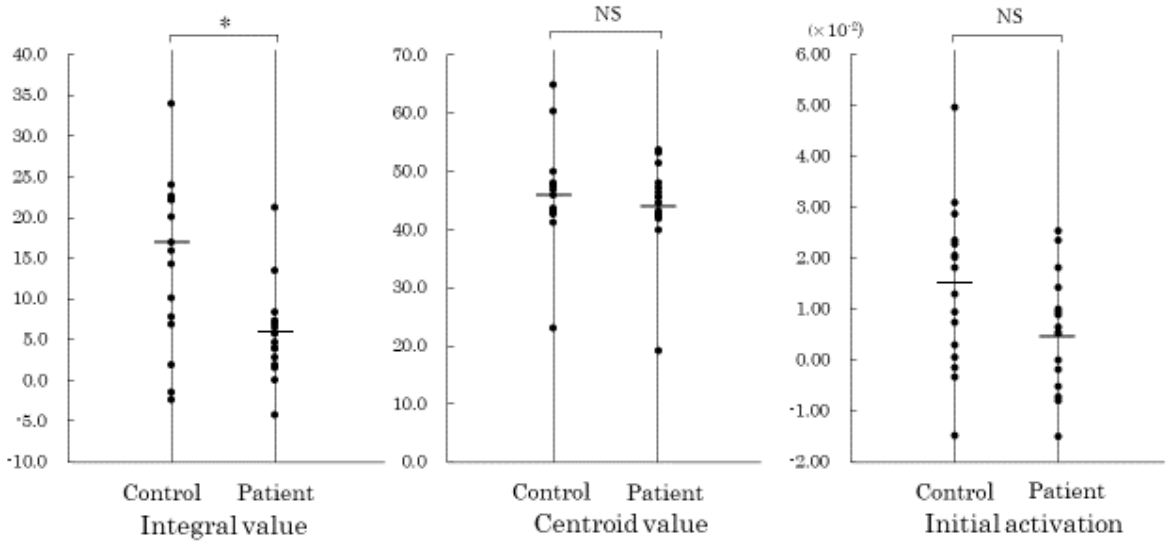

*
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
-10.0
Control
Patient
Integral value
NS
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Control
Patient
Centroid value
NS
(×10⁻²)
6.00
5.00
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
Control
Patient
Initial activation

Fig. 7

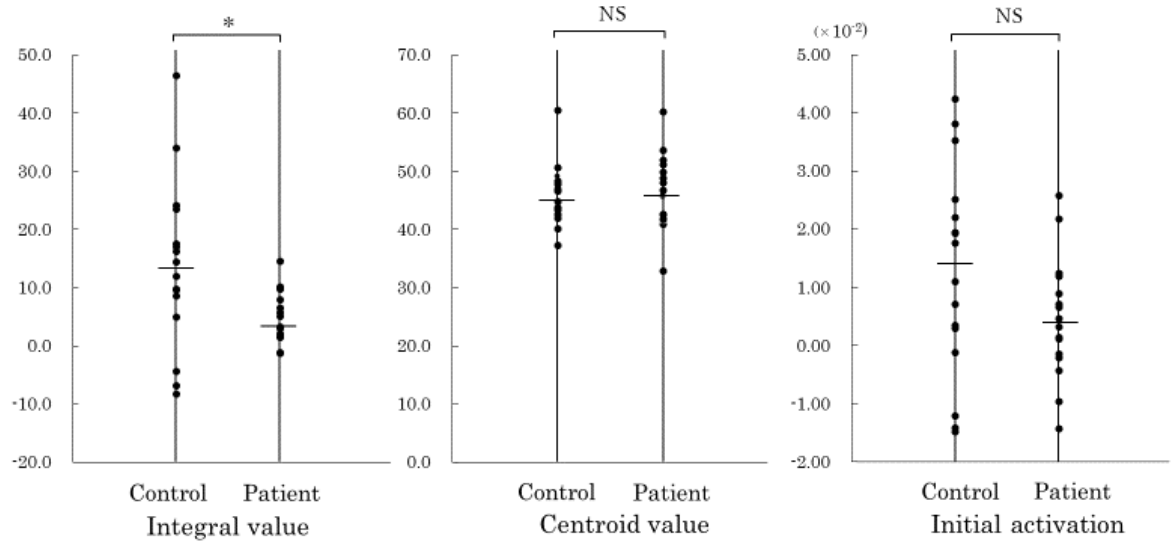

*
50.0
40.0
30.0
20.0
10.0
0.0
-10.0
-20.0
Control
Patient
Integral value
NS
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Control
Patient
Centroid value
(×10-2)
NS
5.00
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
Control
Patient
Initial activation

Fig. 8

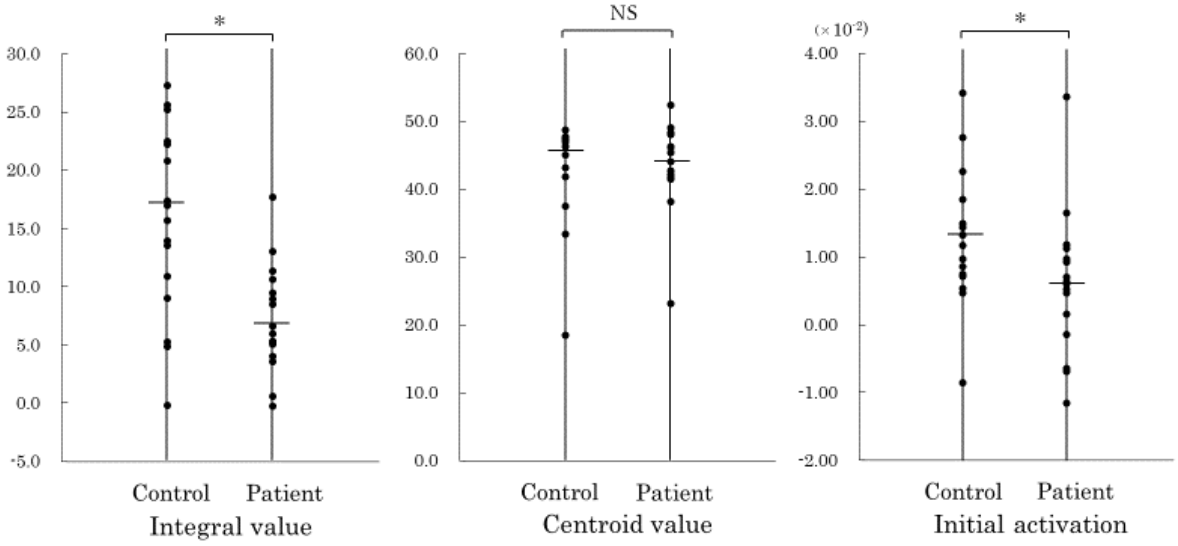

*
30.0
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
Control
Patient
Integral value
NS
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Control
Patient
Centroid value
(×10-2)
*
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
Control
Patient
Initial activation

Fig. 9