Title

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

Short running title: Emotional perception in depression.

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The manuscript consists of 1 title page, an abstract (254 words), 21 pages of text (4,541words and 41 references), 1 table, and 7 figures (3 color figures) as a regular article, and is being submitted to Psychiatry and Clinical Neuroscience

Primary field, neurophysiology

Secondary field, neuroimaging

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

Aim

Patients with major depressive disorder (MDD) have been reported to show cognitive impairment in attention, cognition control, and motivation. The prefrontal cortex (PFC) 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 the brain function during pleasant and unpleasant image recall tasks using multi-channel 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 (δ Oxy-Hb) 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

δ Oxy-Hb 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 HAM-D score and δ Oxy-Hb, was observed in the left frontal region during the unpleasant condition.

Conclusion

We suggested 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, it was suggested that the decrease in δOxy-Hb in the left frontal lobe is related to the severity of depression.(No. 16122).

Key words

Depression, Emotion-inducing task, Near infrared spectroscopy,

Neuroimaging in Psychiatry, Pleasant and unpleasant,

Introduction

Major 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 WHO 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 ICD – 10 (2) and DSM – V (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 impairment of social cognition also affect individual participation in society. (4) Thereafter, several studies on the brain function in depressed patients using modalities such as fMRI and PET reported a decrease in blood flow in the prefrontal cortex of depressed patients, and a decrease in the activity of the cingulate cortex. (5)(6)(7)(8)

However, the method to understand the pathology in depressed patients 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 by the Ministry of Health, Labour and Welfare in 2009 as an advanced medicine for assisting with the diagnosis of depression in Japan. Furthermore, in 2013, NIRS received medical insurance coverage as a supplementary diagnosis. NIRS examination has been used clinically as a psychophysiologically useful objective indicator reflecting cognitive function.

NIRS uses non-invasive light, and has a high temporal resolution (0.1 sec) and low spatial resolution (2 to 3 cm), but it can be used relatively easily, to measure dynamic changes of brain function. The technique makes it possible to visually grasp such changes. (9)(10) Changes in the hemoglobin concentration measured by NIRS have been shown to closely correlate with the blood oxygenation level on fMRI (BOLD signal) and be reproducible. (11) (12)

Under these circumstances, many previous studies using NIRS for depressed patients showed a reduced change in the oxygenated hemoglobin concentration (δOxy-Hb) in the frontal lobe area in general. In a previous study using NIRS, Noda et al. (13) investigated the relationship between the severity of depression and frontal lobe activation using NIRS. It was shown that the right lateral lobe has a significant negative correlation with the total score of the Hamilton Rating Scale for Depression (HAM-D) 21 item version. In contrast, Kameyama et al. (14) did not identify a correlation between the depression symptom severity and frontal lobe activity using NIRS in patients with bipolar disorder. There are still unclear aspects regarding frontal lobe dysfunction in patients with depression. As a reason for this, most fNIRS studies used verbal frequency task (15), as well as reaction of patients to passively photographs and facial expressions that would trigger their emotions (16, 17) as a means of activation. These tasks may not fully reflect emotional disturbances and negative automatic thoughts that are characteristics of 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. (18) Therefore, we hypothesized that it is 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.

To summarize the research objectives: firstly, to investigate the brain function in depressed patients during emotion arousal tasks. Secondly, to investigate the relationship between the frontal lobe function and severity of depression in patients during these tasks.

Methods

Subjects

The subjects were 25 patients with MDD and 25 healthy volunteers matched for age, sex, and the premorbid intelligence quotient (IQ). The premorbid IQ was estimated using the Japanese version of the National Adult Reading Test. (19)

All subjects were right-handed according to the Edinburgh Inventory (20) 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 the Diagnostic Statistical Manual of Mental Disorders, 4th edition (DSM-Ⅳ) Axis I Disorders (SCID- I) (21) 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 2 psychiatrists using HAM-D. The state of depressed patients was targeted in those with moderate depression, with an average 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 provided informed consent. This study was performed with the approval of the Ethical Committee of Kurume University.

Measurement

Cerebral blood flow was measured by a multichannel NIRS device (ETG-4000; Hitachi, Tokyo, Japan). Oxy-Hb 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 ㎐. The distance between the irradiation part and light receiving part was set at 3 ㎝, And the optical fibers were arranged in 3 rows vertically and 5 rows horizontally so that the channel in the front lower row closely matched the T3-FPZ-T4 line of the international 10-20 EEG 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 identified channel 3 as a motor field by pinching the fingers with the same probe arrangement, and it is considered that channels 6, 10, 11, and 15 on both sides exit the dorsolateral prefrontal cortex and channels 14 and 19 exit the frontal pole region. (25) (26) Figure 1 shows the actual mounting arrangement. (**Fig. 1-1 A**).

The measurement environment was a quiet and dimly 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. 1-1 B, 1-1 C**)

Task design

Generally, we presented photographs in advance that engender pleasant feelings (**Fig. 1-2 D**) and pictures that cause unpleasant feelings, including those of snakes and spiders (**Fig. 1-2 D**). (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 seconds, 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 seconds.

During execution, control and task sessions were alternately repeated five times in succession, and the two conditions of pleasant and unpleasant images were respectively applied. **(Fig. 1-2 E)** 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 Hb concentration accompanying the task are corrected as changes from the fitting line, displayed as an average addition waveform, Next, an averaged waveform for 5 Oxy-Hb concentration changes was created, and an area approximation value obtained by analyzing every 100 ms was used as an analysis target. (28)

Statistics

Descriptive analysis of statistical and clinical variables was performed using Student's t-test except for data on the sex (chi-square). Because the variance of the data obtained in this research was large and a normal distribution could not be assumed, we conducted the following tests, ① to ④, using a nonparametric method. Also, because there is a possibility of selecting false-positives, correction of the significance level was carried out using the False Discovery Rate (FDR) method. (29) In this study, the corrected significance level was set as α FDR.

① In order to identify the channels showing a significant change in the Oxy-Hb concentration under each condition in both healthy and depressed 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 healthy and depressed groups.

