**Regular Article**

Characteristics of oxygenated hemoglobin concentration change during pleasant and unpleasant image-recall tasks in patients with depression: Comparison with healthy subjects

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**Aim:** Patients with major depressive disorder (MDD) have been reported to show cognitive impairment in attention, cognition control, and motivation. The prefrontal cortex plays an important role in the pathophysiology of depression. Neurophysiological abnormalities have been examined in MDD patients by several neuroimaging studies. However, the underlying neural mechanism is still unclear. We evaluated brain function during pleasant and unpleasant image-recall tasks using multichannel near-infrared spectroscopy (NIRS) in MDD patients.

**Methods:** The subjects were 25 MDD patients and 25 age- and sex-matched healthy controls. Patients were classified according to DSM-IV-TR criteria. We measured the oxygenated hemoglobin concentration change (δoxyHb) in the forehead and temporal lobe during image-recall task with pleasant (e.g., puppy) and unpleasant (e.g., snake) images using NIRS. To check whether all subjects understood the task, they were asked to draw pictures of both image tasks after NIRS measurement.

**Results:** The δoxyHb in the healthy group was significantly higher than that in the MDD group in the bilateral frontal region during the unpleasant condition. A significant negative correlation between the Hamilton Rating Scale for Depression score and δoxyHb was observed in the left frontal region during the unpleasant condition.

**Conclusion:** We suggest that image-recall tasks related to emotion measured by NIRS might be a visually useful psychophysiological marker to understand the decrease in the frontal lobe function in MDD patients. In particular, we suggest that the decrease in δoxyHb in the left frontal lobe is related to the severity of depression.

**Key words:** depression, emotion-inducing task, near-infrared spectroscopy, neuroimaging in psychiatry, pleasant and unpleasant.

**M**AJOR DEPRESSIVE DISORDER (MDD) is a common psychiatric disorder with a lifetime prevalence of 6% and a frequency of 2.9% at 12 months according to a study conducted by the World Health Organization in Japan.1 Also, as a diagnostic criterion for patients, symptoms such as a depressed mood and a loss of interest and joy are usually mentioned based on diagnostic criteria such as the ICD-102 and the DSM-5.3 In addition, it is clinically well known that depressed patients show pessimistic thinking. However, disorders of cognitive function are suggested in depressed patients, such as in the depression cognitive theory advocated by Beck, and it is thought that emotional cognition and

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impairment of social cognition also affect individual participation in society. Accordingly, several studies on brain function in depressed patients using modalities such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have reported a decrease in blood flow in the prefrontal cortex (PFC) of depressed patients, and a decrease in the activity of the cingulate cortex.

The method for understanding the pathology in depressed patients, however, has yet to be clarified and clinical assessment depends on the experience and subjectivity of clinicians. Near-infrared spectroscopy (NIRS), a relatively new neuroimaging method, was approved in Japan by the Ministry of Health, Labour and Welfare in 2009 as an advanced medicine for assisting with the diagnosis of depression. Furthermore, in 2013, NIRS received medical insurance coverage as a supplementary diagnosis. NIRS examination has been used clinically as a psychophysiological useful objective indicator reflecting cognitive function.

NIRS uses non-invasive light, and has a high temporal resolution (0.1 s) and low spatial resolution (2–3 cm); however, it can be used relatively easily to measure dynamic changes of brain function. The technique makes it possible to visually grasp such changes. Changes in the hemoglobin concentration measured by NIRS have been shown to closely correlate with the blood oxygenation level on fMRI (blood oxygenation level-dependent signal) and to be reproducible.

Under these circumstances, many previous studies using NIRS for depressed patients have shown a reduced change in the oxygenated hemoglobin concentration (OxyHb) in the frontal lobe area in general. In a previous study using NIRS, Noda et al. investigated the relation between the severity of depression and frontal lobe activation using NIRS. It was shown that the right lateral lobe had a significant negative correlation with the total score of the 21-item Hamilton Rating Scale for Depression (HAM-D). In contrast, Kameyama et al. did not identify a correlation between depression symptom severity and frontal lobe activity using NIRS in patients with bipolar disorder.

