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Ⅳ．　研究成果の刊行物・別刷

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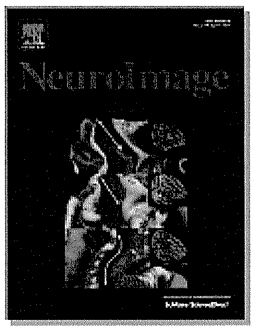

Neuroimaging-aided differential diagnosis of the depressive state

Takizawa, R.; Fukuda, M.; Kawasaki, S.; Kasai, K.; Mimura, M.; Pu, S.; Noda, T.; Niwa, S.i.; Okazaki, Y.

NeuroImage, Volume(s) 85, 10-Jun-2013, Pages 498-507

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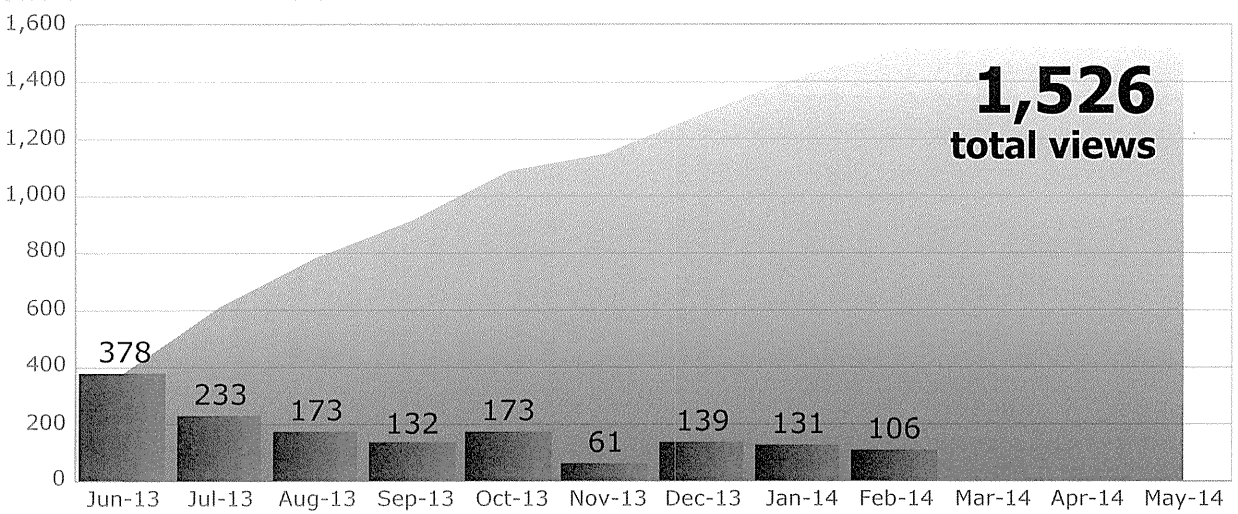

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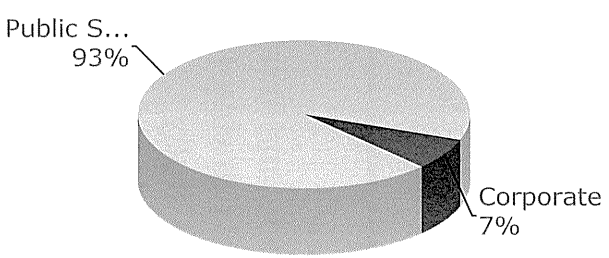

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Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study

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ABSTRACT

Schizophrenia (SC) is marked by poor social-role performance and social-skill deficits that are well reflected in daily conversation. Although the mechanism underlying these impairments has been investigated by functional neuroimaging, technical limitations have prevented the investigation of brain activation during conversation in typical clinical situations. To fill this research gap, this study investigated and compared frontal and temporal lobe activation in patients with SC during face-to-face conversation. Frontal and temporal lobe activation in 29 patients and 31 normal controls (NC) ($n = 60$) were measured during 180-s conversation periods by using near-infrared spectroscopy (NIRS). The grand average values of oxyhemoglobin concentration ([oxy-Hb]) changes during task performance were analyzed to determine their correlation with clinical variables and Positive and Negative Syndrome Scale (PANSS) subscores. Compared to NCs, patients with SC exhibited decreased performance in the conversation task and decreased activation in both the temporal lobes and the right inferior frontal gyrus (IFG) during task performance, as indicated by the grand average of [oxy-Hb] changes. The decreased activation in the left temporal lobe was negatively correlated with the PANSS disorganization and negative symptoms subscores and that in the right IFG was negatively correlated with illness duration, PANSS disorganization, and negative symptom subscores. These findings indicate that brain dysfunction in SC during conversation is related to functional deficits in both the temporal lobes and the right IFG and manifests primarily in the form of disorganized thinking and negative symptomatology.

1. Introduction

Schizophrenia (SC) is marked by poor social performance, which is a complex phenomenon influenced by many affective, motivational, and environmental factors. Deficiency in *social skills*, a behavioral construct reflecting the smooth application of several specific verbal and nonverbal abilities and cognitive capacities involved in daily conversation, is a critical component of SC. Typically, clinicians diagnose SC on the basis of behavioral observation and analysis of speech content, attitude, and emotional response during interviews. Neuropsychological testing and functional neuroimaging have confirmed that patients with SC have basic cognitive deficits, such as deficits in working and verbal memory and attention (Mohamed et al., 1999; Riley et al., 2000), which are related to impairment in various brain regions, primarily the frontal and temporal lobes, and contribute to their social-skill deficits.

Social cognition is one of the crucial factors necessary for having a conversation. The mainstream of social cognition studies is mental-state attribution, i.e., "theory of mind" (ToM) or "mentalizing," which involves the ability to assume the intentions, beliefs, wishes, feelings, and knowledge states of other individuals based on either observational input ("mental-state decoding") or inferential processes ("mental-state reasoning") (Brune and Schaub, 2012). Many recent studies have reported that the reduced volume and/or reduced activation of gray matter in specific brain regions, mainly the temporal lobe, ventromedial prefrontal cortex (PFC), and cingulate cortex, are associated with the ToM deficits shown by patients with SC (Benedetti et al., 2009; Hooker et al., 2011; Sugranyes et al., 2011). Although the mechanism underlying this phenomenon has been investigated by functional neuroimaging, technical limitations have prevented the investigation of brain activation during conversation in typical clinical situations.