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

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

JMP PRO 12 (SAS Institute, INC) was used for all statistical processing. ($p<0.05$)

Results

Confirmation of image tasks

In these tasks, since 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 **Fig. 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 (**Fig. 3-1, 3-2**)

During the pleasant image task, healthy subjects showed a significant increase in the Oxy-Hb concentration in the bilateral frontal temporal regions (right : CH 13, 21,22; left : CH 16,20,21,22, q=0.05 α FDR>0.0125). However, in the depressed group, there was a significant increase in the Oxy-Hb concentration only in a part of the left frontal region (left CH20). During the unpleasant image task, in the bilateral frontal temporal region (right side: CH12,14-17,18-21; left: CH11,13-15,17-22,q=0.05 α FDR>0.025), the healthy group showed a significant increase in the Oxy-Hb 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 (CH19, p=0.0014) between pleasant and unpleasant conditions. In the patients with depression, no channels showed a significant difference between pleasant and unpleasant conditions.

Areas showing a significant difference between groups **(Fig. 4)**.

In the pleasant image task, there was no significant difference between the healthy and depressed groups. However, in the unpleasant image task, the Oxy-Hb concentration in the healthy group significantly increased in the bilateral frontal lobe area (right: CH16,19, 20; left: CH13,15,19) (p=0.0002~0.0104).

The correlation between channels showing a difference between groups and HAM-D total score **(Fig. 5)**

Regarding the correlation between the NIRS recording site and HAM-D total score, a negative correlation was noted in a part of the left prefrontal cortex (left: CH14,15,19) in the unpleasant image task.

Discussion

In a previous study 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. (30) (31) Furthermore, it focused on the reduction of activation of the striatum-anterolateral prefrontal cortex. 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 δOxy-Hb in the brain blood during active pleasure / 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 relationship between depression of the frontal lobe and the severity of depression.

NIRS waveform under pleasant / unpleasant conditions

In the healthy subject group, the Oxy-Hb concentration increased in the frontal temporal region in both the pleasant image and unpleasant image tasks. This is in agreement with the fMRI study results of cognitive emotional regulation in humans by Delgad et al. (32) In order to suppress unpleasant emotions, the prefrontal cortex becomes activated, and an increase in the concentration of Oxy-Hb occurs. In patients with depression, the Oxy-Hb concentration was slightly increased in the left temporal region in the pleasant image task, but no significant increase in the concentration of Oxy-Hb was observed during the unpleasant image task. These results are similar to those of previous studies suggesting dysfunction of the frontal lobe function in emotional control, such as a down regulation to the amygdala, with a decreased function of the frontal lobe in depressed patients. (33) (34) (35)

Recording channels showing a difference between pleasant and unpleasant conditions in the healthy subjects

Only one channel in the right frontal pole region (CH19) showed a difference between unpleasant image tasks in healthy subject group. In the emotional value asymmetric hypothesis advocated by Davidson (36) the left frontal region is involved in positive emotion and the right frontal region is involved in negative emotion. In NIRS studies that used the previous VFT as a task, 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 et al.

Recording channels showing a difference between healthy and depressed groups

We compared the channels between healthy and depressed groups. In the pleasant image task, there was no significant difference between the groups regarding Oxy-Hb concentration fluctuations. However, during the unpleasant image task, there was a significant difference between the groups in Oxy-Hb concentration fluctuations in bilateral frontal regions. Kanske et al. suggested it, depressed patients showed a selective deficit in down-regulating amygdala responses to negative emotional stimuli using reappraisal. This down-regulation of amygdala activity was strongest in participants high in habitual reappraisal use. Activity in the regulating control-network including 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 Oxy-Hb concentration of the prefrontal cortex during VFT before and after treatment with antidepressant drugs, so they also confirmed that the NIRS signal of the prefrontal cortex in depressed patients is a trait marker. However, Noda et al. (13) showed a negative correlation between the depression severity and Oxy-Hb 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 relationship between the amygdala and prefrontal cortex in the emotional control of healthy subjects and patients with depression. In the presence of severe symptoms of depression, the prefrontal cortex inhibits amygdala activity. It has been reported that that cortical activity decreases.

Our findings suggest that in comparison between healthy volunteers and patients with depression, the function of the frontal lobe of the depressed group had already deteriorated at the time of the negative emotional recall task, being similar to the results of Kankake and Tomioka. However, when examining the correlation between the channel showing the significant difference of Oxy-Hb 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 and Erk et al. 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 the HAM-D total score

As a result of examining the correlation between HAM-D total scores and each recording channel, as shown in **Fig. 5**, a negative correlation was noted in the left frontal lobe area. In the fNIRS survey using the VFT task of Noda et al. (13), it was reported that a negative correlation exists between Oxy-Hb concentration fluctuation in the blood flow in the right frontal and temporal regions and HAM-D. However, in the meta-analysis study using fMRI of Groenewold et al. (20), subjects with depression showed activation of the left dorsolateral prefrontal cortex on negative stimulation; on positive stimulation, the activity in the orbitofrontal cortex increased. Our results are consistent with those of Groenewold (20) and colleagues, and the results showing the negative correlation between the HAM-D total score of depressed patients and Oxy-Hb concentration fluctuation of the left prefrontal cortex. 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 δOxy-Hb 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 conducted by Liu et al. (41), showing a positive correlation with anxiety. It is also necessary to examine the relationship 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. and Kameyama et al. （14） reported no change in the Oxy-Hb concentration in the prefrontal cortex during VFT before and after the administration of drugs, and that the decrease in the prefrontal cortex 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, etc., 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 involves performance evaluation of the image recall task. Only the performance, interview, and recall drawing were about performance. However, since there are individual differences in the ease of image recall. It may be necessary to more objectively confirm the extent of how pleasant or unpleasant it is in the future using a visual analog scale, etc.

In this study, fluctuation of the Oxy-Hb 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 image recollection task. As a result, there was no significant difference between the healthy and depressed patient groups in the pleasant image task, but there was in the unpleasant image task, in the frontal lobe region, the increase in Oxy-Hb significantly decreased in the depressed patient group. Regarding the correlation between HAM-D total scores and Oxy-Hb concentration fluctuations, negative correlations were noted in the left frontal region, suggesting that this region is a disease-dependent marker. We could demonstrate the characteristics of oxygenated hemoglobin concentration changes on the brain surface of depressed patients using an image task related to emotion.

Acknowledgments.

We thank the subjects who participated in this study. We thank Ms. Naoko Annou for preparation of the manuscript and data.

