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Near-infrared spectroscopic study of frontopolar activation during face-to-face conversation in major depressive disorder and bipolar disorder

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ABSTRACT

Major depressive disorder (MDD) and bipolar disorder (BD) patients show speech characteristics that vary greatly according to mood state. In a previous study, we found impaired temporal and right inferior frontal gyrus (IFG) activation in schizophrenia during face-to-face conversation; no study had, however, previously investigated mood disorders during face-to-face conversation. Here, we investigated frontal and temporal lobe activation during conversation in patients with MDD and BD. Frontal and temporal lobe activation was measured using near-infrared spectroscopy (NIRS) in 29 patients with MDD, 31 patients with BD, and 31 normal controls (NC). We compared continuous activation and rapid change of activation with talk/listen phase changes during the conversation and analyzed the correlation between these indices and clinical variables. Both the MDD and BD groups showed decreased continuous activation in the left dorsolateral prefrontal (DLPFC) and left frontopolar cortices (FPCs); they also showed decreased rapid change in bilateral FPC activation. In the MDD group, the rapid change of activation was positively correlated with Global Assessment of Functioning (GAF) scores. In the BD group, continuous activation was negatively correlated with age of onset. These results indicate that frontal activation during conversation decreases in both MDD and BD. However, both continuous activation and rapid change may reflect the pathophysiological character of MDD and BD; in particular, the reduced amount of rapid change in the right FPC may be related to impaired adaptive ability in MDD.

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1. Objectives of the study and background

Psychiatrists investigating mental illness can diagnose specific diseases using various characteristics exhibited by patients during the course of a conversation. Patients suffering from major depressive disorder (MDD) and bipolar disorder (BD) show particular conversational characteristics, which can be divided into those that do or do not change according to disease state (American Psychiatric Association, 1994; Bouhuys and Sam, 2000).

In the depressive state, patients use few words, show psychomotor retardation, and exhibit poor choices of conversation topics. Their emotional reactivity becomes poor, and smiles are not exhibited even when discussing pleasant topics. In contrast, in a manic or hypomanic state, patients with BD are more talkative than usual and speak one-sidedly; it may be difficult to understand the content of their speech due to the manifestation of flights of ideas. In the euthymic state, these symptoms disappear. Although these state-dependent characteristics of conversation are not specific to MDD and BD, it is essential to observe them because they are key to diagnosing these disorders using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM–IV; American Psychiatric Association, 1994). These state-dependent characteristics are crucial in clinical assessments (Hamilton Rating Scale for Depression; Hamilton, 1960; Young Mania Rating Scale; Young et al., 1978).

There are several studies that investigated links between personality and social communication, as well as the direct communication between patients and interviewers. Patients with BD and MDD in the euthymic state have been found to differ from normal control (NC) participants in that they show high scores for harm avoidance and/or low scores for self-directedness and cooperativeness, as measured by the Temperament and Character Inventory (TCI; Celikel et al., 2009; Hansenne et al., 1999). With

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regards to direct communication, Coyne et al. stated that deficits in human communication play an important role in theories of development, persistence, and recurrence of depression (Coyne and Downey, 1991). Bouhuys et al. indicated that the lack of coordination during MDD interviews may be a risk factor for the condition's recurrence (Bouhuys and Sam, 2000). These characteristics may be associated with vulnerability in patients with mood disorders.

Cognitive and emotional dysfunctions underlying these characteristic conversational differences between healthy adults and mood disorder patients have been previously investigated by functional magnetic resonance imaging (fMRI). These studies suggest an altered activation of the amygdala, as well as the frontal, cingulate, and temporal cortices in patients with MDD and BD during various cognitive tasks (Savitz and Drevets, 2009). Although such data may assist in diagnosis, and may be directly related to the Global Assessment of Functioning (GAF), brain activation during conversation has not yet been investigated in patients with MDD and BD due to methodological difficulties.

Near-infrared spectroscopy (NIRS) is a recently developed noninvasive functional neuroimaging technique (Koizumi et al., 1999; Strangman et al., 2002). NIRS can detect regional cerebral blood volume (rCBV) changes through the fluctuating concentrations of oxyhemoglobin ([oxy-Hb]) and deoxyhemoglobin ([deoxy-Hb]). NIRS has some advantages over other functional neuroimaging methodologies due to (i) its complete noninvasiveness, enabling repeated measurements; (ii) the portability and compactness of the NIRS apparatus, enabling measurements under natural conditions with participants comfortably seated; and (iii) little sensitivity to motion artifacts, allowing the NIRS to be used in the study of conversation. Considering these advantages, NIRS allows for brain activation to be evaluated in a naturalistic environment. Indeed, several recent studies reported the use of NIRS during face-to-face interaction (Costantini et al., 2013; Cui et al., 2012; Konvalinka and Roepstorff, 2012).

Our group previously investigated frontal and temporal lobe activation during face-to-face conversations with normal control participants (Suda et al., 2010, 2011). Our results showed activity in the frontal and temporal lobes, as well as substantial cyclical activity in the frontal lobe corresponding to the time course of the conversation task — where participants were required to talk to a person facing them — especially around the frontopolar region. Both of these studies assessed only the sustained activities as grand average [oxy-Hb] data (GAOD) of the conversation and control tasks. In the present study, we sought to assess this substantial cyclical activity, measured by the averaged amount of [oxy-Hb] change (AAOC) over time. We measured this fluctuation in activity during the speech and listening phases superimposed on the base large [oxy-Hb] change during the task in order to evaluate the effects of switching turns during the conversation and control tasks. Although the meaning of the AAOC has not yet been clarified, we presumed that there are different physiological meanings assigned to the GAOD and AAOC. We posited that the GAOD represents the global functioning of an individual required to face to another person (i.e., a conversation situation-related function), while the AAOC mainly reflects speech itself (i.e., a speech-related function).