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Therefore, the manner of brain functioning and the consequent integration of various cognitive functions during conversation remain unclear.

Near-infrared spectroscopy (NIRS) has the advantage that brain activation can be evaluated in a naturalistic environment. Several recent studies reported use of NIRS during face-to-face interaction (Costantini et al., 2013; Cui et al., 2012; Konvalinka and Roepstorff, 2012). However, few studies have investigated its application during face-to-face conversation (Suda et al., 2010, 2011).

In this study, we used NIRS to investigate frontal and temporal lobe activation in patients with SC during conversation. Because SC characteristics are well reflected in conversation, we hypothesized that (i) patients with SC and NCs exhibit differences in frontal and temporal lobe activation during conversation, (ii) patients with SC and NCs exhibit differences in behavior during conversation, and (iii) alterations in frontal and temporal lobe activations correlate with clinical symptoms and/or behavior.

2. Materials and methods

2.1. Participants

We recruited 29 patients with SC and 31 NCs ($n = 60$) from the Department of Psychiatry and Neuroscience, Gunma University Hospital, Japan (Table 1). SC diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Patients older than 60 were not included, to eliminate the possible interference of additional pathophysiological factors, such as aging and cerebrovascular changes. All patients were taking medications, including antipsychotics, mood stabilizers, antidepressants, anxiolytics, hypnotics, and/or antiparkinsonian drugs. The chlorpromazine equivalent dose of antipsychotics, imipramine equivalent dose of antidepressants, diazepam equivalent dose of anxiolytics, and flunitrazepam equivalent dose of hypnotics were calculated for each patient (Inagaki, 2006). All patients were clinically stable, as indicated by their scores on the Positive and Negative Syndrome Scale (PANSS), which assesses the 5 psychiatric factors of positive symptomatology, negative symptomatology, disorganization, excitement, and emotional distress (Kay et al., 1987; van der Gaag et al., 2006). NCs had no history of major psychiatric or physical illness or took any medications. All subjects were right-handed and native Japanese speakers. The exclusion criteria for both groups included clear abnormality in brain magnetic resonance imaging (MRI) results, 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 presence of hearing or vision impairment. This study was performed in accordance with the Helsinki Declaration, as revised in 1989, and was approved by the Institutional Review Board of the Gunma University Hospital. Written informed consent was obtained from all subjects before study initiation. If a patient was younger than 20 years or had been forcibly committed to hospitalization, written informed consent was obtained from his/her legal representative. Because we could not obtain behavioral data of conversations from subjects who had not provided consent for videotape recording, we describe the clinical characteristics of all subjects 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).

Table 1
Subject characteristics. The data presented on the left side (groups of total subjects) indicate the characteristics of the subjects who participated in this study, whereas the data presented on the right side (subgroups of subjects with behavioral data) indicate the characteristics of the subgroup of subjects with behavioral data. Antipsychotics, chlorpromazine equivalent dose; antidepressants, imipramine equivalent dose; anxiolytics, diazepam equivalent dose; and hypnotics, flunitrazepam equivalent dose. M, male; F, female; SC, schizophrenic subjects; NC, normal controls; ST, speaking time score; RS, receiving aspect score; SS, sending aspect score; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Symptom Scale.

	Groups of total subjects				Subgroups of subjects with behavioral data			
	SC ($n = 29$)		NC ($n = 31$)		SC ($n = 15$)		NC ($n = 28$)	
	M	F	M	F	M	F	M	F
Sex	19	10	20	11	9	6	18	11
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (year)	35.4	11.9	33.5	10	34.3	12.1	32.6	9.7
Age range (year)	19–58		23–58		19–57		23–58	
Age of onset (year)	23.6	7.3			24.3	8.4		
Illness duration (year)	11.6	8.8			10.2	7.9		
GAF					55.8	13.0		
PANSS five-factor model	Mean	SD			Mean	SD		
Positive symptoms	11.6	4.1			10.3	3.3		
Negative symptoms	21.4	8.4			19.8	5.9		
Disorganization	10	4.2			8.1	1.7		
Excitement	6.6	3.1			5.3	1.5		
Emotional distress	8.5	2.7			8.0	2.6		
Medications	Mean	SD	*n*		Mean	SD	*n*	
Antipsychotic (mg/day)	621.9	574.1	26/29		471.8	435.5	14/15	
Antipsychotic (mg/day)	51.8	65.7	4/29		60.7	77.5	3/15	
Anxiolytic (mg/day)	7.4	6.3	10/29		6.0	6.2	5/15	
Hypnotic (mg/day)	1.9	1.1	10/29		1.8	1.0	4/15	
Behavioral data					Mean	SD	Mean	SD
Time (s)					70.3	9.9	77.7	4.9
RS					3.0	0.9	4.0	0.2
SS					2.6	1.0	3.4	0.9