Disclosure statement

The author has no conflict of interest

Author Contributions

Conception and design of the study: Morita Kiichiro

Analysis and interpretation of data: KONDO AKIHIKO, Ishii Youhei, Morita Kiichiro, Sato Mamoru

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Drafting of the article: KONDO AKIHIKO

Critical revision of the article for important intellectual content: Shoji Yoshihisa

Final approval of the article: Shoji Yoshihisa, Uchimura Naohisa

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Figure legends

Fig. 1-1 Measurement points of 44 channels for near-infrared spectroscopy (NIRS).

Ａ: Jaw fixation in order to eliminate influence of head movement.
Ｂ: Plane view of the channel placed on the head.
Ｃ: Spatial position of the channel arranged on MRI.

Fig.1-2 Measurement protocol.
Ｄ: Emotion-evoking images presented to subjects.
Prior to the task, a picture is shown that induces emotions in the subject.
Ｅ: Task design
Control: (50 sec) Images of simple circle.
Image recall tasks: (20 sec) Pleasant (unpleasant) recall during task period.

Fig.2
In this task, we could not measure performance, and so we asked subjects to draw after measurement in order to confirm whether an image had actually been formed. The left side shows drawings by the healthy group. The right side shows those by the depressed group.

Fig.3-1 Oxy-Hb concentration fluctuation under the pleasant condition.
Fig.3-2 Oxy-Hb concentration fluctuation under the unpleasant condition.
Comparison of the average waveforms between healthy and depressed groups.
Red line: Healthy group
Blue line: Depressed group

Fig.4 Recording sites showing differences between healthy and depressed 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 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: Depressed group

Fig.5 Recording section showing a negative correlation with the HAM-D total score in a channel showing an inter-group difference. A negative correlation with the HAM-D total score was confirmed in Ch 19 and 15.

A list of supporting information
Nothing to disclose

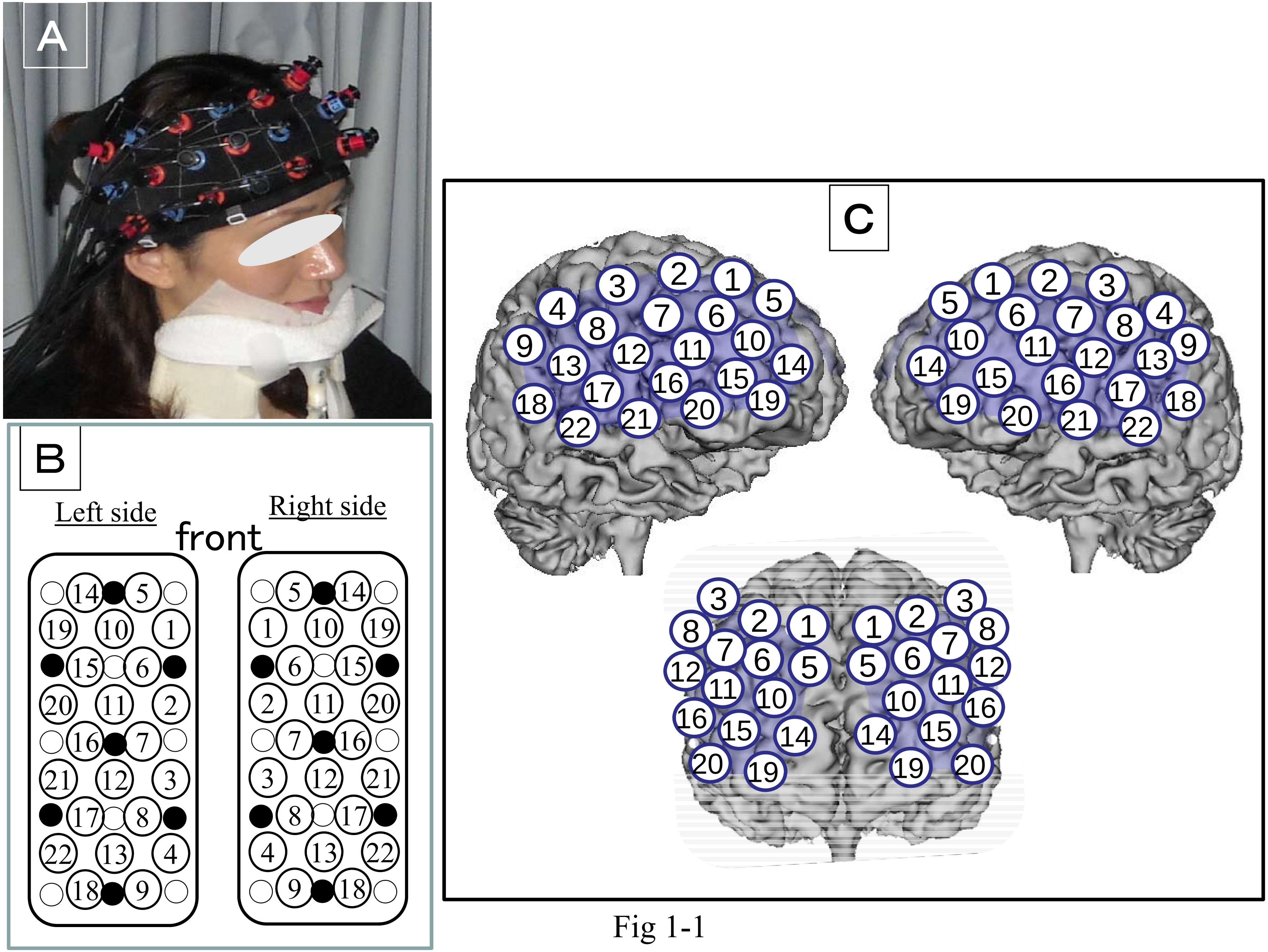
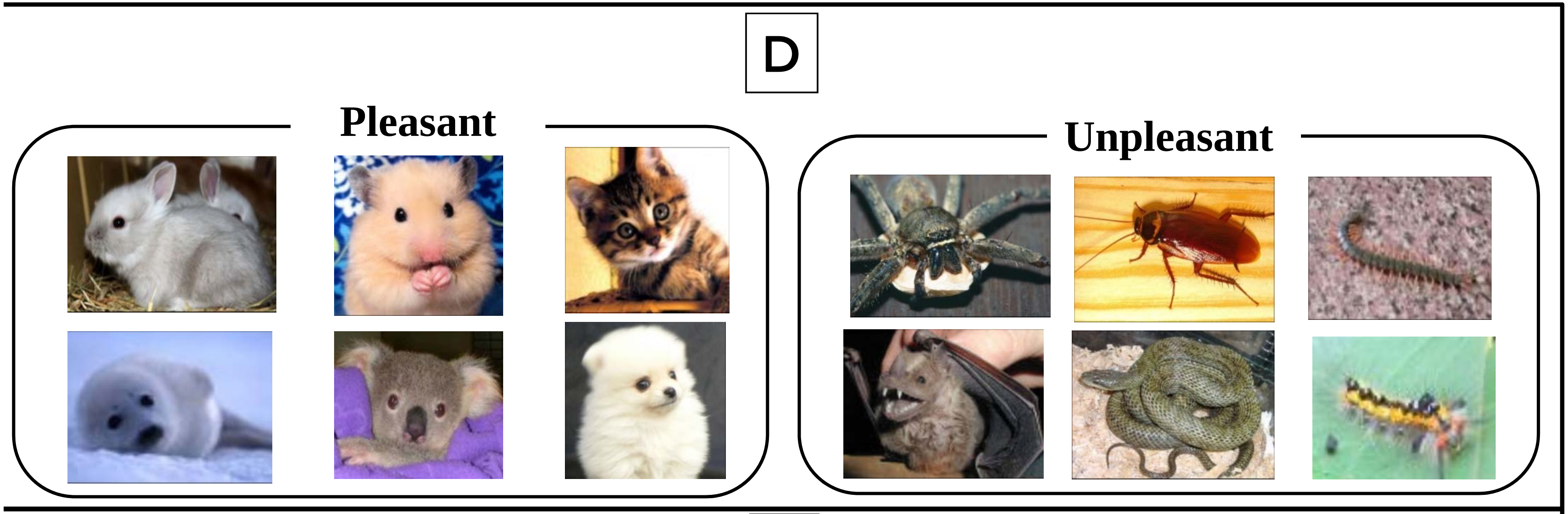