Most functional NIRS (fNIRS) studies have used verbal fluency tasks (VFT) as well as examining reactions of patients passively viewing photographs and facial expressions that could trigger their emotions as a means of activation. These tasks may not fully reflect the emotional disturbances and negative automatic thoughts that are characteristic of patients with depression. Consequently, there are still unclear aspects regarding frontal lobe dysfunction in patients with depression.

Yamawaki stated that care should be taken when interpreting brain function analysis results, and stressed the necessity of devising activation tasks and accumulating data from brain functional image analyses. Therefore, we hypothesized that it would be possible to clearly grasp the state of brain functions in depressed patients using active emotion-recognition tasks eliciting emotional disturbance in depressed patients. Also, in order to reflect negative automatic thinking of depressed patients, we conducted active image-recall tasks.

Our research objectives are summarized as follows: First, we investigated brain function in depressed patients during emotion-arousal tasks. Second, we investigated the relation between frontal lobe function and severity of depression in patients during these tasks.

**METHODS**

**Subjects**

The subjects were 25 MDD patients and 25 healthy volunteers matched for age, sex, and premorbid IQ. Premorbid IQ was estimated using the Japanese version of the National Adult Reading Test.

All subjects were right-handed according to the Edinburgh Inventory and were native speakers of Japanese. All MDD subjects were outpatients of the Kurume University Hospital Department of Neuropsychiatry in Fukuoka, Japan. They were diagnosed according to the Structured Clinical Interview for DSM-IV Axis I Disorders by experienced psychiatrists. In this study, anxiety disorder was excluded using DSM-IV-TR diagnostic criteria. All subjects were medicated with antidepressants. The clinical status of all patients was evaluated by two psychiatrists. The state of depressed patients was targeted in those with moderate depression, with a mean ± SD HAM-D score of 16 ± 5.21.

The exclusion provision is assumed to have an effect on cognitive tasks, such as cerebrovascular disease, neurodegenerative disease, head trauma, electrostimulation therapy, and alcohol/substance abuse and dependence in all groups. Each profile is shown in Table 1.

A written explanation of this study was given to all subjects prior to the investigation, and all
Measurement

Cerebral blood flow was measured by a multichannel NIRS device (ETG-4000; Hitachi, Tokyo, Japan). OxyHb changes were calculated from the difference in absorbance based on the modified Beer–Lambert law. The middle point of the transmitting–receiving probe pair was defined as a channel. A total of 44 channels, 22 channels on both the left and right, were collectively monitored as a recording unit at a sampling frequency of 10 Hz. The distance between the irradiation part and light-receiving part was set at 3 cm, and the optical fibers were arranged in three rows vertically and five rows horizontally so that the channel in the front lower row closely matched the T3-FPZ-T4 line of the International 10–20 electroencephalography method.22 In previous studies based on the assessment of multiple examinations, it was possible to roughly estimate the measurement site of the brain surface by mapping the site on the scalp in this way.23,24 In addition, Shoji et al. identified channel (CH) 3 as a motor field by pinching the fingers with the same probe arrangement, and it is considered that CH 6, 10, 11, and 15 on both sides exit the dorsolateral PFC and CH 14 and 19 exit the frontal pole region.25,26 Figure 1a shows the actual mounting arrangement.

The measurement environment was a quiet, dim room, and the subjects were seated. In order to minimize the influence of motion, the jaw was lightly fixed. In addition, participants were instructed to minimize strong biting, eye blinking, and head movements. Further, the NIRS machine was placed behind the subject to maintain concentration on examination during the tasks by avoiding the influence of the NIRS machine and inspector (Fig. 1b,c).

Task design

Generally, we presented photographs in advance that engender pleasant feelings and pictures that cause unpleasant feelings, including those of snakes and spiders (Fig. 1d).27 We confirmed orally whether each image engendered pleasant or unpleasant feelings, and selected five out of six photos that the subjects had to remember. In order to investigate the influence of emotion, during the baseline task, subjects were instructed to recall the image of the basic figure (full circle) for 50 s, and during the emotion-related image task subjects were instructed to recall the preceding presented image after receiving a cue from the examiner for 20 s. During execution, control and task sessions were alternately repeated five times in succession, and the two conditions of pleasant and unpleasant images were applied, respectively (Fig. 1e). Furthermore, in order to confirm whether it was actually possible to imagine the contents of the tasks, after having completed the tasks, the contents remembered by the subject were drawn by hand and confirmed.