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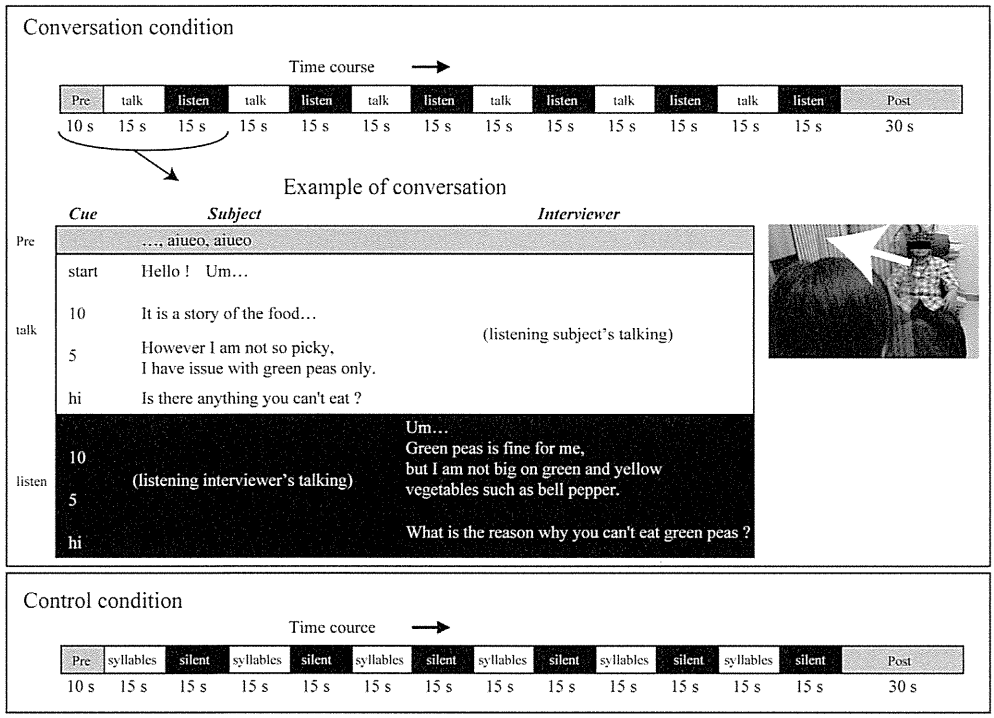

Fig. 1. Time course of task conditions and photograph of study setting. Two activational task conditions, a conversation condition and a control condition, were evaluated. Each task consisted of a pretask, task, and posttask segment. During the task segment of the conversation condition, the subjects engaged in 6 cycles of 30 s conversational exchanges, for a total conversation time of up to 180 s, while facing the interviewer. During the pretask and posttask segments, the subject and interviewer were separated by a partition so that they could not see each other. The example of a conversation shows the time course of conversation during first 40 s. As shown in the right-hand photograph, the subjects wore a near-infrared spectroscopy probe on their foreheads while they were sitting and facing the interviewer. During the task segment of the control condition, the subjects repeated meaningless syllables during their turn to speak.

The order of the 2 tasks was counterbalanced among the subjects. The interviewers who engaged in the conversation task were selected among hospital staff members not acquainted with the subjects.

2.2.1. Conversation task

The conversation task, which comprised *pretask*, *task*, and *posttask* segments, was designed to simulate a typical conversation in an experimental setting. Each session began after NIRS probes had been placed on the subject's frontal and temporal regions as he/she sat face-to-face and 1-m apart from an interviewer on a comfortable chair. To eliminate the possible influence of facial cues before and after engaging in conversation, a partition was placed between the subject and interviewer during the pretask and posttask segments and was removed during the task segment.

To avoid qualitative and quantitative differences among conversations, all subjects 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 an *a priori* time course of conversation according to which the subject and interviewer spoke in turn every 15 s, which was maintained via spoken cues regarding elapsed time from the experimenter every 5 s. Thus, the task consisted of 6 cycles of 30-s speech segments, with the entire conversation lasting for 180 s. Second, the participants were to limit the subjects of the conversation to food-related topics. During the pretask and posttask segments, subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/, that is, the Japanese counterparts of the sounds "A," "B," and "C" in English, to exclude the effects of phonation and stabilize baseline conditions. The conversations of 15 patients with SC 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 the subjects was quantitatively evaluated as *speaking time* (ST), which corresponded to the duration of the subjects' speech, as measured by videotaped data analysis. Second, the content was qualitatively evaluated by 2 expert psychiatrists in terms of the *receiving aspect score* (RS), which indicates speech appropriateness in the context of a conversation, and the *sending aspect score* (SS), which indicates the extent of production of new topics. Before assessment, these experts knew the subject's group, but did not have any more detailed information. To measure the RS, the subjects' replies to the preceding conversation were scored as 1 = inappropriate, 2 = partially inappropriate, 3 = partially appropriate, or 4 = appropriate. To measure the SS, the subjects' questions to the interviewer were scored as 1 = no new topic(s), 2 = nearly the same topic(s), 3 = partially new topic(s), or 4 = completely new topic(s). We used the averaged RS and SS evaluated by 2 expert psychiatrists for correlational analyses.

2.2.2. Control task

To examine brain activation and artifact contamination induced by phonation alone, the subjects 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 during the task segment of the conversation task. All subjects were able to repeat the syllables without interruption.

2.3. NIRS measurement

[oxy-Hb] changes were measured as an index of changes in cerebral blood volume and in deoxyhemoglobin concentration [deoxy-Hb] using a 52-channel NIRS machine (Hitachi ETG-4000;

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Hitachi Medical Systems, Tokyo, Japan). As the machine measures points at a depth of 2–3 cm from the scalp, i.e., at the surface of the cerebral cortex (Hock et al., 1997; Toronov et al., 2001), a distance of 3 cm was maintained between the emission and detector probes placed on the subject's frontal and temporal regions. To allow the frontal and temporal probes to measure [oxy-Hb] changes at 52 measurement points over a 6 × 30-cm area, the lowest probes were positioned along the Fp1–Fp2 line in accordance with the international 10/20 system, and the measurement points were labeled Ch1–Ch52, from top to bottom.

The correspondence between the NIRS channels and measurement points on the cerebral cortex was confirmed by comparison with the results of a multisubject study of anatomical craniocerebral correlation (Okamoto et al., 2004), and was displayed based on the results obtained using the virtual registration method (Fig. 3) (Tsuzuki et al., 2007). The absorption of near-infrared light at 2 wavelengths (780 and 830 nm) was measured at a time resolution of 0.1 s, and the data collected were analyzed using the integral mode. The pretask baseline was determined as the mean across the last 10 s of the 30-s pretask segment, and the posttask baseline was determined as the mean across the last 10 s of the 30-s posttask segment; linear fitting was applied subsequently to the data between these 2 baselines. A moving average window of 5 s was applied to exclude the interference of short-term motion artifacts from the analyzed data.