Fig 1-1

Fig ① Measurement points of 44 channels for near-infrared spectroscopy (NIRS).

Ａ; The fixed jaw in order to eliminate influence of the movement of the head.
Ｂ; The plane view of the channel placed on the head
Ｃ; Spatial position of the channel arranged on the MRI image


D
Pleasant
Unpleasant

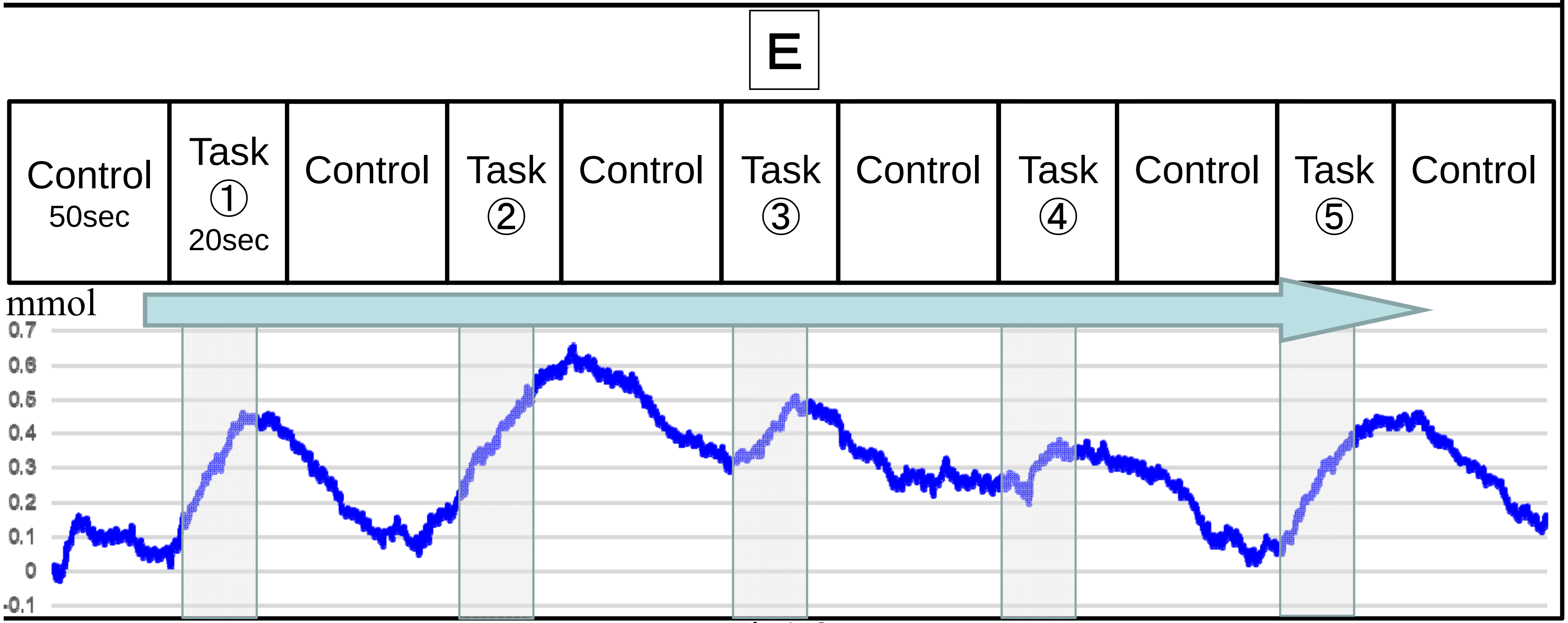

E
Control
50sec
Task
①
20sec
Control
Task
②
Control
Task
③
Control
Task
④
Control
Task
⑤
Control
mmol
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1