Because the characteristics of BD and MDD are well reflected in conversation, we hypothesized that (i) the GAOD and AAOC of the frontal cortex in MDD and BD would be altered compared to NC participants; and (ii) the GAOD or AAOC of the frontal cortex in MDD and BD would correlate with both GAF and depressive symptoms.

Table 1
Participant characteristics.

Sex (male)	MDD ($n = 29$)			BD ($n = 31$)			NC ($n = 31$)	
	M	F		M	F		M	F
	14	15		14	17		11	20
	Mean	SD		Mean	SD		Mean	SD
Age	34.5	9.0		34.9	6.6		33.6	10.0
Age range	19–51			20–45			23–58	
Age of onset	30.3	8.9		26.0	6.4		–	–
Illness duration	4.1	3.6		9.7	7.0		–	–
HRSD	9.8	4.4		6.4	5.5		–	–
YMRS	–	–		1.9	3.6		–	–
GAF	56.7	8.2		54.1	12.5		–	–
Subtype	–	–		BP I	1/31		–	–
	–	–		BP II	30/31			
	Mean	SD	*n*	Mean	SD	*n*		
Antidepressant (imipramine equivalent dose mg/day)	72.0	50.6	22/29	122.7	85.2	17/31	–	–
Antipsychotic (chlorpromazine equivalent dose mg/day)	112.5	63.5	6/29	213.5	122.8	11/31	–	–
Anxiolytic (diazepam equivalent dose mg/day)	7.1	6.4	14/29	12.6	17.2	15/31	–	–
Hypnotic (flunitrazepam equivalent dose mg/day)	2.0	1.5	16/29	2.5	2.0	16/31	–	–
Lithium mg/day	300.0	–	1/29	618.8	242.8	16/31	–	–
Carbamazepine mg/day	0	–	0/29	500.0	258.2	4/31	–	–
Valproate mg/day	300.0	200.0	2/29	552.9	194.0	17/31	–	–

M, male; F, female; MDD, major depressive disorder; BD, bipolar disorder; NC, normal controls; BPI, bipolar I disorder; BPII, bipolar II disorder; HRSD, 17-item Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale; GAF, The Global Assessment of Functioning.

2. Materials and methods

2.1. Sample

Twenty-nine patients with MDD, 31 patients with BD, and 31 healthy volunteers (NC) were recruited from the Department of Psychiatry and Neuroscience of Gunma University Hospital in Japan to participate in this study. All participants were right-handed native Japanese speakers. Participants had been previously diagnosed with MDD or BD according to the DSM-IV criteria (American Psychiatric Association, 1994). Patients over 60 years old were not included in this study in order to eliminate the effects of additional pathophysiological factors such as aging and possible cerebrovascular changes. Depressive symptoms among patients with MDD and BD were evaluated using the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Manic symptoms in BD patients were evaluated using the Young Mania Rating Scale (YMRS; Young et al., 1978). Nearly all participants were on medication such as mood stabilizers, antipsychotics, antidepressants, anxiolytics, and/or hypnotics. Equivalent dosages were calculated for each class of medication, as follows: chlorpromazine-equivalent dose of antipsychotics; imipramine-equivalent dose of antidepressants; diazepam-equivalent dose of anxiolytics; and flunitrazepam-equivalent dose of hypnotics (Inagaki and Inada, 2006).

Exclusion criteria for MDD and BD groups were determined using clinical interviews. Criteria included any observable brain abnormality in magnetic resonance imaging (MRI) results, past or present neurological illness, traumatic brain injury with any of the known cognitive consequences or loss of consciousness for more than 5 min, substance use or addiction, and present hearing or vision impairment. Exclusion criteria for the NC participants were also determined using clinical interviews. These included a history of any major psychiatric disorder or major physical illness and a current prescription for major psychiatric medication.

This study was performed in accordance with the Helsinki Declaration, as revised in 1989, and was approved by the Institutional Review Board of Gunma University Hospital. Written informed consent was obtained from all participants prior to study initiation. For patients under 20 years of age or those who had been forcibly committed to hospital, written informed consent was obtained from the patient's legal representative. Because we could not obtain the behavioral data from conversations with participants who had not provided consent for videotape recordings, we describe the clinical characteristics of all participants using the behavioral data listed in Table 1.

2.2. Activation tasks

Two types of activation tasks—a conversation and a control task—were used to assess brain activation during conversation (Fig. 1). The order of the two tasks was counterbalanced between participants.

2.3. Conversation task

The conversation task, which comprised the pre-task, task, and post-task segments, was designed to simulate typical, daily life conversation in an experimental setting. The interviewers who led the conversation task had been selected from hospital staff that had not been previously acquainted with the participants. Each session began after NIRS probes had been placed on the participants' frontal and temporal regions while they were seated in a comfortable chair, face-to-face (1 m apart) with an interviewer. To eliminate the possible influence of facial cues before and after engaging in conversation, a partition was placed between the participant and interviewer during the pre-task and post-task segments, and was removed during the task.

To prevent the emergence of qualitative and quantitative differences in the nature of conversations from one participant to the next, all participants were instructed to engage in face-to-face conversation with the interviewer during the task segment according to 2 criteria. First, they were to follow a set time course of conversation, according to which the participant and the interviewer alternated speaking every 15 s; this plan was reinforced through spoken cues about the elapsed time from the experimenter every 5 s. The task thus consisted of 6 cycles of 30-s speech segments, with the entire conversation lasting as long as 180 s. Second, participants were to limit the subjects of the conversation to food-related topics. During the pre-task and post-task segments, participants were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/, that is, the Japanese counterparts of the English sounds "A," "B," and "C," to exclude the effects of phonation and stabilize baseline conditions. The conversations of 23 patients with MDD, 17 patients with BD, and 28 NCs who had given consent for recording were videotaped for later analysis of visual and audio data.