2.4. Data analysis

We analyzed Cohen's kappa for SS and RS of both the groups to investigate inter-rater reliability. The behavioral data (ST, RS, and SS) collected from the 2 groups were compared using 1-way analysis of variance (ANOVA). Spearman's r values between the PANSS scores and behavioral data were calculated, because the number of subjects with behavioral data in both groups was small. The waveforms of [oxy-Hb] changes in all 52 channels during the conversation and control conditions were calculated for all subjects. NIRS data from channels 1 to 21, which clearly contained motion artifacts, as determined by close observation of the subjects, were excluded from further analysis. The [oxy-Hb] data collected during the pretask, task, and posttask segments from each channel for both the conversation and control tasks were averaged by each channel and each task, excluding the pretask and posttask segments. The averaged [oxy-Hb] data for the conversation and control tasks were analyzed using a mixed-design repeated-measures ANOVA by using diagnosis (SC or NC) as the between-subjects variable and task type (conversation task or control task) as the within-subjects variable. Results were corrected for the number of channels by using false discovery rate (FDR) correction, to avoid type I errors. When an interaction was indicated, a post-hoc t test with diagnosis was performed for both conditions ($P < 0.05$).

When averaged [oxy-Hb] data collected during tasks indicated significant differences among patients with SC, Pearson's r value was calculated (i) among the grand-average value of [oxy-Hb] changes showing significant differences and (ii) among current age, age of onset, illness duration, GAF score, PANSS subscores, and drug dosage ($P < 0.05$); in addition, Spearman's r was calculated for the grand-average value of [oxy-Hb] changes showing significant differences in behavioral parameters (ST, RS, and SS).

3. Results

3.1. Participant characteristics (Table 1)

The age and sex ratios of the 2 groups were not significantly different ($F = 0.418$, $P = 0.520$; chi-squared [1] = 0.007, $P = 0.935$).

3.2. Behavioral data analysis

The weighted Cohen's kappa for RS of the NC ($\kappa w = 1$) and SC ($\kappa w = 0.75$) groups indicated high agreement, whereas that for SS of the NC ($\kappa w = 0.54$) and SC ($\kappa w = 0.21$) groups indicated moderate or poor agreement. The mean total ST observed during the conversation task was 70.3 s (SD, 9.9) for the SC group and 77.7 s (4.9) for the NC group (F [1, 42] = 10.79, $P = 0.002$). The mean total RS was 3.0 (0.9) and 4.0 (0.2) for the SC and NC groups, respectively (F [1, 42] = 32.481, $P = 0.000$). The mean total SS was 2.6 (0.9) for the SC group and 3.4 (0.9) for the NC group (F [1, 42] = 8.314, $P = 0.006$). The percent histogram of behavioral data results shows that almost 50% of the patients with SC had ST and RS similar to that of NCs (Fig. 2). Further, the pattern for SS was different from those of ST and RS; both patients with SC and some NCs had a low SS score.

3.3. Analysis of the grand averaged [oxy-Hb] changes during conversation and control tasks

The results of the mixed-design repeated-measures ANOVA for [oxy-Hb] changes in each channel using diagnosis as the between-subjects variable and task as the within-subjects variable revealed a significant main effect of task for 31 channels (Ch22–52; F [1, 57] = 10.30–95.67; FDR-corrected $P = 0.000$–0.002), a significant main effect of subject for 2 channels (Ch45 and Ch52; F [1, 57] = 10.23–12.78; FDR-corrected $P = 0.001$–0.002), and interactions between diagnosis and task for 12 channels (Ch23, Ch32–35, Ch41–45, Ch51, and Ch52; F[1, 57] = 5.86–13.39; FDR-corrected $P = 0.001$–0.019). Because diagnosis and task showed significant interactions, we performed a post-hoc t test of [oxy-Hb] changes during the conversation and control tasks. The results of this test for the conversation task, using diagnosis as the independent variable, revealed significant effects of diagnosis on [oxy-Hb] changes at 6 channels (Ch34, Ch41, Ch44, Ch45, Ch51, and Ch52; t [1, 58] = 2.74–4.05; FDR-corrected $P = 0.000$–0.008). The results of the post-hoc t test indicated that the brain areas showing differences between the groups were the 2 temporal lobes and the right inferior frontal gyrus (IFG), according to the virtual registration method (Fig. 3). The results of the post-hoc t test for [oxy-Hb]

