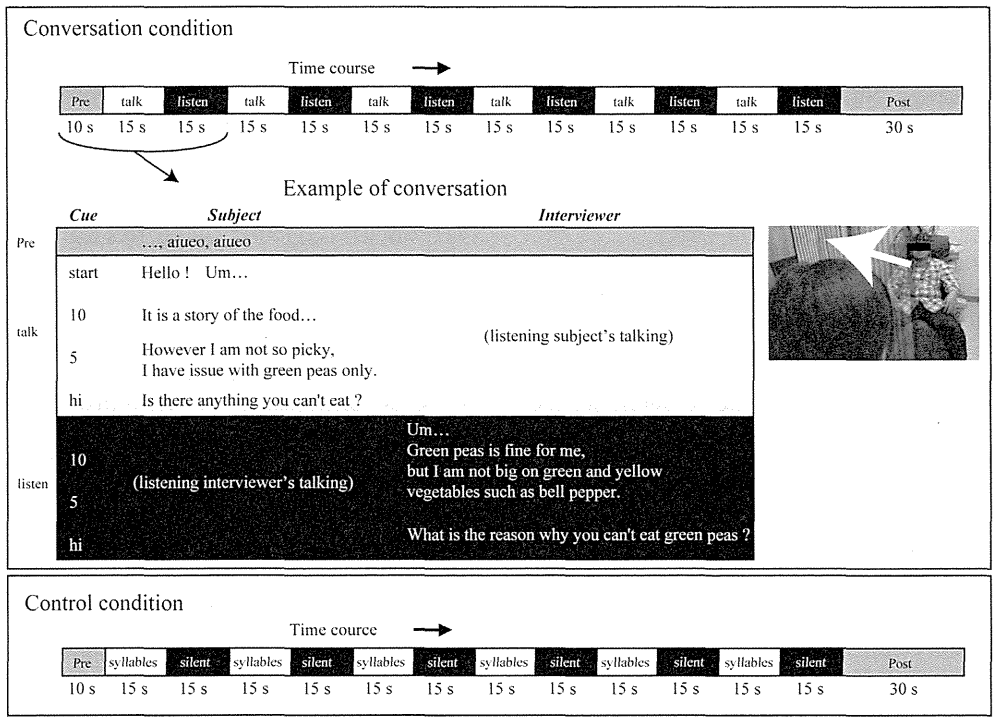

Fig. 1. Time course of task conditions and photograph of study setting. Two activational task conditions, a conversation condition and a control condition, were evaluated. Each task consisted of a pretask, task, and posttask segment. During the task segment of the conversation condition, the subjects 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;

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]

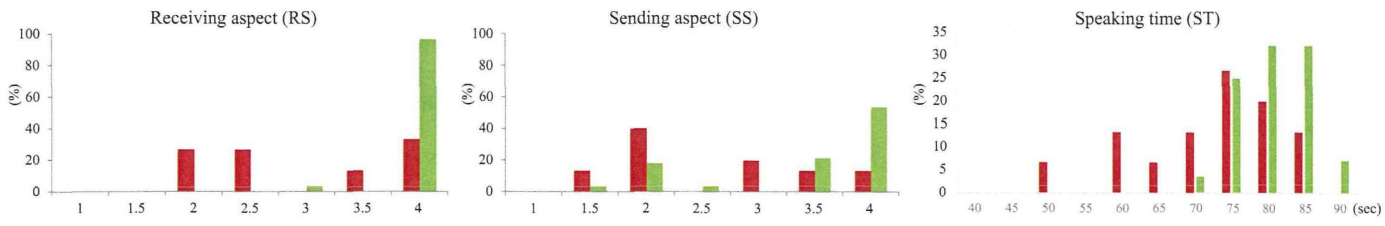

Fig. 2. Percent histogram of behavioral data results. Averaged receiving aspect score (RS, left) and sending aspect score (SS, middle), as evaluated by 2 expert psychiatrists, and speaking time (ST, right). The x-axes of the left and middle figures indicate RS and SS and that of the right figure indicates 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.