Fig1-2

Ｄ；Emotion-evoked photographs presented to subjects

Ｅ；Task design

Control:（50sec）:　Basic shapes images

Tasks:（20sec）:　pleasant (unpleasant) image recall tasks

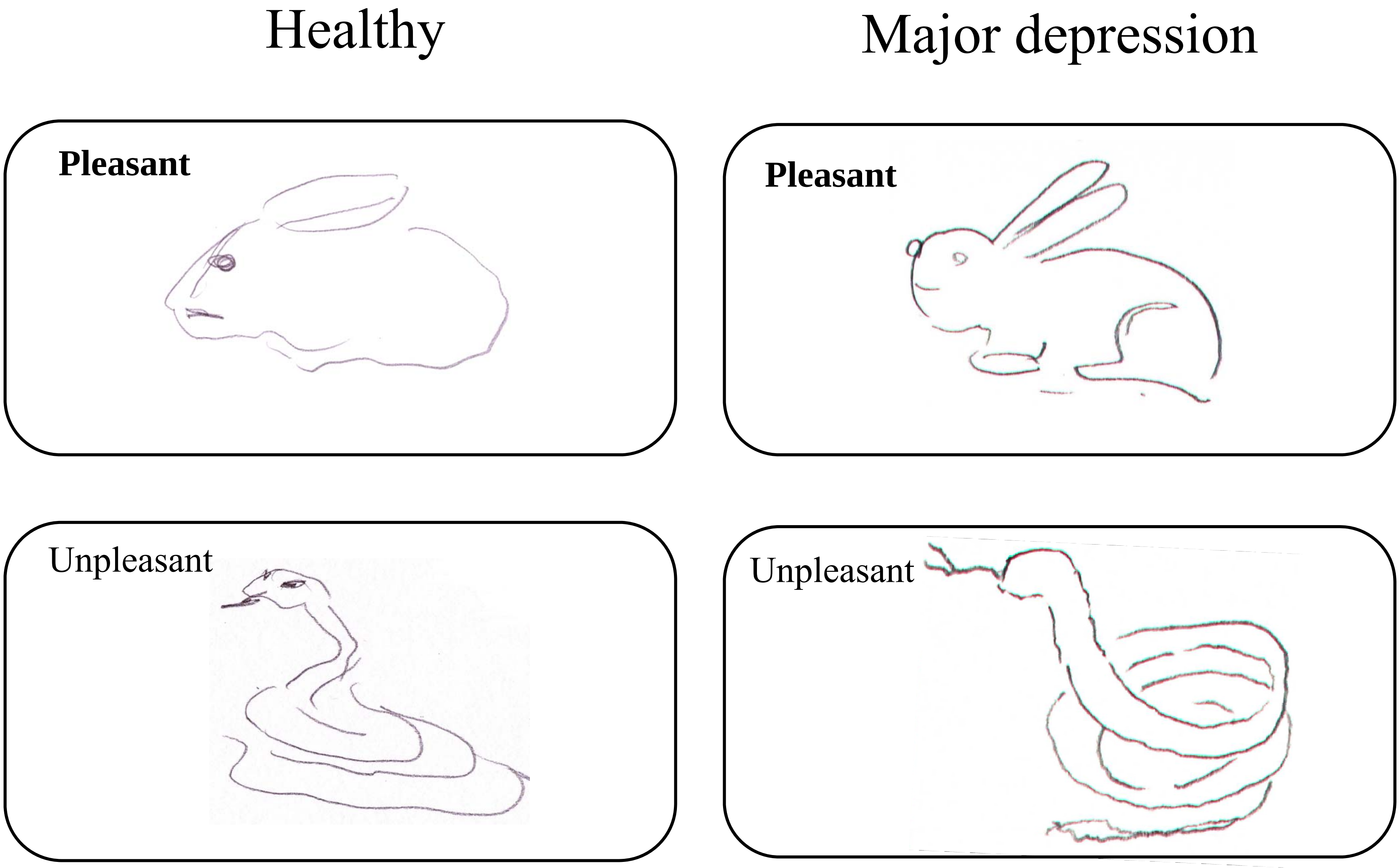

Healthy
Major depression
Pleasant
Pleasant
Unpleasant
Unpleasant

Fig2

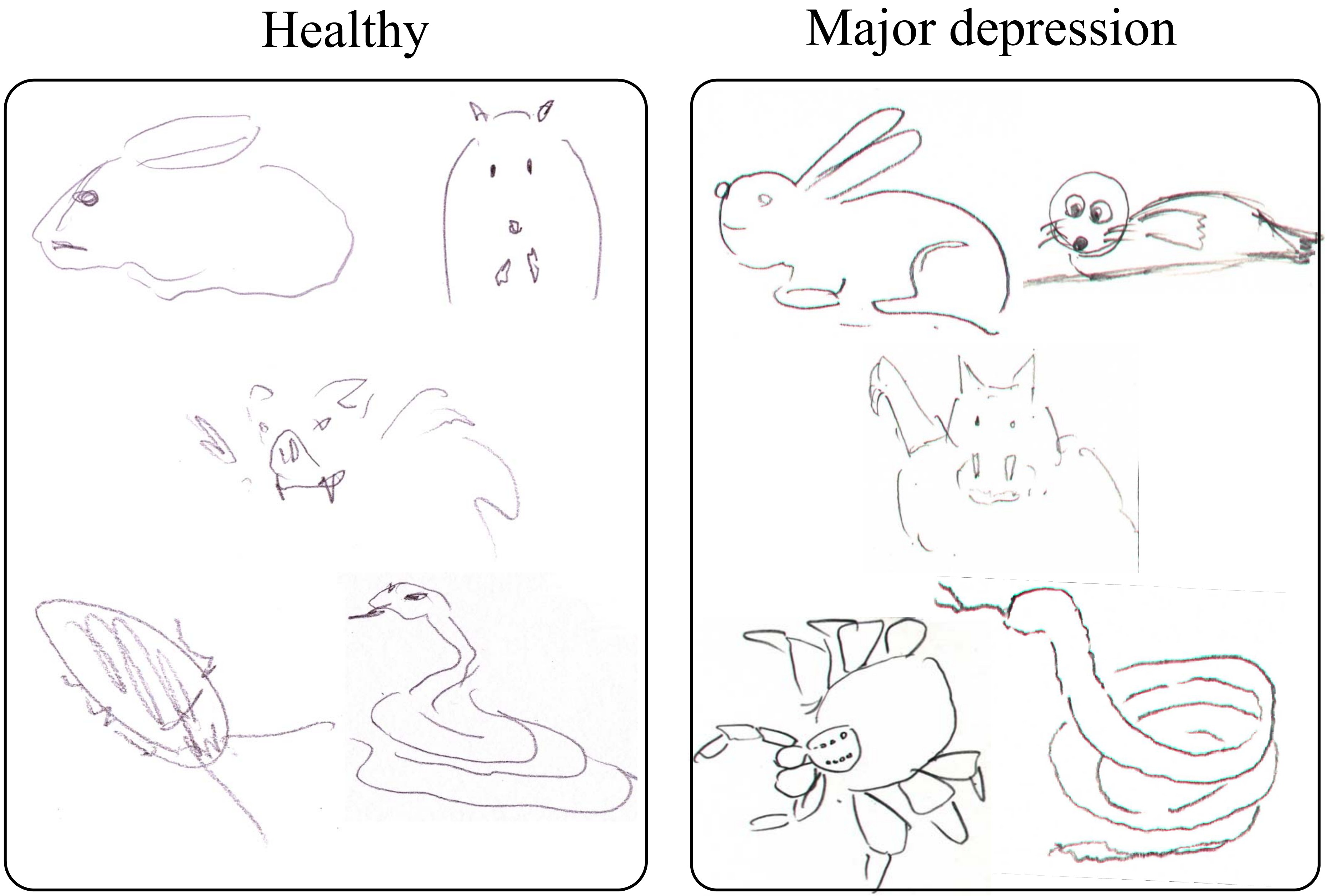


Fig 2

Fig 2