Data processing

For the data obtained by NIRS, integral analysis was performed in which base correcting processing by fitting data is extracted for each task section, a fitting line is drawn using the least squares method for pre- and post-sections, and then, changes in the hemoglobin concentration accompanying the task are corrected as changes from the fitting line, displayed as an average addition waveform. Next, an averaged waveform for five oxyHb concentration changes was
Figure 1. (a–c) Measurement points of 44 channels for near-infrared spectroscopy. (a) Jaw fixation in order to eliminate influence of head movement. (b) Plane view of the channels placed on the head. (c) Spatial position of the channels arranged on magnetic resonance imaging. (d,e) Measurement protocol. (d) Emotion-evoking images presented to subjects. Prior to the task, a picture was shown to induce emotions in the subject. (e) Task design. Control: Images of a simple circle (50 s). Image-recall tasks: Pleasant (unpleasant) recall during task period (20 s).
created, and an area approximation value obtained by analyzing every 100 ms was used as an analysis target.\textsuperscript{28}

Statistics
Descriptive analysis of statistical and clinical variables was performed using the Student’s \textit{t}-test except for data on the subject’s sex (\(\chi^2\)). Because the variance of the data obtained in this research was large and a normal distribution could not be assumed, we conducted tests 1–4 (listed below) using a non-parametric method. Also, because there was a possibility of selecting false-positives, correction of the significance level was carried out using the false discovery rate (FDR) method.\textsuperscript{29} In this study, the corrected significance level was set as \(\alpha_{FDR}\).

The following nonparametric tests were carried out:

1. In order to identify the channels showing a significant change in the oxyHb concentration under each condition in both healthy and MDD groups, the Wilcoxon signed rank test was conducted.

2. To examine the difference between pleasant and unpleasant conditions, the Wilcoxon test was conducted for both the healthy and MDD groups.

3. The Wilcoxon test was conducted to examine group differences in pleasant/unpleasant image tasks in the healthy and MDD groups.

4. Pearson’s moment correlation was used to investigate the relation between the severity of depression and each channel.

JMP PRO 12 (SAS Institute, Cary, NC, USA) was used for all statistical processing (\(P < 0.05\)).

RESULTS
Confirmation of image tasks
In these tasks, as we could not measure the performance, we actually asked subjects to draw after the measurement to confirm whether an image had actually been formed (Fig. 2).

We interviewed subjects regarding whether they could truly form mental images. All the subjects stated that they could do so. As shown in Figure 2, actual images could be drawn, suggesting that the subjects could understand the images presented in the task. Some patients with depression said that it was easier for them to imagine unpleasant rather than pleasant images.

NIRS waveforms during the pleasant/unpleasant image tasks (Figs 3–4)
During the pleasant image task, healthy subjects showed a significant increase in the oxyHb concentration in the bilateral frontal temporal regions (right: CH 13, 21, 22; left: CH 16, 20, 21, 22, \(q = 0.05 \alpha_{FDR} > 0.0125\)). However, in the MDD
group, there was a significant increase in the oxyHb concentration only in a part of the left frontal region (left CH 20). During the unpleasant image task, in the bilateral frontal temporal region (right: CH 12, 14–17, 18–21; left: CH 11, 13–15, 17–22, \( q = 0.05 \alpha FDR > 0.025 \)), the healthy group showed a significant increase in the oxyHb concentration; however, in patients with depression, no channel showed a significant increase in this concentration.

**Channels showing differences between conditions**

In the group of healthy subjects, there was only a significant difference in the frontal pole region (CH 19, \( P = 0.0014 \)) between the pleasant and unpleasant conditions. In the patients with depression, no channels showed a significant difference between the pleasant and unpleasant conditions.