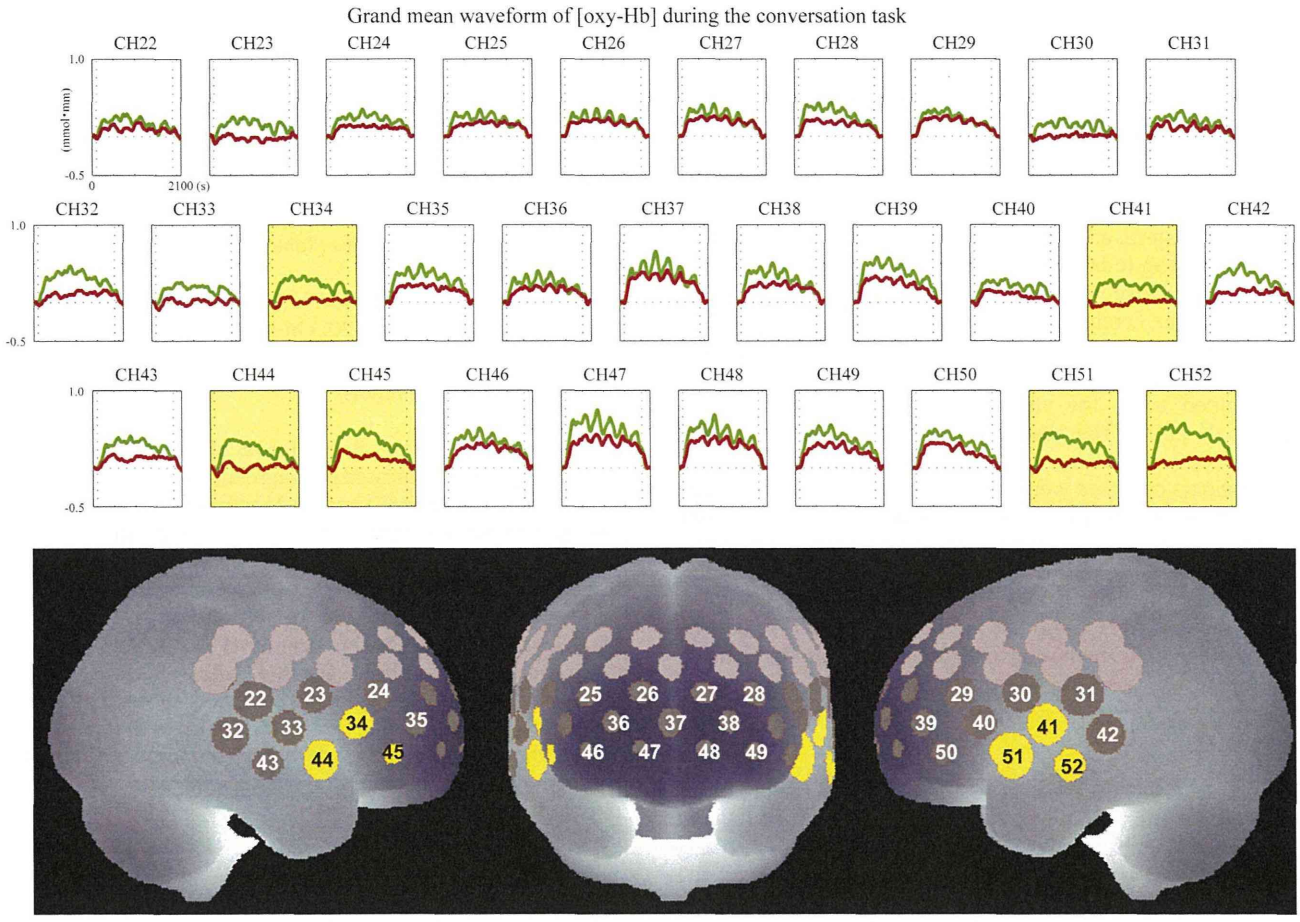

Fig. 3. Grand mean waveform of [oxy-Hb] during the conversation task. Upper 31 figures (Ch22–52): green line, control subject; red line, schizophrenic subject. The yellow channels of the upper figures show significant differences between groups, as assessed using the post-hoc *t* test. The 3 figures 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.