Conversation task performance was evaluated both quantitatively and qualitatively. First, the amount of conversation contributed by participants was quantitatively evaluated using speaking time (ST)—the duration of the participants' speech as measured by videotaped data analysis. Second, the content of their speech was qualitatively evaluated by 4 expert psychiatrists in terms of the receiving aspect (RS), or the appropriateness of speech content in the context of a conversation; and the sending aspect (SS), or the extent of production of new topics. To measure the RS, the participants' replies to the preceding interviewer's speech were scored as inappropriate, partially inappropriate, partially appropriate, or

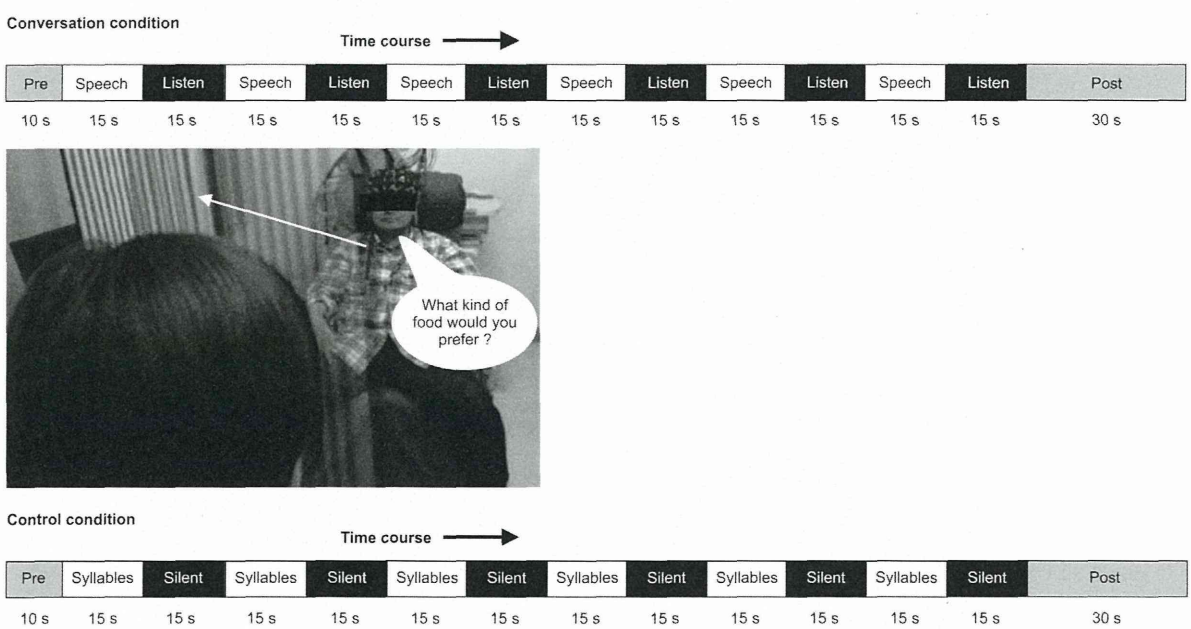

Fig. 1. Task procedures and picture of the measurement setting. Two types of activation task conditions, a conversation condition and a control condition, were employed in this study. Both tasks consisted of three segments: pre-task, task, and post-task. Under the conversation condition, participants were required to speak with the interviewer facing them during the task segment. The task period consisted of six cycles of such 30-s talks; the total conversation lasted up to 180 s. Before starting (pre-task) and after finishing the experiment (post-task), the participant and interviewer were separated by a partition so that they could not see each other. Under the control condition, participants were instructed to repeat meaningless syllables during their turns to speak during the task period. As shown in the picture, the participant is wearing the near-infrared spectroscopy probe on his forehead, and the participant and interviewer are seated facing each other.

appropriate. To measure the SS, the participants' questions to the interviewer were analyzed to determine whether they had introduced no new topic(s), nearly the same topic(s), partially new topic(s), or completely new topic(s).

2.4. Control task

To examine brain activation and artifact contamination induced by phonation alone, the participants were instructed to perform a control task consisting of repeating meaningless syllables (e.g., "a," "ka," "sa," "ta," and "na") during their turn to speak over the course of the task segment of the conversation task. All participants were physically able to repeat the syllables without interruption.

2.5. NIRS measurement

Changes in [oxy-Hb] were measured as an index of changes in cerebral blood volume and in [deoxy-Hb] using a 52-channel NIRS machine (Hitachi ETG-4000; Hitachi Medical Systems, Tokyo, Japan). The correspondence between NIRS channels and measurement points on the cerebral cortex was confirmed by comparison with the results of a multi-participant study of anatomical cranio-cerebral correlation (Okamoto et al., 2004), and was displayed on the basis of the results obtained using the virtual registration method (Fig. 2; Tsuzuki et al., 2007). For details about NIRS measurement, refer to Supplement No. 1.

2.6. Data analyses

We calculated Ebel's intraclass correlation coefficient (Ebel's ICC) for SS and RS of both the groups to investigate inter-rater reliability. The behavioral data (ST, RS, and SS) were compared between the three groups using a one-way analysis of variance (ANOVA). The waveforms of [Hb] changes in all 52 channels during the conversation and control conditions were calculated for all participants. NIRS data from channels 1–21 that clearly contained motion artifacts, as determined by close observation of the participants, were excluded from further analyses. The most common causes of artifacts were large movement and poor contact with the probes due to abundant hair. A probe placed on an area with abundant hair could not be securely fastened to the head and was easily displaced.