In this task, we can not measure performance, so we actually asked to draw after measurement in order to check if the image was actually formed. The left side is a part of the drawing of healthy group. The right side is depiction of depression group.

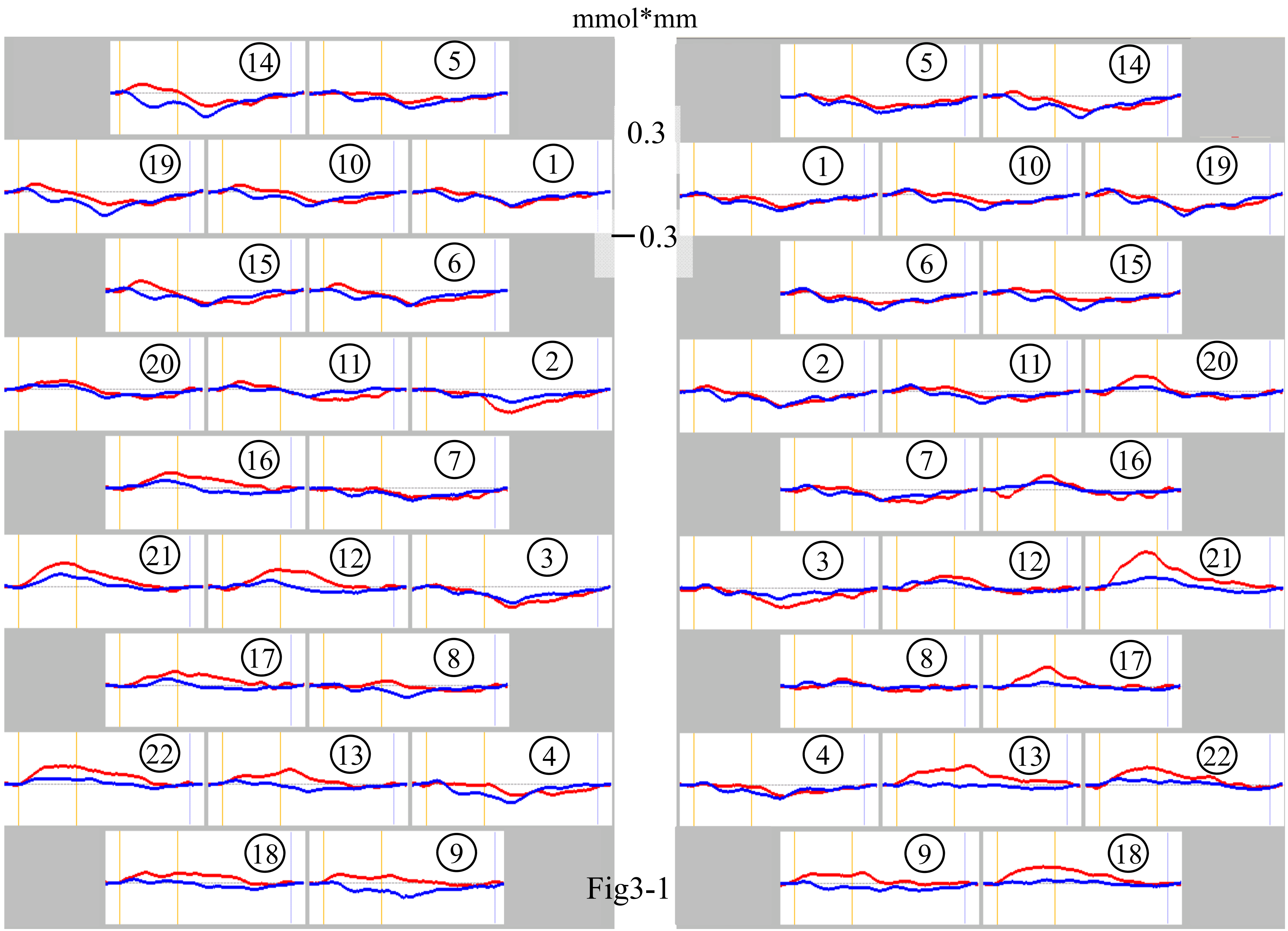

mmol*mm
0.3
−0.3
14
5
19
10
1
15
6
20
11
2
16
7
21
12
3
17
8
22
13
4
18
9
5
14
1
10
19
6
15
2
11
20
7
16
3
12
21
8
17
4
13
22
9
18