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

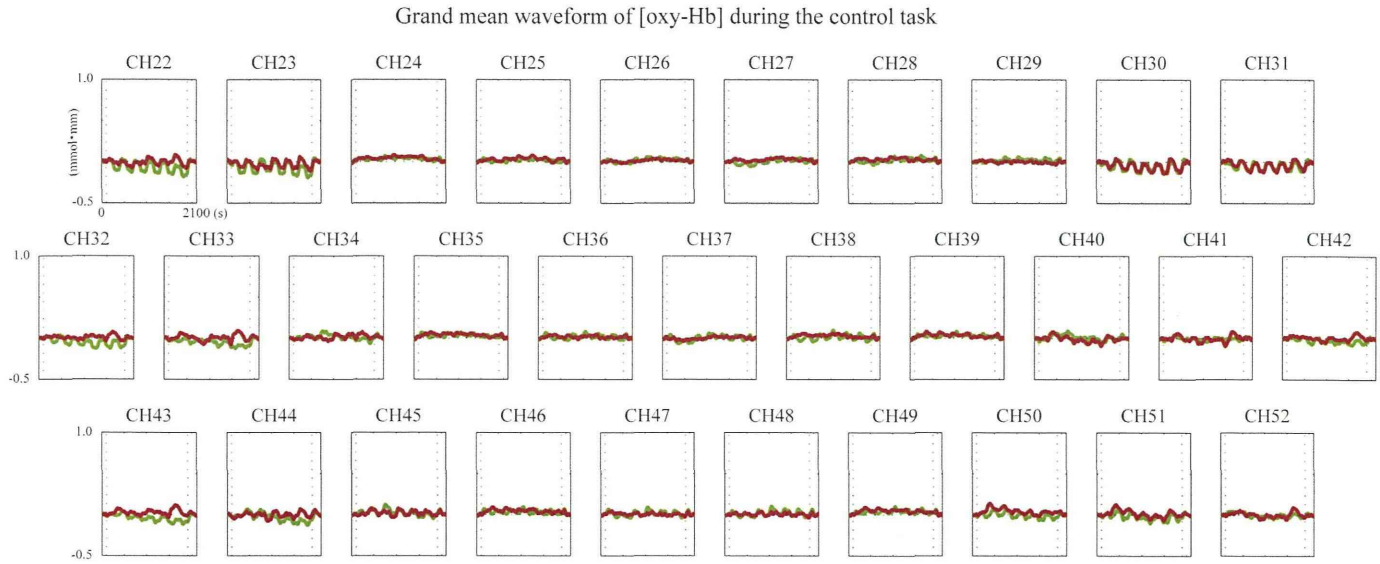

Fig. 4. Value of mean total changes in the waveform of [oxy-Hb] during the control task. Green line, normal controls; red line, schizophrenic subjects.