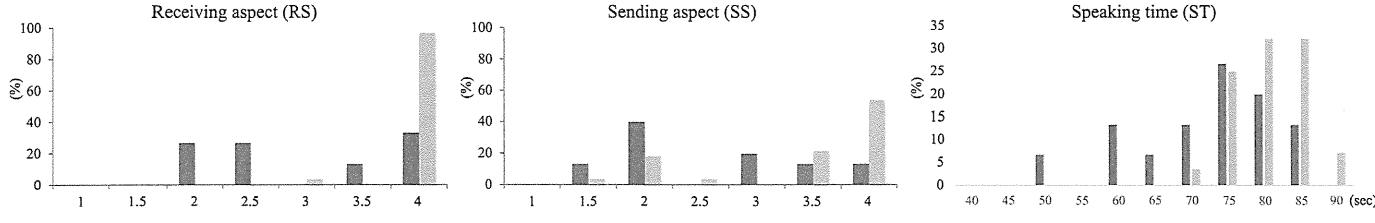

Fig. 2. Percent histogram of behavioral data results. Averaged receiving aspect score (RS, left) and sending aspect score (SS, middle), as evaluated by 2 expert psychiatrists, and speaking time (ST, right). The x-axes of the left and middle figures indicate RS and SS and that of the right figure indicates ST. The y-axes of the 3 figures indicate the percentage of subjects for each score. Green bar, normal controls; red bar, patients with schizophrenia. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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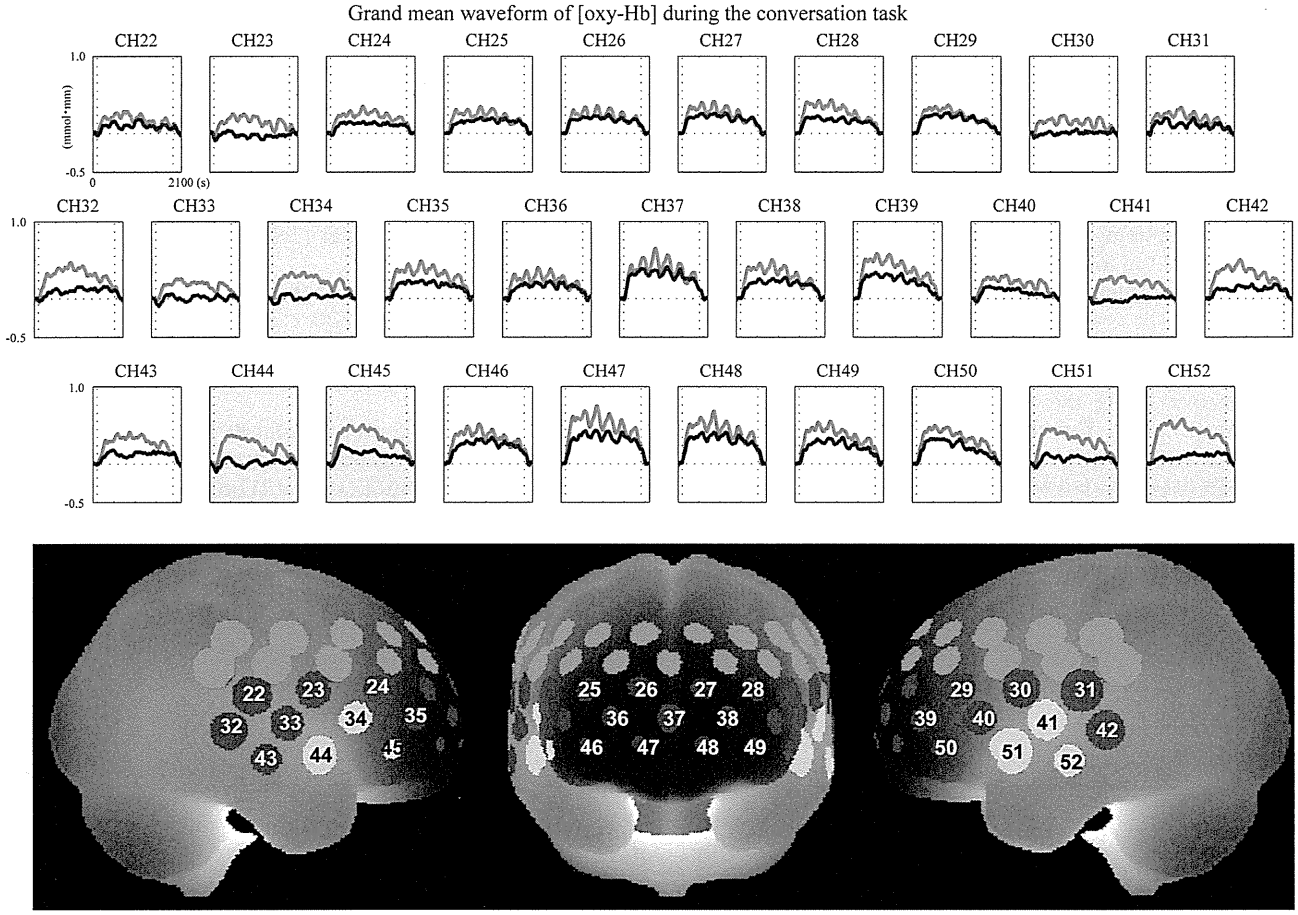

Fig. 3. Grand mean waveform of [oxy-Hb] during the conversation task. Upper 31 figures (Ch22–52): green line, control subject; red line, schizophrenic subject. The yellow channels of the upper figures show significant differences between groups, as assessed using the post-hoc *t* test. The 3 figures 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 areas indicate the corresponding brain areas that differed between the groups, according to the results of the post-hoc *t* test. Gray channels without a number are channels that were excluded because of detection of clear motion artifacts. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

changes during the control task, using diagnosis as the independent variable, revealed no significant effect of diagnosis on [oxy-Hb] changes (Fig. 4).

3.4. Correlation analysis of brain activation, PANSS subscores, and behavioral data

In the SC group, the mean total [oxy-Hb] change was negatively correlated with illness duration (Ch45, $R = -0.389$, $P = 0.037$), PANSS disorganization subscore (Ch45, $R = -0.429$, $P = 0.020$; Ch51, $R = -0.503$, $P = 0.005$; and Ch52, $R = -0.422$, $P = 0.023$), and PANSS negative symptom subscore (Ch34, $R = -0.370$, $P = 0.048$; and Ch52, $R = -0.430$, $P = 0.020$; Fig. 5). The mean total [oxy-Hb] change was not correlated with behavioral parameters (ST, RS, and SS), current age, age of onset, GAF score, PANSS positive symptom, emotional distress subscore, or drug dosage. However, the PANSS excitement subscore was negatively correlated with SS ($r = -0.677$, $P = 0.006$).