The GAOD was calculated for both the conversation and control tasks by averaging by each channel and task, excluding the pre- and post-task segments. The GAOD of the conversation and control tasks were analyzed using a mixed-design repeated measures ANOVA with diagnosis (MDD, BD, or NC) as the between-subjects variable and task (conversation or control task) as the repeated measure variable. Results were corrected for the number of channels using a false discovery rate (FDR) correction to avoid Type I errors. When an interaction was found, Scheffé's post hoc *t*-test with diagnosis was conducted for both conditions ($p < 0.05$).

The AAOC was calculated to evaluate the effect of switching turns during the conversation and control tasks (Fig. 2). The first two time segments were excluded from the analysis because they served as baseline measurements. The obtained amounts of [oxy-Hb] change value were averaged by task. The AAOC of the conversation and control tasks were analyzed using a mixed-design repeated measures ANOVA, with diagnosis (MDD, BD, or NC) as the between-subjects variable and task (conversation or control task) as the repeated measure variable. Results were corrected for the number of channels using the FDR correction ($p < 0.05$). When an interaction was indicated, Scheffé's post hoc *t*-test with diagnosis was conducted for both conditions ($p < 0.05$).

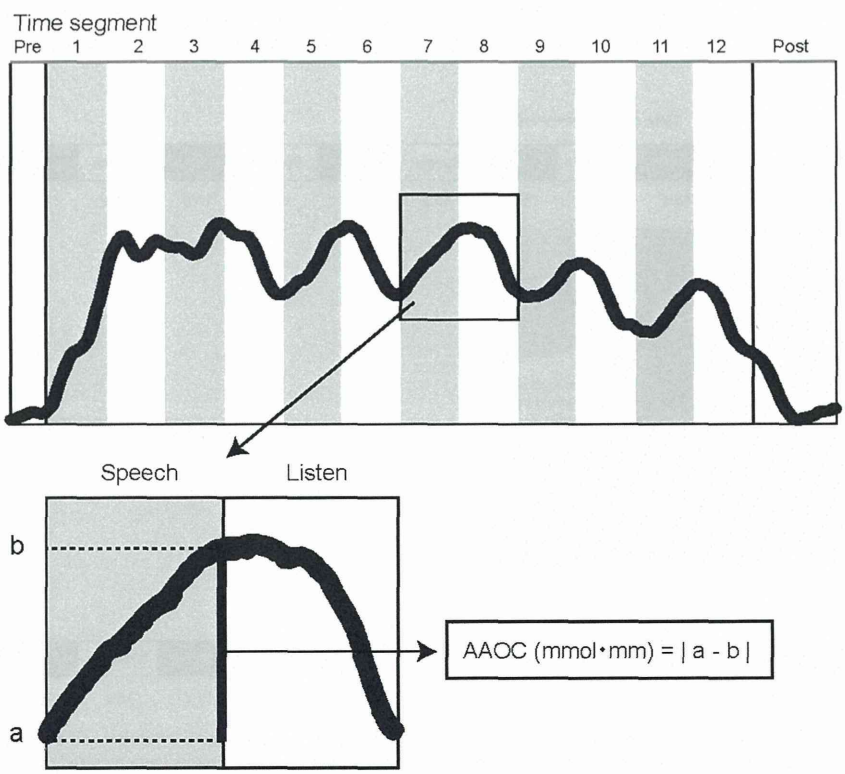

Fig. 2. Formula for calculating the averaged amount of [oxy-Hb] change (AAOC). In this formula, "a" is the [oxy-Hb] data at segment start, and "b" is the [oxy-Hb] data at segment end. The upper panel shows the waveform of an individual during the conversation task. The segment represented by the square in the top image is enlarged in the lower image. The gray panels indicate the speech phase while the white panels indicate the listening phase.

Pearson's r was calculated for both correlations between GAOD/AAOC and behavioral data, which included ST, RS, SS, current age, age of onset, illness duration, GAF score, HRSD score, YMRS score, and drug dosage. Results were corrected for the number of channels by way of FDR correction ($p < 0.05$).

3. Results

3.1. Sample characteristics

Table 1 summarizes the demographic characteristics of the sample. Age and sex ratios were not significantly different between the three groups ($F[2, 90] = 0.2$, $p = 0.83$; chi square $(2) = 1.1$, $p = 0.58$). At the time of the study, the Patients with MDD were euthymic or depressive, as indicated by their scores on the HRSD. Patients with BD were euthymic, depressive, or hypomanic, as indicated by their scores on the HRSD and the YMRS.

3.2. Behavioral data analysis (Table 2, Fig. 3)

Ebel's ICC for the RS of the NC ($r = 0.441$, $p = 0.023$) and MDD ($r = 0.718$, $p = 0.000$) groups indicated significant correlations, while that of the BD group ($r = 0.392$, $p = 0.084$) indicated a trend–level correlation. Ebel's ICC for SS of the NC ($r = 0.712$, $p = 0.000$), MDD ($r = 0.524$, $p = 0.010$), and BD ($r = 0.607$ $p = 0.005$) groups indicated significant correlations.

The results of the one-way ANOVA for RS revealed a significant main effect of diagnosis, and Scheffé's post hoc t-test of the RS revealed a lower score for MDD patients than controls (Table 2). The ST and SS were not significantly different between the three groups.