(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

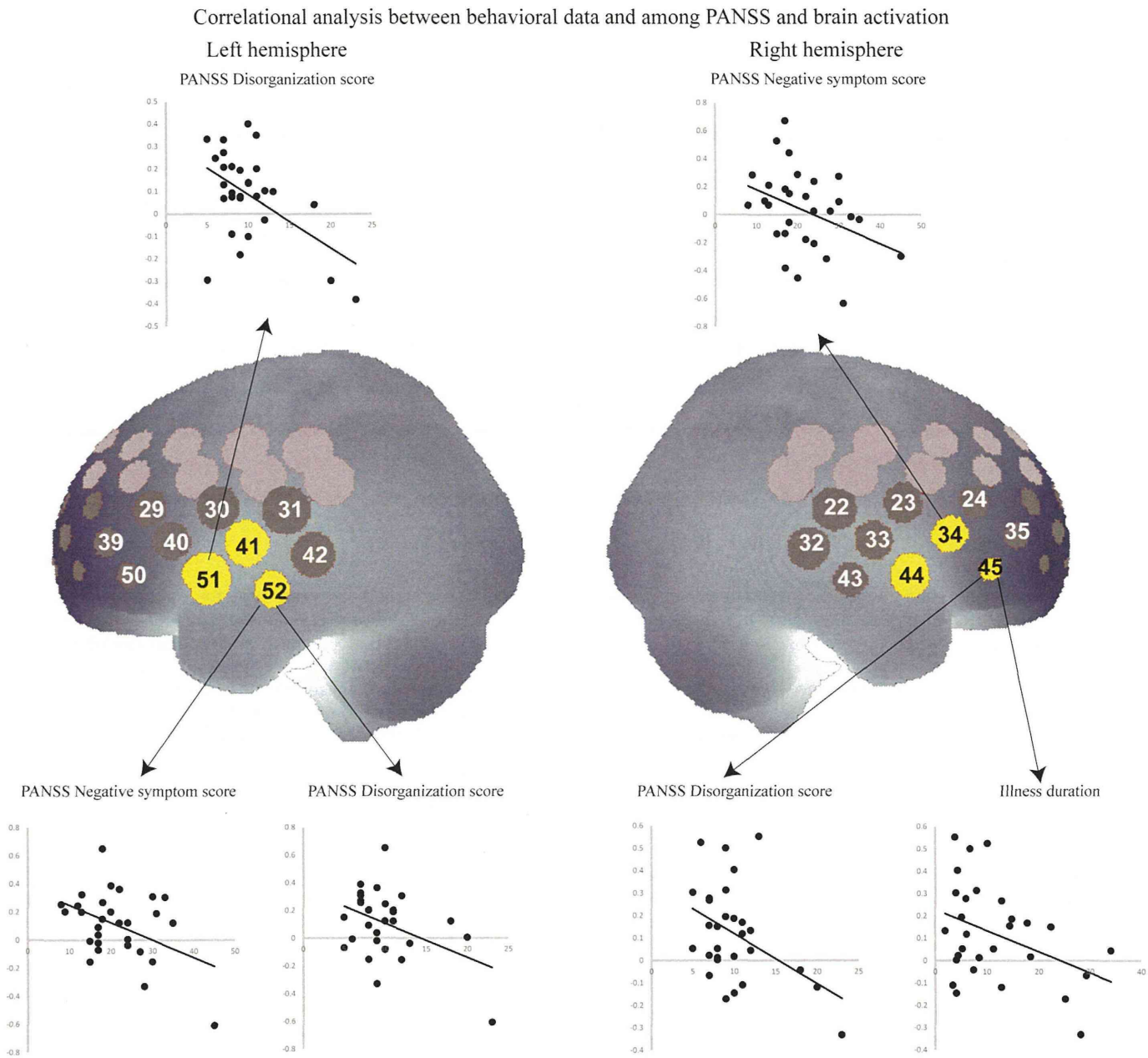

Fig. 5. Correlation analysis of behavioral data, PANSS subscores, and brain activation. Correlation analysis of illness duration and PANSS negative symptom and disorganization subscores and value of mean total changes in the waveform of oxygenated hemoglobin concentration ([oxy-Hb]) during the conversation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

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.

Role of the funding source

This work was supported in part by grants awarded to MF from the Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for Scientific Research on Innovative Areas [4301]); the Japan Society for the Promotion of Science (Grants-in-Aid for Scientific Research [B] [No. 23390286] and for Challenging Exploratory Research [No. 22659209]); the Ministry of Health, Labour and Welfare (Health and Labour Sciences Research Grants, Comprehensive Research on Disability, Health and Welfare, No. H23-Seishin-Ippan-002); the National Center for Neurology and Psychiatry (Intramural Research Grant for Neurological and Psychiatric Disorders, No. 21-1 and 23-10); and the SENSHIN Medical Research Foundation.

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.

Acknowledgments

The authors thank the trainee doctors (Dr. Kameyama, Dr. Narita, Dr. Majima, and Dr. Yonemura) of Gunma University Hospital and the students of Gunma University Faculty of Medicine for serving as study participants. Gunma University (Dr. Fukuda and Dr. Mikuni) and the Hitachi Group (Advanced Research Laboratory, Hitachi Ltd., and the Research and Developmental Center, Hitachi Medical Corporation) have maintained an official contract with Gunma University Hospital for a collaborative study on the clinical application of NIRS in psychiatric disorders since 2002.

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Schizophrenia Research 150 (2013) 459–467

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

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

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ARTICLE INFO

Article history:
Received 15 April 2013
Received in revised form 9 August 2013
Accepted 19 August 2013
Available online 7 September 2013

Keywords:
Schizophrenia
Major depressive disorder
Near-infrared spectroscopy
Prefrontal cortex
Verbal fluency task
Global Assessment of Functioning

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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http://dx.doi.org/10.1016/j.schres.2013.08.026

activations, although the exact regions involved and extent of signal reduction were different between these patient groups. This led us to expect that apparent similar PFC signal reductions observed for patients with SZ and MDD could be derived from differential neurophysiological findings. These functional brain abnormalities might be valuable for investigating differential brain pathophysiology in different psychiatric disorders. Furthermore, neuroimaging techniques could possibly be promising candidates for translation of imaging-guided differential diagnosis and evaluation into clinical settings.