4. Discussion

4.1. Correlation between conversation performance and PANSS subscores

Almost 50% of the patients with SC showed ST and RS similar to those of NCs. There is evidence suggesting that about 20–50% of patients with SC perform at the same level as controls on a wide range of tasks devised to examine social cognition (Brune and Schaub, 2012). Although the conversation task contains several other elements of the cognitive domain, in addition to elements of social cognition, our results were consistent with those of previous studies. Further, the pattern for SS was different from those of ST and RS; both patients with SC and some NCs had a low SS. In patients with SC, the PANSS excitement subscore was negatively correlated with SS. This was expected, because compared to poor performers, fair mental-state performers show lesser disorganization and excitement (Brune et al., 2011). However, the brain activation of patients with SC was not correlated with any behavioral parameter; this unexpected finding may be due to 3 factors. First, only a small amount of behavioral data could be collected and analyzed, as only 15 of the 31 patients agreed to be video recorded. If more behavioral data had been collected, significant correlations between brain activation and task performance might have been detected. Second, among the 3 parameters used to evaluate behavior during speech—ST, RS, and SS—only ST could be considered relatively objective, as RS and SS reflected the subjective views of the experts evaluating behavior. The weighted Cohen's kappa of SS indicated moderate or poor agreement. The establishment of an entirely objective measurement of behavior during speech may help identify significant correlations between brain activation and task performance. Third, the imposition of an unnatural situation

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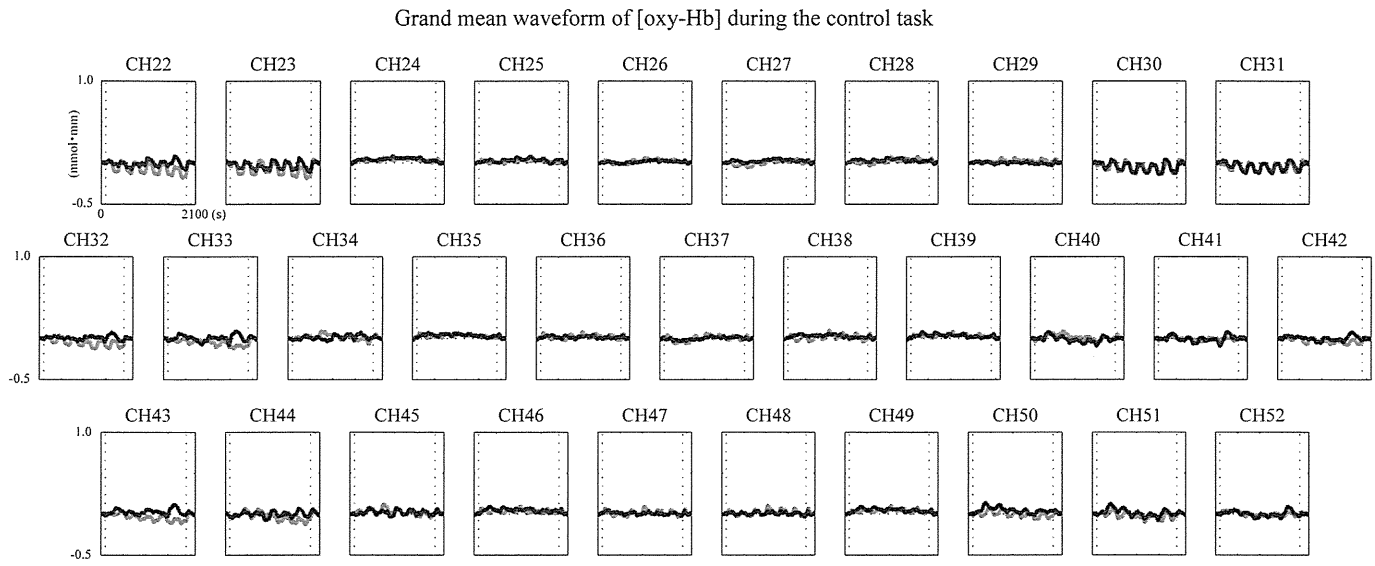

Fig. 4. Value of mean total changes in the waveform of [oxy-Hb] during the control task. Green line, normal controls; red line, schizophrenic subjects. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(15-s conversation cycles) and a limited conversation topic (food), which were selected for ease of data analysis, may have masked social-cognition deficits during conversation.

4.2. Decreased activation during face-to-face conversation

No intergroup difference in activation was found during the control task, indicating that baseline activation during the task segment was not been affected by phonation. The decreased activation in both the temporal lobes and in the right IFG observed in patients with SC during conversation is difficult to interpret directly, as activation during conversation encompasses various cognitive functions, but is consistent with the findings of previous voxel-based morphometry studies. In a review of that type of studies on schizophrenia, Honea et al. concluded that the left superior temporal gyrus and medial temporal lobe are the key regions involved in structural differences among patients with SC (Honea et al., 2005). Considering that NIRS cannot be used to evaluate deep brain regions (e.g., the hippocampus and medial frontal cortex), the findings of this study are in accordance with those of MRI volume studies. Although we acknowledge that the effect of the distance between NIRS probes and the cortex must be considered, the differences in temporal activity found in this study cannot be attributed to this distance, as no intergroup difference in activation was found during the control task.

Considering the theorized inverted-U-shaped nature of prefrontal PFC functioning (Callicott et al., 2003), we hypothesized that the patients with SC have decreased frontal activation during conversation because their frontal lobe becomes highly loaded during conversation. However, no significant differences in frontal lobe activity, with the exception of that observed in the right IFG, were found between the 2 groups. One possible interpretation for this finding is that patients with SC modulate conversation to optimize frontal lobe activation to compensate for temporal lobe dysfunction.

4.3. Temporal lobe hypoactivation and clinical assessment

Many studies have reported a correlation between superior temporal gyrus functioning and auditory hallucinations (Barta et al., 1990; Nenadic et al., 2010). Several researchers have reported a correlation between superior temporal gyrus functioning and thought disorders: Shenton et al. reported a correlation between left temporal lobe volume and thought-disorder severity (Shenton et al., 1992), whereas Nestor et al. showed a significant relationship between reduced volume in the temporal lobe regions and neuropsychological deficits in abstraction, categorization, and verbal memory (Nestor et al., 1993). Koutsouleris et al. found that the PANSS dimension of disorganization is associated with bilateral alterations in the temporal, insular, and medial prefrontal cortices, whereas the PANSS dimension of negative symptoms is linked to the temporal, orbitofrontal, medial prefrontal, and lateral prefrontal cortices, as well as to the limbic and subcortical structures (Koutsouleris et al., 2008). These findings are consistent with a major finding of this study: decreased activation in the left temporal lobe is correlated with PANSS disorganization and negative symptom subscores.