3.3. Analysis of GAOD during conversation and control tasks

The results of the mixed-design repeated measures ANOVA of the GAOD, with diagnosis as the between-subjects variable and task as the within-subjects variable, revealed a significant main effect of task in 31 channels (Ch22–Ch52; $F[1, 85] = 16.22–143.01$; FDR-corrected $p = 0.000$) and interactions of diagnosis and task in 3 channels (Ch28, Ch39, Ch50; $F[2, 85] = 7.16–8.16$; FDR-corrected $p = 0.001$). Scheffé's post hoc t-test of the conversation task with diagnosis revealed a larger activation in the NC group than in the MDD and BD groups for Ch28 and Ch39, and in the BD group for Ch50. On the other hand, there was no significant difference between groups in the control task. Scheffé's post hoc t-test results for the conversation task indicated that the brain areas exhibiting differences between the groups tended to be the left dorsolateral prefrontal cortex (DLPFC), frontopolar cortex (FPC), and inferior frontalgyrus (IFG), according to the virtual registration method (Fig. 4).

3.4. AAOC during conversation and control tasks (Fig. 5)

The results of the mixed-design repeated measures ANOVA of the AAOC, with diagnosis as the between-subjects variable and task as the within-subjects variable, revealed a significant main effect of task in 31 channels (Ch22–Ch52; $F[1, 85] = 8.63–62.63$; FDR-corrected p: 0.000–0.004) and interactions of diagnosis and task in 7 channels (Ch25–Ch29, Ch36, Ch37; $F[2, 85] = 4.74–7.58$; FDR-corrected p: 0.001–0.011). Scheffé's post hoc t-test of the conversation task with diagnosis revealed a larger activation in the NC group than in the MDD and BD groups for Ch25–Ch28 and Ch37, and in MDD for Ch29 and Ch36. No significant difference was found between groups in the control task.

Table 2
Behavioral data results.

	MDD		BD		NC		F	p
	Mean	SD	Mean	SD	Mean	SD		
ST (s)	73.2	12.0	74.1	10.2	77.7	4.9	1.736	0.184
RS	3.6	0.4	3.7	0.3	3.9	0.2	4.863	0.011
SS	3.2	0.6	3.2	0.5	3.3	0.7	0.164	0.849

MDD, major depressive disorder; BD, bipolar disorder; NC, normal controls; ST, speaking time; RS, scoring of qualitative evaluation of receiving aspects; SS, scoring of qualitative evaluation of sending aspects.

3.5. Correlation analysis of brain activation, clinical symptoms, medications, and behavioral data (Fig. 6)

NC group: The GAOD during the conversation task was not correlated with either behavioral data (ST, RS, and SS) or current age. The AAOC during the conversation task was likewise not correlated with behavioral data (ST, RS and SS) or current age.

MDD group: The AAOC during the conversation task was positively correlated with GAF in 3 PFC channels: Ch36, Ch38, and Ch46 ($r = 0.53–0.61$; FDR-corrected p: 0.000–0.003, Fig. 6). However, the GAOD during the conversation task was not correlated with GAF, and HRSD was correlated with neither GAOD nor AAOC. The GAOD and AAOC during the conversation task were not correlated with behavioral data (ST, RS, and SS), current age, age of onset, illness duration, or drug dosage (antidepressant and anxiolytics). HRSD score was not correlated with behavioral data (ST, RS, and SS).

BD group: We did not find significant correlations between the GAOD or AAOC and GAF and HRSD. However, we found a significant negative correlation between the GAOD during the conversation task and current age in 2 channels (Ch37 and Ch39; $r = -0.58$ to -0.55; FDR-corrected $p = 0.001$), and also age of onset in 3 channels (Ch35, Ch42, Ch43; $r = -0.63$ to -0.48; FDR-corrected p: 0.000–0.008, Fig. 6). Neither GAOD nor AAOC during the conversation task were correlated with behavioral data (ST, RS, and SS), illness duration, GAF score, HRSD score, or drug dosage (antidepressants, antipsychotics, lithium, and valproate). Any significant correlations between the GAOD or AAOC and YMRS or dosage of hypnotics and anxiolytics were the result of the effect of outliers on the correlational analysis. HRSD and YMRS score were not correlated with behavioral data (ST, RS, and SS).

4. Discussion

4.1. Summary of obtained results

Our results showed that the GAOD in the left DLPFC and FPC of MDD and BD groups was lower than that of the NC group during the conversation task, and that the AAOC in the FPC of both the MDD and BD groups decreased during the conversation task. Both the GAOD and AAOC during the control task did not differ between the 3 groups. In the patients with MDD, the AAOC tended to be positively correlated with GAF in the FPC. In the BD group, the GAOD was negatively correlated with age of onset in the right DLPFC and both middle temporal lobes.

4.2. Behavioral data

We found low RS scores in patients with MDD. This result is reasonable, because MDD is not only associated with various neuropsychological deficits (to memory, learning, attention, alertness, and executive functions) during a depressive episode, but also during a euthymic state (Austin et al., 1992; Tham et al., 1997; Veiel, 1997; Zakzanis et al., 1998). However there were no significant