**Areas showing a significant difference between groups (Fig. 5)**

In the pleasant image task, there was no significant difference between the healthy and MDD groups. However, in the unpleasant image task, the oxyHb concentration in the healthy group significantly increased in the bilateral frontal lobe area (right: CH 16, 19, 20; left: CH 13, 15, 19; \( P = 0.0002–0.0104 \)).

**Correlation between channels showing a difference between groups and HAM-D total score (Fig. 6)**

Regarding the correlation between the NIRS recording site and HAM-D total score, a negative
correlation was noted in a part of the left PFC (left: CH 14, 15, 19) in the unpleasant image task.

**DISCUSSION**

In previous studies using fMRI or PET, the model to explain the correlation between biased emotional process in depressed patients and the neural basis focused on increasing the activation of the anterior cingulate gyrus and amygdala. Furthermore, previous studies have focused on the reduction of activation of the striatum-anterolateral PFC. However, fMRI and PET are costly, require physical restraint, and subjects suffer with pain. In these studies, there were many reports of passive stimuli from facial expressions in photographs presented and pictures that induce emotions. Therefore, we considered that the characteristics of the emotional process in depressed patients may not be sufficiently reflected. Therefore, in this study, we assessed changes in δoxyHb in the brain blood during active pleasant/unpleasant image-recall tasks in healthy subjects and depressed patients using NIRS with minimal physical restraint. We compared the activation sites of the brain. Then, we aimed to clarify the characteristics of brain activity in depressed patients and investigate the relation between depression of the frontal lobe and the severity of depression.

**NIRS waveform under pleasant/unpleasant conditions**

In the healthy subject group, the oxyHb concentration increased in the frontal temporal region in both
In order to suppress unpleasant emotions, the PFC becomes activated, and an increase in the concentration of oxyHb occurs. In patients with depression, the oxyHb concentration was slightly increased in the left temporal region in the pleasant image task, but no significant increase in the concentration of oxyHb was observed during the unpleasant image task. These results are similar to those of previous studies suggesting dysfunction of frontal lobe function in emotional control, such as a downregulation to the amygdala, with a decreased function of the frontal lobe in depressed patients.

**Figure 5.** Recording sites showing differences between healthy and major depressive disorder (MDD) groups. There was no significant difference between the conditions of the two groups, and only right CH 19 of the healthy group showed a significant difference between the pleasant and unpleasant conditions. Under the unpleasant condition, a channel showing a significant difference in both frontal regions (right CH 16, 19, 20, left CH 15, 19) was identified. Pink background: Pleasant condition. Light blue background: Unpleasant condition. Red bar: Healthy group. Blue bar: MDD group. FDR, false discovery rate.
unpleasant image tasks in the healthy subject group. In the emotional value asymmetric hypothesis advocated by Davidson, the left frontal region is involved in positive emotion and the right frontal region is involved in negative emotion. In previous NIRS studies using a VFT, there are few reports confined to the left and right functions. In this study, a significant difference was noted in the right frontal pole region in healthy subjects on performing a task related to emotion, which is partially consistent with the emotional value asymmetric hypothesis proposed by Davidson.

Recording channels showing a difference between healthy and MDD groups

We compared the channels between the healthy and MDD groups. In the pleasant image task, there was no significant difference between the groups regarding oxyHb concentration fluctuations. However, during the unpleasant image task, there was a significant difference between the groups in oxyHb concentration fluctuations in the bilateral frontal regions. Kanske et al. suggested that depressed patients showed a selective deficit in downregulating
amygdala responses to negative emotional stimuli using reappraisal.37 This downregulation of amygdala activity was strongest in participants high in habitual reappraisal use. Activity in the regulating control network, including the anterior cingulate and lateral orbitofrontal cortex, was increased during both emotion-regulation strategies. The findings in remitted patients with previous episodes of major depression suggest that altered emotion regulation is a trait-marker for depression.37 Also, Tomioka et al.38 showed no fluctuation in the oxyHb concentration of the PFC during a VFT before and after treatment with antidepressant drugs, so they also confirmed that the NIRS signal of the PFC in depressed patients is a trait marker. However, Noda et al.13 showed a negative correlation between depression severity and oxyHb concentration. Meanwhile, Milak et al.33 conducted analysis with PET and indicated a positive correlation between bilateral ventral frontal cortical metabolism and the severity of depression. Erk et al.39 studied the relation between the amygdala and PFC in the emotional control of healthy subjects and patients with depression. In the presence of severe symptoms of depression, PFC activity decreases and it is difficult to suppress the activity of the amygdala.39