Fig3-1

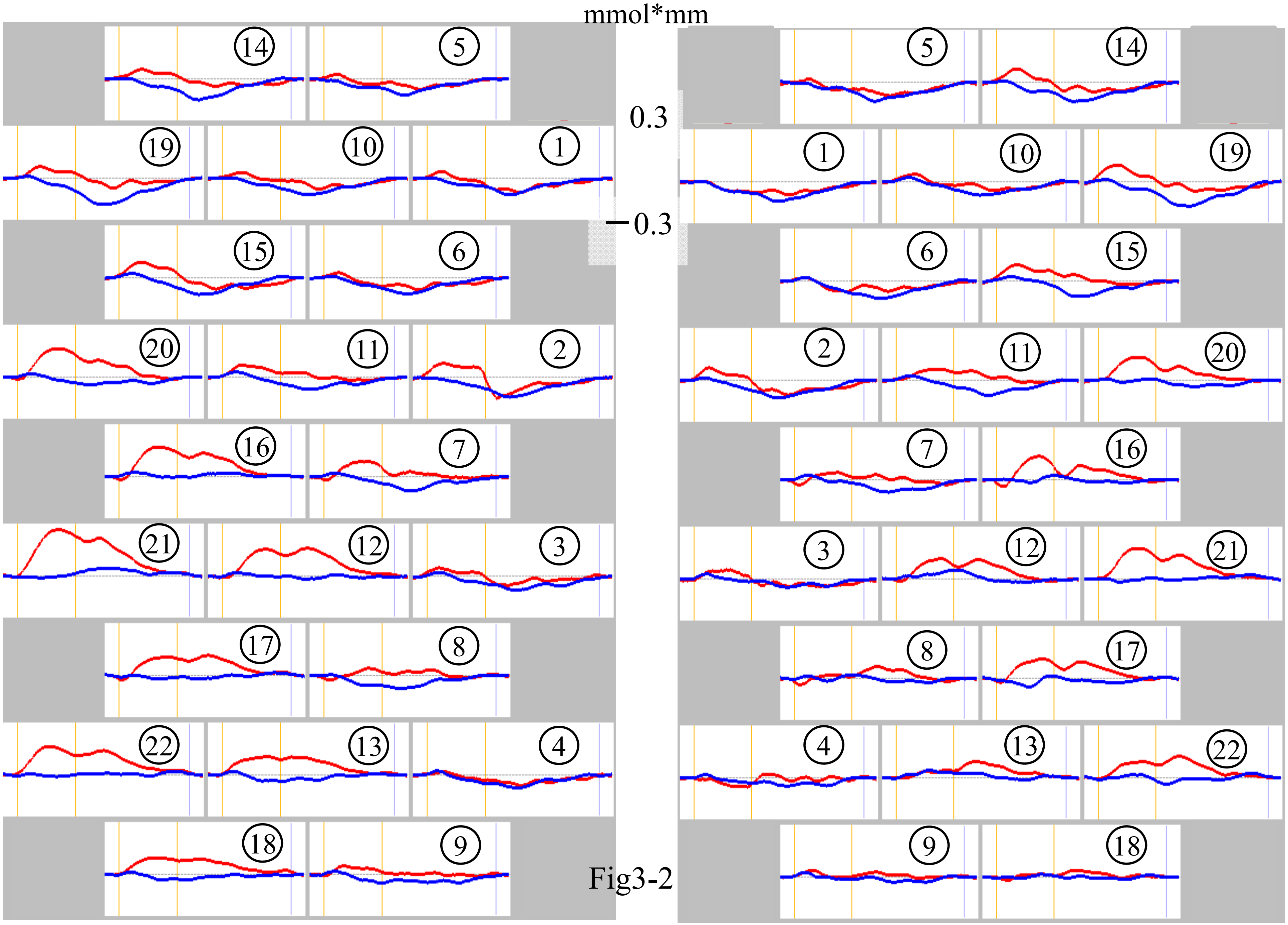
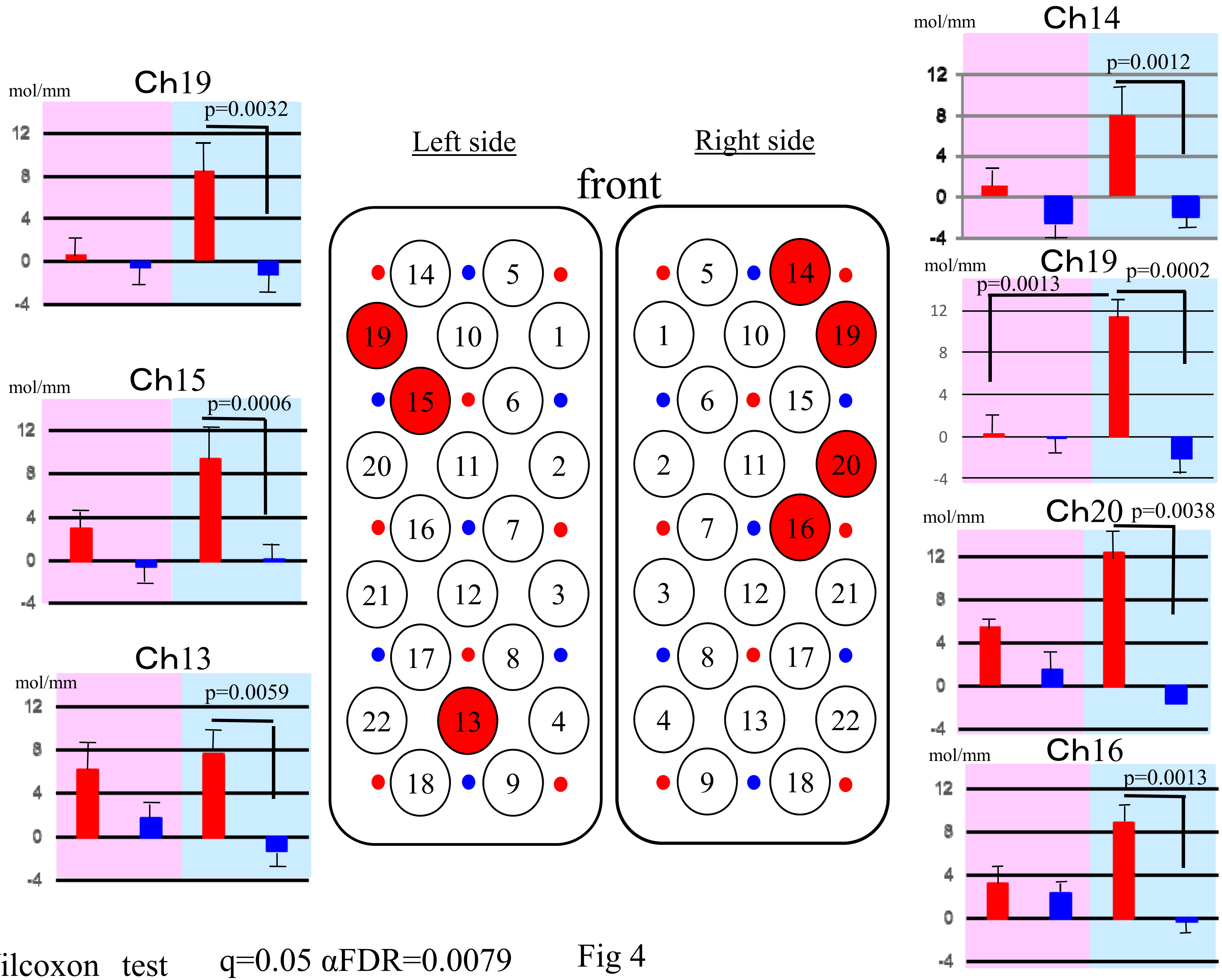