Recently, the number of neuroimaging studies using near-infrared spectroscopy (NIRS), a relatively new method for investigating cerebral hemodynamic activity, has increased (Ferrari and Quaresima, 2012; Irani et al., 2007). NIRS involves irradiation of near-infrared light into the skull and measuring its reflection from oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) (Jobsis, 1977; Koizumi et al., 1999). Compared to other hemodynamic neuroimaging methods (fMRI or PET), NIRS has superior time resolution and inferior spatial resolution and lesser usefulness for detection of deep brain functions. NIRS has the benefits of producing no harmful radiation and being flexible because the NIRS device is compact and portable.

Few fMRI or PET studies have presented the time course of signal change; however, several previous NIRS-based studies have measured time-specific hemodynamic changes in patients with SZ, MDD, and bipolar disorder and clarified the abnormal time course of prefrontal activity in each major psychiatric disorder (Kameyama et al., 2006; Shimodera et al., 2012; Suto et al., 2004). Some of these NIRS studies have also elucidated the association between prefrontal NIRS signals and global functioning levels in psychiatric disorders (Pu et al., 2008; Takizawa et al., 2008). Thus, the specific spatiotemporal characteristics of brain activation patterns in each disorder might become candidate biomarkers of differential brain pathophysiology. However, the previous NIRS studies did not directly compare NIRS signal patterns among different disorders.

In this study, we measured hemodynamic changes during the VFT in patients with SZ and MDD and HCs using concise NIRS measurements in a natural setting. In expansion of a previous study that covered a limited PFC area (Suto et al., 2004), we investigated 3 groups including more subjects ($n = 32$ in each group) with comparable demographic characteristics using a multichannel NIRS machine with a wide coverage over the prefrontal cortical surface area (52 channels, ETG-4000 HITACHI Medical Co.). We also examined the relationship between hemodynamic changes and clinical scores. We hypothesized that the spatiotemporal characteristics of the time course in prefrontal activation patterns differentiate MDD from SZ and are related to global functioning levels in both disorders.

2. Methods

2.1. Participants

This study included 96 individuals: 32 patients with SZ, 32 patients with non-psychotic unipolar MDD, and 32 demographically matched HCs (Table 1). Patients with SZ or MDD did not have any psychiatric comorbidity. The diagnoses of the 2 disorders were established by well-trained psychiatrists (R.T. and K.K.) using DSM-IV criteria. Patients with drug or alcohol dependence and neurological disorders or other organic disorders were excluded. Written informed consent was obtained from all participants. This study was approved by the ethics committees of the University of Tokyo and JR Tokyo General Hospital.

All subjects were right-handed, according to the modified version of the Edinburgh Handedness Inventory (score > 70) (Oldfield, 1971). Participants of each group were matched for age ($F[2, 93] = 1.135$, $p = 0.33$), sex (male:female, 15:17; $p = 1.00$), task performance ($F[2, 93] = 0.113$, $p = 0.33$), and educational level ($F[2, 93] = 1.031$, $p = 0.36$) (Table 1). Hemodynamic response measured by NIRS varies according to the effects of age and sex (Herrmann et al., 2006; Kameyama et al., 2004). Thus, we matched the age and sex of each group to decrease these effects.

Table 1
Clinical characteristics of the study groups.[a]

	Healthy subjects ($n = 32$)	Patients with schizophrenia ($n = 32$)	Patients with depression ($n = 32$)	p value
Sex (male/female)	15/17	15/17	15/17	1.00
Age, years	45.7 ± 13.5	41.7 ± 10.1	44.8 ± 9.8	0.33
Education, years	15.1 ± 2.58	14.9 ± 2.37	14.3 ± 1.91	0.36
Task performance[b]	14.3 ± 3.3	14.8 ± 5.6	13.2 ± 4.7	0.33
PANSS				
Positive	–	15.7 ± 5.00	–	–
Negative	–	22.0 ± 7.11	–	–
General psychopathology	–	38.7 ± 8.47	–	–
HRS-D	–	–	19.6 ± 3.64	–
GAF	–	45.7 ± 14.0	53.3 ± 5.57	–
Medication	–	843 ± 707 (Cp eq. mg)	113 ± 65.7 (Imp eq. mg)	–

Abbreviations: Cp eq., chlorpromazine-equivalent; Imp eq., imipramine-equivalent.
[a] Chi-squared test was used to test group differences in sex distribution. Otherwise, a t test was used.
[b] Number of correct words generated (mean ± SD).