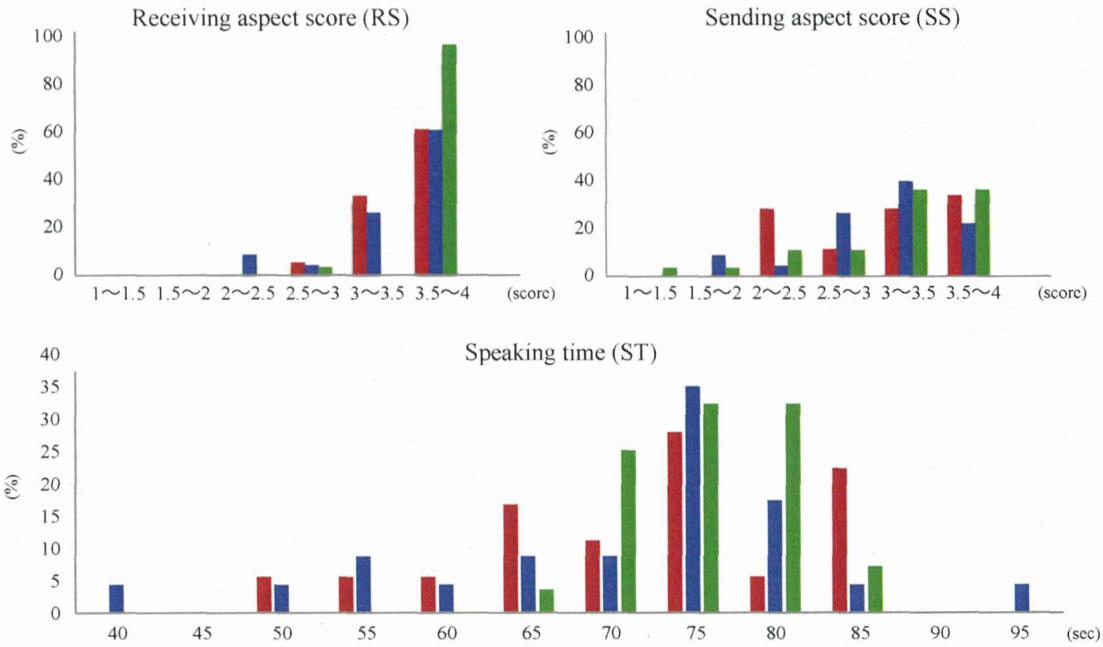

Fig. 3. Percent histogram of behavioral data results: averaged receiving aspect score (RS, left) and sending aspect score (SS, right), as evaluated by two expert psychiatrists, and speaking time (ST, bottom). The x-axes of the left and right figures indicate RS and SS, and that of the bottom figure indicates ST. The y-axes of the three figures indicate the percentage of subjects for each score. The green bar represents normal controls; the blue bar, patients with major depression; and the red bar, patients with bipolar disorder.

differences in ST and SS among three groups, potentially due to a ceiling effect: almost all participating patients were in the euthymic state, and performed well. The lack of correlation between behavioral data and HRSD or YMRS in both MDD and BD patients may also be due to patient state.

4.3. Difference in physiological meaning between the GAOD and the AAOC

We found that the frontal and temporal regions were continuously activated during face-to-face conversation. In addition to the blockwise activations of the frontal and temporal lobes during the 180-s conversation task, rhythmic activations tended to be superimposed on the FPC area, as shown in Fig. 2. In our previous studies, we obtained similar waveform data (Suda et al., 2010, 2011).

Although we cannot clearly explain the cognitive meanings of the GAOD and AAOC, we posit that their physiological meanings differ. In terms of task construction, the GAOD is obtained by subtracting the response to repeated syllables from responses to all the cognitive elements necessary for speech, such as context processing, monitoring, referencing, emotional processing, and mentalizing. In terms of waveform patterns, this basic activation is stable from beginning to end during the conversation. Thus, the GAOD may represent the global function required to interact with another person and may be related to mentalizing as well as processing various types of information received from another person (i.e., conversation situation-related function).

The AAOC is obtained by subtracting the response to the ending time point data of the listening phase from the ending time point data of the talk phase. However, it is difficult to compare these results with those of previous studies since prior research did not utilize the same analytical techniques; therefore, we interpret the physiological meaning of AAOC solely within the context of the task design. In the present study, participants needed to speak, monitor their speech, and change speech content in response to the partner's statements during the conversation; thus, we considered the AAOC to be a speech-related function.

4.4. Decreased GAOD and clinical variables in MDD and BD

The GAOD decreased in the left DLPFC and FPC in both MDD and BD groups, and in the IFG in the BD group, when compared to the NC group. In the BD group, the GAOD was negatively correlated with age of onset in the right DLPFC and both middle temporal lobes, and with current age in the FPC.

Various neuroimaging studies have found decreased frontal activation in patients with MDD (Drevets et al., 2002; Kameyama et al., 2006; Kennedy et al., 2001; Ohta et al., 2008; Suto et al., 2004) and BD (Frangou et al., 2008; Kronhaus et al., 2006; Roth et al., 2006; Strakowski et al., 2005). These findings support the decreased GAOD and AAOC of the frontal regions in MDD and BD. The GAOD in the left DLPFC and FPC of MDD and BD groups tended to be lower. In our previous study, when compared to NC, patients with schizophrenia exhibited decreased activation in the bilateral temporal lobes and the right IFG during conversation (Takei et al., 2013). These results indicate a hemodynamic difference that reflects conversation situation-related function in MDD, BD, and schizophrenia patients. This different regional pattern of mood disorders (MDD and BD) and schizophrenia is supported by meta-analyses of volumetric MRI studies (Arnone et al., 2009; Koutsouleris et al., 2008; Sacher et al., 2012). These previous studies reported frontal volume reduction of MDD, BPD, and schizophrenia; temporal volume reduction was also emphasized in schizophrenia. The GAOD reflects multiple functions related to conversation situations; therefore, it may reflect the impaired brain region central to the pathophysiology of the disorder. To be clear, the lack of difference in the GAOD and AAOC during the control task indicates that the obtained difference was not due to brain volume reduction or phonation.