Previous neuropsychological studies have reported a pattern of deficits related to frontal and temporal lobe functioning in patients with SC (Gur, 2011; Liddle, 1996; Suto et al., 2004). Although basic cognitive function deficits have been investigated more than social cognitive function deficits have, the latter have begun to garner increased attention in studies on SC. The brain mechanism underlying social interactions is currently one of the most enthusiastically discussed topics in neuroscience, within which the temporal lobe, orbitofrontal cortex, amygdala, medial prefrontal cortex, anterior cingulate cortex, insula, and parietal region have been described as the substrates of the "social brain" (Frith, 2007; Frith and Frith, 2006; Frith, 2001; Gallagher and Frith, 2003; Van Overwalle and Baetens, 2009).

Although we did not directly assess social cognitive ability by using neuropsychological methods, such as the ToM task, this ability is essential for smooth face-to-face conversation. Brune et al. reported that mentalizing skills were the best cognitive predictor of social skills in SC, whereas neurocognition (i.e., executive planning skills) did not mediate this effect, and fair mental-state performers showed lesser disorganization and excitement symptoms than did poor performers (Brune et al., 2011). SC symptoms, as evaluated by PANSS subscores, especially the disorganization subscore, are negatively correlated with ToM skills (Abdel-Hamid et al., 2009). This finding concurs with that of previous ToM research on schizophrenia, which identified a relationship between poor ToM

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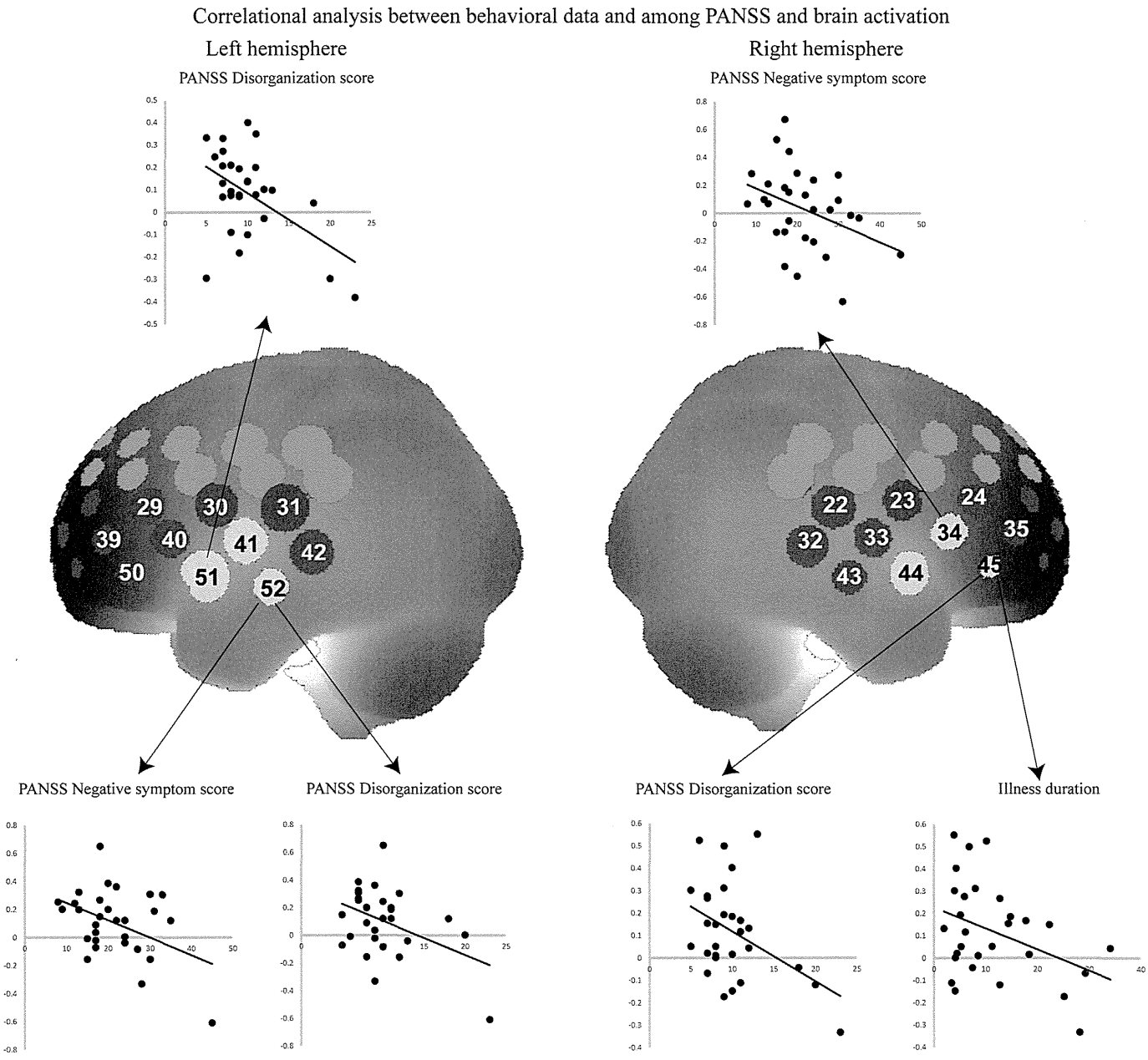

Fig. 5. Correlation analysis of behavioral data, PANSS subscores, and brain activation. Correlation analysis of illness duration and PANSS negative symptom and disorganization subscores and value of mean total changes in the waveform of oxygenated hemoglobin concentration ([oxy-Hb]) during the conversation task in brain regions Ch34, 45, 51, and 52.

skills and decreased activation or decreased gray matter volume, mainly in the temporal lobe and ventromedial PFC (Benedetti et al., 2009; Hooker et al., 2011; Sugranyes et al., 2011). Taken together, these previous findings suggest that the decreased temporal lobe activation observed in this study may be related to the use of ToM skills by patients with SC during conversation. Frith et al. argued that the primary role of the temporal lobes is the application of general knowledge (specifically, knowledge regarding thoughts and feelings most likely to occur in a particular context) to a current situation (Frith, 2007). Considering the role of the temporal lobes in social cognition, the SC symptoms observed during conversation are well explained by decreased temporal lobe activation. The correlation found here between left temporal lobe activation and PANSS disorganization and negative symptom subscores provides further support for this relationship between SC symptomatology and decreased temporal lobe activation.