The exclusion criteria for all the groups were neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy (Tess and Smetana, 2009), and alcohol/substance abuse or addiction that might be potential confounders for cognitive tasks. An additional exclusion criterion for the control group was a history of psychiatric disease or a family history of axis I disorders in any first-degree relatives. Any patients with MDD and SZ who had other psychiatric or physical comorbidities were excluded. All patients with SZ, a majority of whom had experienced the first or second episode of acute psychotic symptoms and had had the illness for <10 years, were taking various types of antipsychotic medication, including typical and newer atypical antipsychotics. The average dose of antipsychotic medication was 843 ± 707 mg, as a chlorpromazine-equivalent dose. None of the patients with SZ was in an acute phase, but all had some residual psychiatric symptoms at the time of NIRS measurement. Patients with MDD who also met the DSM-IV criteria for a major depressive episode unipolar type were diagnosed by the same well-trained psychiatrists. The total Hamilton Rating Scale for Depression (HRS-D; 17-item version) (Hamilton, 1960) scores of all patients with depression were above 15, which means in a "full symptomatic" state, to confirm the diagnosis and existence of symptoms (Frank et al., 1991). All, except 3, subjects with MDD were taking various types of antidepressants, such as selective serotonin reuptake inhibitors. The average dose of antidepressant medication was 113 ± 65.7 mg, as an imipramine-equivalent dose.

Psychiatric symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) in patients with SZ, the HRS-D in patients with MDD, and the Global Assessment of Functioning (GAF) scale in both groups of patients (Table 1).

2.2. Task design

We used the VFT (letter fluency version) as a cognitive task. Previous brain imaging studies have consistently shown abnormal brain activations during the VFT in various psychiatric disorders (Audenaert et al., 2000; Okada et al., 2003; Ragland et al., 2008; Videbech et al., 2003). Participants can be easily instructed on the VFT, and this task has a high successful execution rate for subjects, including psychiatric patients. Recent fMRI studies also used the VFT as a cognitive task; however, the noise in the environment in which the VFT is conducted may influence fMRI measurements. During NIRS measurements, participants are in a silent condition, and hence, observers can expect more natural measurements of cerebral activity induced by VFT using auditory stimuli and utterances.

The whole measurement time was 160 s, including 3 segments (30, 60, and 70 s). Concentration changes for the 2 types of hemoglobin molecules ([deoxy-Hb] and [oxy-Hb]) were measured according to our previous methods (Takizawa et al., 2008, 2009). During the first 30-s and last 70-s segments, participants vocalized 5 Japanese vowels repeatedly, which were used as control tasks. During the middle 60-s interval, the participants were instructed to pronounce in overt speech as many words as possible beginning with the letters indicated by a recorded human voice. To avoid a pause in thinking, the indicated letters were changed every 20 s. Thus, in this 60-s cognitive task period, 3 letters were counterbalanced. The number of words produced throughout the cognitive task period were recorded by an observer and counted as task performance.

2.3. NIRS measurements

The 52-channel NIRS machine (ETG-4000; Hitachi Medical Corporation) measures the relative changes in [oxy-Hb] and [deoxy-Hb] using 2 wavelengths (695 and 830 nm) of infrared light, based on the modified Beer–Lambert law. The distance between pairs of detector probes was set at 3.0 cm. A channel was defined as the measurement area between a pair of source–detector probes. [oxy-Hb] and [deoxy-Hb] changes measured by each of the 52-channel detectors were processed to a numerical value [mM · mm] and recorded on the machine every 0.1 s. Further details of the NIRS have been provided elsewhere (Yamashita et al., 1999).

Subjects placed the plastic frame with the injectors and detectors on their head, covering the bilateral prefrontal area. Using this arrangement, hemodynamic changes could be measured in approximate frontopolar PFC (FPPFC), DLPFC, and ventrolateral PFC (VLPFC) areas (Fig. 1), as corroborated by a multisubject study of anatomical craniocerebral correction using the international 10–20 system.

Furthermore, some studies (Kakimoto et al., 2009; Schecklmann et al., 2008), including ours (Kono et al., 2007), have supported the reliability of multiple NIRS measurements during VFT.