mmol*mm
0.3
−0.3
14 5
19 10 1
15 6
20 11 2
16 7
21 12 3
17 8
22 13 4
18 9
5 14
1 10 19
6 15
2 11 20
7 16
3 12 21
8 17
4 13 22
9 18

Fig3-2

Fig3-1 Oxy-Hb concentration fluctuation in the pleasant condition.
Fig3-2 Oxy-Hb concentration fluctuation in the unpleasant condition.
Comparison of the average waveforms between the healthy group and patients with depression group.
Red line ; Healthy group
Blue line ; Patients group with depression



Wilcoxon test q=0.05 αFDR=0.0079 Fig 4

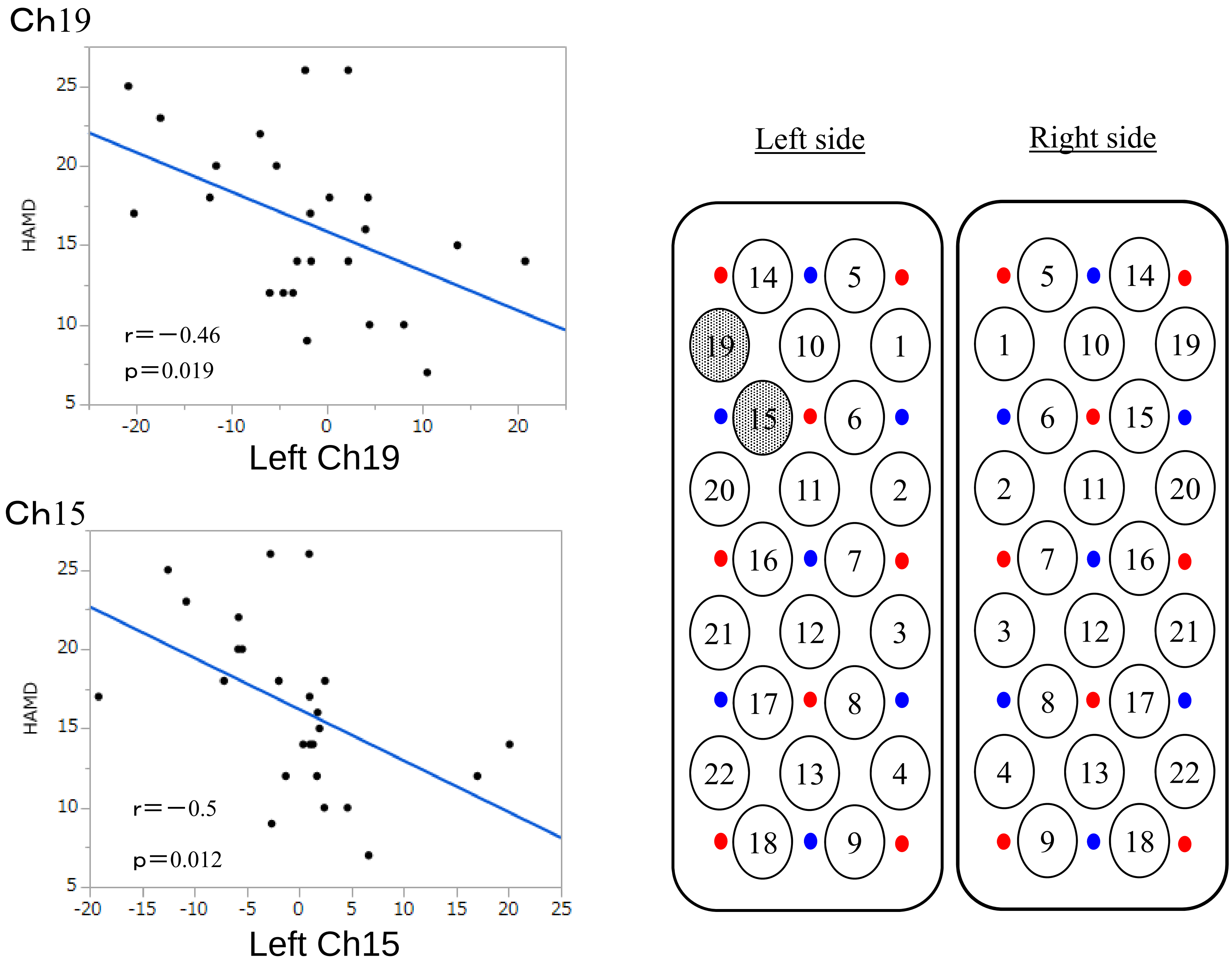
Fig4 Recorded sites with differences between the conditions of healthy group and depression group and differences between groups.

There was no significant difference between the conditions in both groups, and only the right Ch 19 of the healthy group showed a significant difference between pleasant and unpleasant conditions.

In the unpleasant condition, a channel with significant difference in both frontal regions (right Ch 16, 19, 20, left Ch 15, 19) was obtained.

Background is pink ;pleasure condition Background is light blue; Unpleasant condition

Red bar ; Healthy group Blue bar ; Patients with Depression group



Pearson's moment correlation coefficient P＜0. 05

Fig 5

Fig 5 Recording section with negative correlation with HAM-D total score in channel with inter-group difference. A negative correlation with HAM-D total scores was confirmed in Ch 19, 15