4.4. Right IFG hypoactivation and clinical assessment

Right IFG activation was negatively correlated with illness duration and with PANSS disorganization and negative symptom subscores. This finding is partly consistent with the previous findings of Suga et al., who observed significant reduction in volume, especially in the right hemisphere, in the IFG (Brodmann area [BA] 44 and BA 45) of patients with SC compared to NCs, and found that the severity of positive and disorganized symptoms is correlated with bilateral BA 45 volume (Suga et al., 2010). It is also partly consistent with the results of Premkumar et al., who reported that the right middle frontal cortex is particularly affected by illness duration, whereas the dorsomedial PFC, fusiform gyrus, and cerebellum are affected by both illness duration and aging (Premkumar et al., 2008). Previous findings suggest that BA 45 might be particularly involved in SC symptoms associated with

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aberrant semantic processing. The negative correlation found between right IFG activation and disorganization in patients with SC may be attributed to right IFG dysfunction during conversation, which can cause aberrant semantic processing resulting in disorganization.

4.5. Limitations

This study has 3 major limitations that may hinder the generalizability of its findings. First, we used imprecise methods to evaluate behavior during conversation. Second, we evaluated data collected primarily from outpatients, most of whom had mild SC; thus, the study lacked representation of patients with severe SC, who are likely to be inpatients. Third, the correlation between NIRS data and psychotropic medication could not be investigated because almost all subjects were taking more than 1 medication at the time of the study. Future studies using precise methods for evaluating behavior during conversation under drug-free conditions, as well as longitudinal follow-up cohort studies involving premorbid patients, are planned.

4.6. Conclusions

NIRS data analysis to investigate frontal and temporal lobe activation in patients with SC and NCs during face-to-face conversation *in situ* indicated intergroup differences in brain activation. Notably, patients with SC showed hypoactivation of both temporal lobes and the right IFG during conversation tasks. This finding, in addition to that of a strong correlation between speech impairments in patients with SC and their PANSS disorganization and negative symptom subscores, suggests that the disorganization and negative symptoms observed in patients with SC in clinical situations is related to dysfunction of the left temporal lobe and right IFG.

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Contributors

Masashi Suda and Yuichi Takei designed the tasks; Masashi Suda, Yuichi Takei, Yoshiyuki Aoyama, Kosuke Narita, Miho Yamaguchi, and Noriko Sakurai conducted the experiments and analyzed the data; and Yuichi Takei, Masashi Suda, Masato Fukuda, and Masahiko Mikuni wrote the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Differential spatiotemporal characteristics of the prefrontal hemodynamic response and their association with functional impairment in schizophrenia and major depression

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ABSTRACT

Recent neuroimaging studies have shown similarities and differences in prefrontal abnormalities between patients with schizophrenia (SZ) and major depressive disorder (MDD). However, the differential spatiotemporal characteristics of these abnormalities and their association with functional impairment remain unclear. To elucidate differential brain pathophysiology in these disorders, we used multichannel near-infrared spectroscopy (NIRS) to measure the spatiotemporal characteristics of prefrontal activation and investigated their association with global functioning levels. The study included 96 individuals: 32 patients with SZ, 32 patients with MDD, and 32 demographically matched healthy subjects. During a verbal fluency task, the changes in oxygenated and deoxygenated hemoglobin ([oxy-Hb] and [deoxy-Hb]) signals over the prefrontal cortex (PFC) were measured using 52-channel NIRS and compared among the 3 groups. Patients with SZ and MDD showed lesser-than-normal [oxy-Hb] activation during the task, whereas the initial slope of [oxy-Hb] activation was steeper for patients with MDD than for patients with SZ. The reduced hemodynamic response was associated with lower global functioning, and the correlative regions were different between the 2 disorders (frontopolar PFC in SZ; dorsolateral and ventrolateral PFC in MDD). The hypofrontality observed in patients with SZ and MDD is consistent with the findings of previous neuroimaging studies. Moreover, the spatiotemporal characteristics and the functional significance of the prefrontal hemodynamic response could differentiate the 2 psychiatric disorders. These results suggest a differential brain pathophysiology between SZ and MDD. Future large-scale studies are needed to determine the practical applicability of these findings for clinical diagnosis and evaluation.

1. Introduction

Psychiatric studies using neuroimaging techniques (functional magnetic resonance imaging [fMRI] and positron emission tomography [PET]) performed during cognitive activation tasks, such as the verbal fluency task (VFT) (Yurgelun-Todd et al., 1996), n-back task (Driesen et al., 2008; Manoach et al., 1999), and mental arithmetic task (Hugdahl et al., 2004), have consistently shown abnormalities in task-associated activation of the prefrontal cortex (PFC) in patients with schizophrenia (SZ) compared with healthy controls (HCs).

Reduced prefrontal activation during cognitive activation tasks has been observed in patients with major depressive disorder (MDD). However, the abnormal increase or decrease in PFC activation in these patients seems to depend on the type of cognitive task and experimental design. Compared to HCs, patients with MDD were shown to have reduced PFC activation in the VFT (Okada et al., 2003), digit-sorting task (Siegle et al., 2007), AX continuous performance task (Holmes et al., 2005), and emotional task (Liotti and Mayberg, 2001; Mayberg et al., 1999). Conversely, patients with MDD have been reported to have increased activation in the bilateral dorsolateral PFC (DLPFC) during the mental arithmetic task (Hugdahl et al., 2004) and in the left DLPFC during the high-loaded working memory task (Harvey et al., 2005).

Some researchers have compared the functional neuroimaging differences in impaired brain functions between SZ and MDD (Barch et al., 2003; Berman et al., 1993; Holmes et al., 2005; Hugdahl et al., 2004; Walter et al., 2007). Holmes et al. (2005) suggested that patients with SZ and MDD exhibit decreased PFC

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