In the BD group, the GAOD was negatively correlated with age of onset in the right DLPFC and both middle temporal lobes, and with

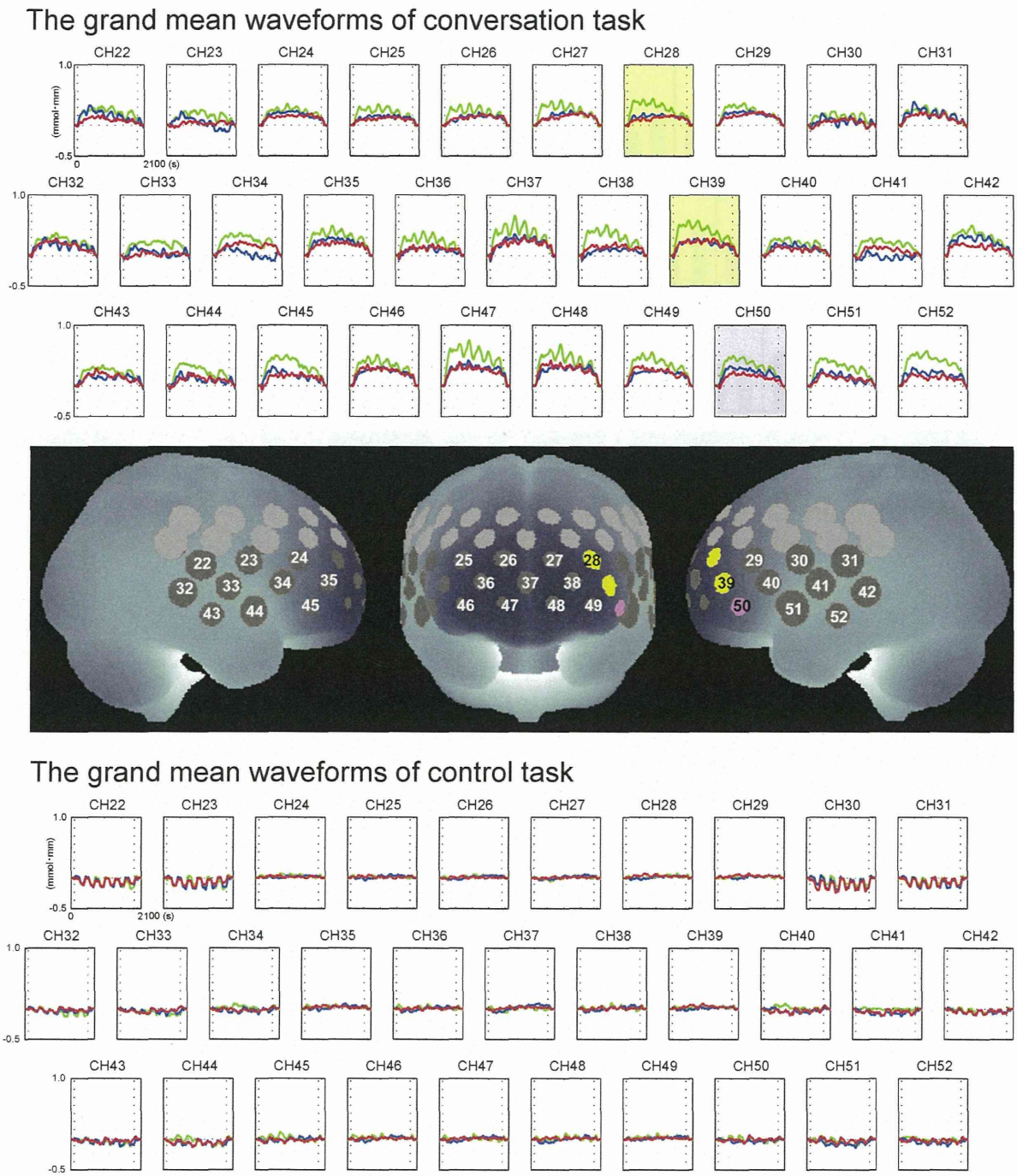

Fig. 4. The upper 31 figures (Ch22–Ch52) indicate the grand mean waveforms of the conversation task: green line, control participant; blue line, major depression; red line, bipolar disorder. The yellow channels of the upper figures indicate a larger grand averaged [oxy-Hb] data (GAOD) in the NC group than in the MDD and BD groups, and the pink channel indicates a larger GAOD in the NC group than in the BD by mixed-design repeated measures ANOVA, followed by Scheffé's post hoc *t*-test. The middle 3 figures below show the probabilistic estimation and anatomical labeling of the locations of NIRS channels in the standard brain space in accordance with Tsuzuki et al. (2007), and the yellow and pink areas indicate the corresponding brain areas that differed between the groups according to the results of the post hoc *t*-test. Light gray channels without a number are channels that were excluded because of detection of clear motion artifacts. The lower 31 figures (Ch22–Ch52) indicate the grand mean waveforms of the control task: green line, control participant; blue line, major depression; red line, bipolar disorder.

current age in the FPC, but not correlated with illness duration. Past epidemiological research suggests that early- and late-onset BD differ in clinical expression and familial risk, and may therefore be considered different subforms of manic-depressive illness (Schurhoff et al., 2000). However, the correlation between GAOD and age of onset in this study may reflect genetic differences between early and late onset BD; indeed, there was only one case of BD with an age of onset over 40. To clarify the influence of age of onset on GAOD, more cases of BD with onset under 20 and over 40 years should be investigated in the future.

4.5. Decreased AAOC and clinical variables in MDD and BD

The AAOC tended to be decreased in the bilateral FPC and the left DLPFC in both MDD and BD groups, compared to the NC group.