Our findings suggest that in a comparison between healthy volunteers and patients with depression, the function of the frontal lobe of the MDD group had already deteriorated at the time of the negative emotional-recall task; this result is similar to those of Kanske et al.37 and Tomioka et al.38 However, when examining the correlation between the channel showing a significant difference of oxyHb concentration fluctuation and the HAM-D total score, a negative correlation was noted in the frontal lobe on the left, and the association with the disease condition was reported by Noda et al.13 and Erk et al.39 Based on these findings, it was suggested that the frontal lobe dysfunction of depressed patients may not be solely associated with trait-dependent markers, but might also be associated with a state-dependent marker.

Recording channels showing a negative correlation with HAM-D total score

As a result of examining the correlation between HAM-D total scores and each recording channel, as shown in Figure 7, a negative correlation was noted in the left frontal lobe area. In the fNIRS survey using a VFT task, Noda et al.13 reported that a negative correlation exists between oxyHb concentration fluctuation in the blood flow in the right frontal and temporal regions and HAM-D. However, in a meta-analysis study by Groenewold et al.40 using fMRI, subjects with depression showed activation of the left dorsolateral PFC on negative stimulation; on positive stimulation, the activity in the orbitofrontal cortex increased. Our results are consistent with those of Groenewold et al.,40 showing a negative correlation between the HAM-D total score of depressed patients and oxyHb concentration fluctuation of the left PFC. NIRS may be able to show the state change of depressed patients relatively easily.

Our research involved several limitations. The first was the size of samples. In this study, we reported the correlation between δoxyHb of the frontal lobe and HAM-D total score. However, since the size of samples was small, 25 cases, we could not assess the relevance to subordinate items, such as that conducted by Liu et al.,41 showing a positive correlation with anxiety. It is also necessary to examine the relation between age difference, sex difference, duration of disease, and use of therapeutic agents. All of the subjects were on medication and had an average disease duration of 1.63 years. Tomioka et al.38 and Kameyama et al.14 reported no change in the oxyHb concentration in the PFC during VFT before and after the administration of drugs, and that the decrease in PFC activity was a trait marker of depression. However, as in this study, it was considered that the problem related to emotion may be a pathological condition-dependent marker. Therefore, considering the duration of disease, medication period, and so forth, we think that it is necessary to investigate the temporal change in the same cases. Therefore, it is necessary to continue research to increase the size of samples in the future. The second limitation involves performance evaluation of the image-recall task. Only the performance, interview, and recall drawing were about performance. However, as there are individual differences in the ease of image recall, it may be necessary in future to more objectively confirm the extent of how pleasant or unpleasant an image is using a visual analog scale.

In this study, fluctuation of the oxyHb concentration in the frontal temporal region of healthy subjects and patients with depression was measured using fNIRS and compared and examined based on a pleasant/unpleasant emotion-inducing image.
recollection task. There was no significant difference between the healthy and MDD groups in the pleasant image task; however, in the unpleasant image task, the increase in oxyHb in the frontal lobe region was significantly less in the MDD group than in the healthy group. Regarding the correlation between HAM-D total scores and oxyHb concentration fluctuations, negative correlations were noted in the left frontal region, suggesting that this region is a disease-dependent marker. We have demonstrated the characteristics of oxyHb concentration changes on the brain surface of MDD patients using an image task related to emotion.

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DISCLOSURE STATEMENT

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Conception and design of the study: K.M. Analysis and interpretation of data: A.K., Y.I., K.M., and M.S. Collection and assembly of data: A.K., Y.I., H.Y., and S.N. Drafting of the article: A.K. Critical revision of the article for important intellectual content: Y.S. Final approval of the article: Y.S. and N.U.

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