2.4. Statistical analyses

The pre- and post-task baselines were determined as the means across the last 10 s of the pre-task period and the last 5 s of the post-task period, respectively. Linear fitting was performed using the data obtained between the 2 baselines. Moving average methods were applied to remove short-term motion artifacts from the analyzed data (moving average window, 5 s). Since all artifacts were not removed using these methods, we used an algorithm developed previously to automatically reject data with artifacts (see supplementary information in our article Takizawa et al., 2008).

Grand mean waveforms averaged across subjects were created separately for the type of [Hb] and for each group. For parametric statistical tests, the measured [Hb] data from each channel were averaged across the 2 periods (pre-task baseline and 60-s task period).

First, to assess any significant increase in [Hb] associated with the task, we compared the mean [Hb] of the pre-task period and that of the task period at each channel by using Student's paired *t* tests. As we performed 52 paired *t*-tests, a correction for multiple comparisons was made using a false-discovery rate (FDR) [two-tailed; we set a value of q that specified the maximum FDR to 0.05, so that there were no more than 5% false-positive results on average (Singh and Dan, 2006)].

For the second analysis, to investigate intergroup differences among the significant channels, we compared the mean [Hb] changes during the task period among the 3 groups for each channel using one-way

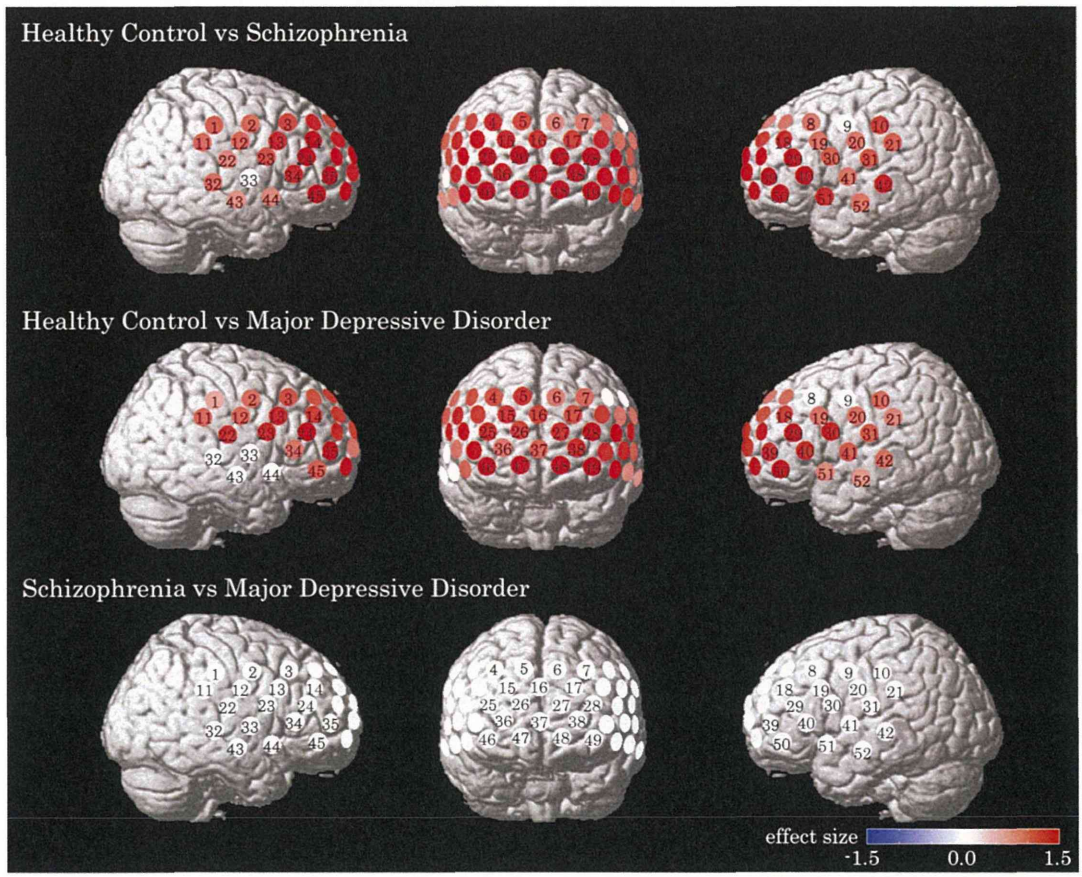

Fig. 1. Group differences in mean [oxy-Hb] increase during the task period. The effect sizes of the group differences are indicated by the color gradient. Channels that did not display significant differences among the 3 groups are colored in white.