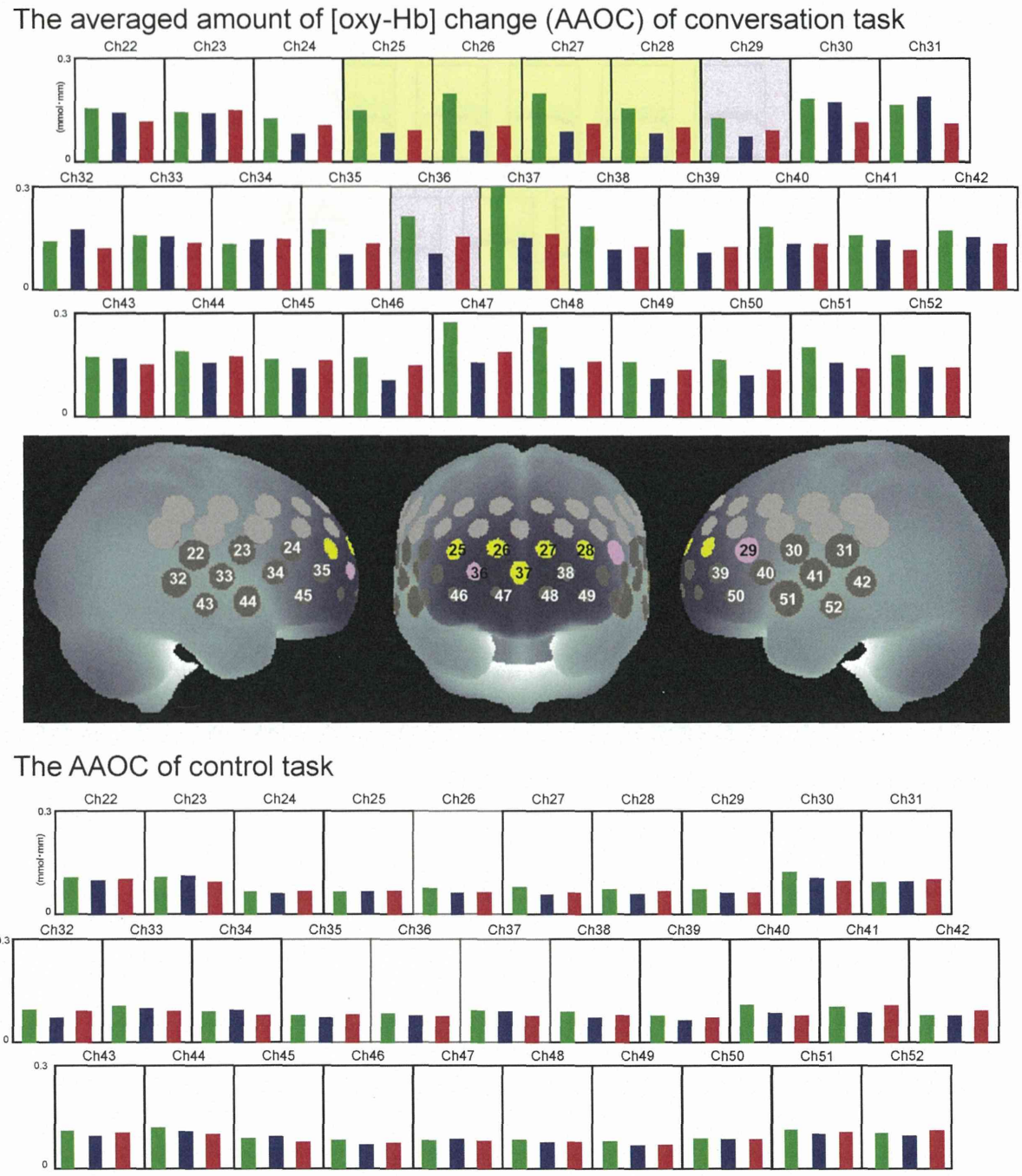

Fig. 5. The upper 31 figures (Ch22–Ch52) indicate the averaged amount of [oxy-Hb] change (AAOC) of the conversation task: green bar, control participant; blue bar, major depression; red bar, bipolar disorder. The yellow channels of the upper figures indicate a larger AAOC in the NC group than in the MDD and BD groups, and the light blue channels indicate a larger AAOC in the NC group than in the MDD group by mixed-design repeated measures ANOVA, followed by Scheffé's post hoc *t*-test. The middle 3 figures below show the probabilistic estimation and anatomical labeling of the locations of NIRS channels in the standard brain space in accordance with Tsuzuki et al. (2007), and the yellow and light blue areas indicate the corresponding brain areas that differed between the groups according to the results of the post hoc *t*-test. Light gray channels without a number are channels that were excluded following the detection of clear motion artifacts. The lower 31 figures (Ch22–Ch52) indicate the AAOC of the control task: green bar, control participant; blue bar, major depression; red bar, bipolar disorder.

However, the decreased area of AAOC for MDD was wider than for BD, contrary to our hypothesis.

The main difference between MDD and BD was the decreased AAOC in the right FPC found in only the MDD group. The right frontal lobe is involved in generating unusual or distant verbal associations while the left frontal lobe is involved in generating "usual" associations (Kiefer et al., 1998; Seger et al., 2000). Clinical research suggests that individuals with MDD are cognitively inflexible, exhibiting ruminative, rigid, and automatic thoughts within a negative schema (Deveney and Deldin, 2006; Remijnse et al., 2013). Researchers reported that individuals with MDD were less flexible than to healthy controls. These previous studies may indicate that decreased AAOC in the right FPC reflected the cognitive inflexibility seen in MDD.

Among the patients with MDD, the AAOC tended to be positively correlated with the GAF in the right FPC. Pu et al. (2012) reported that reduced activation in the prefrontal and temporal regions during a working memory task was significantly related to lower