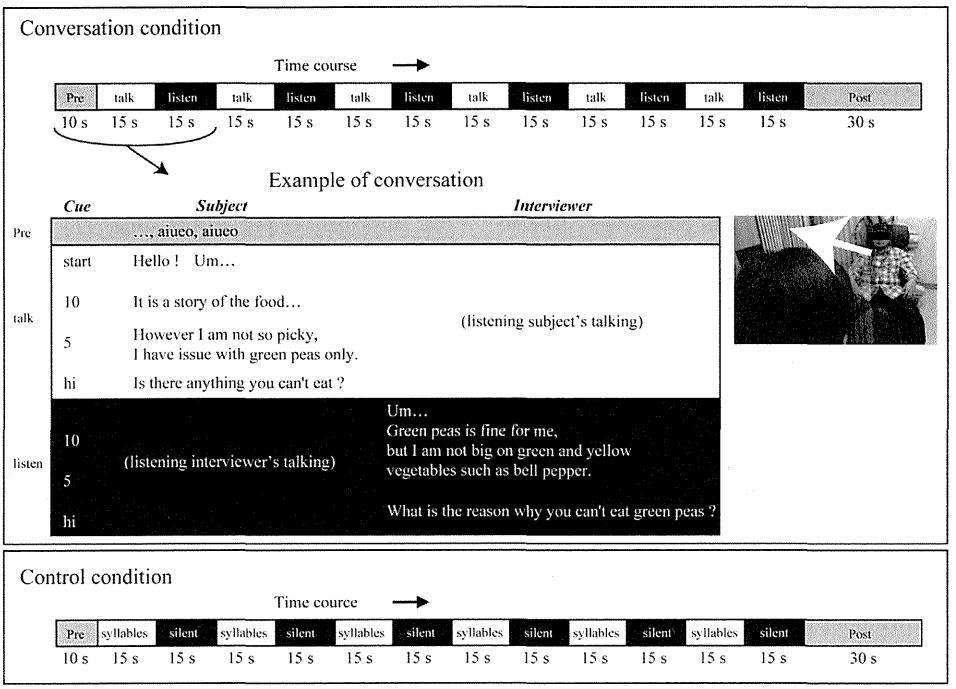

Fig. 1. Time course of task conditions and photograph of study setting. Two activational task conditions, a conversation condition and a control condition, were evaluated. Each task consisted of a pretask, task, and posttask segment. During the task segment of the conversation condition, the subjects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

Please cite this article in press as: Takei Y, et al., Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.07.029

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]

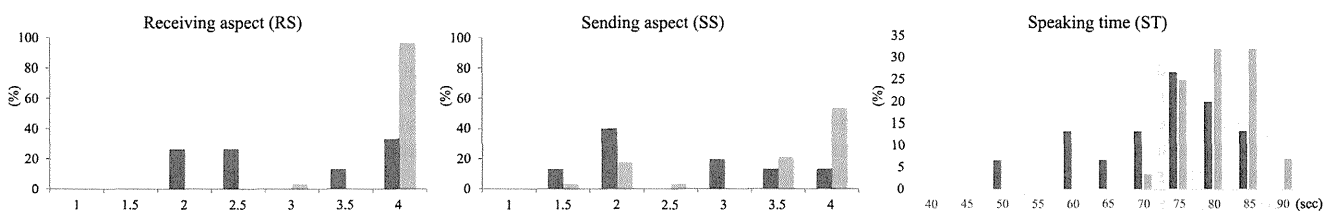

Fig. 2. Percent histogram of behavioral data results. Averaged receiving aspect score (RS, left) and sending aspect score (SS, middle), as evaluated by 2 expert psychiatrists, and speaking time (ST, right). The x-axes of the left and middle figures indicate RS and SS and that of the right figure indicates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

Please cite this article in press as: Takei Y, et al., Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.07.029

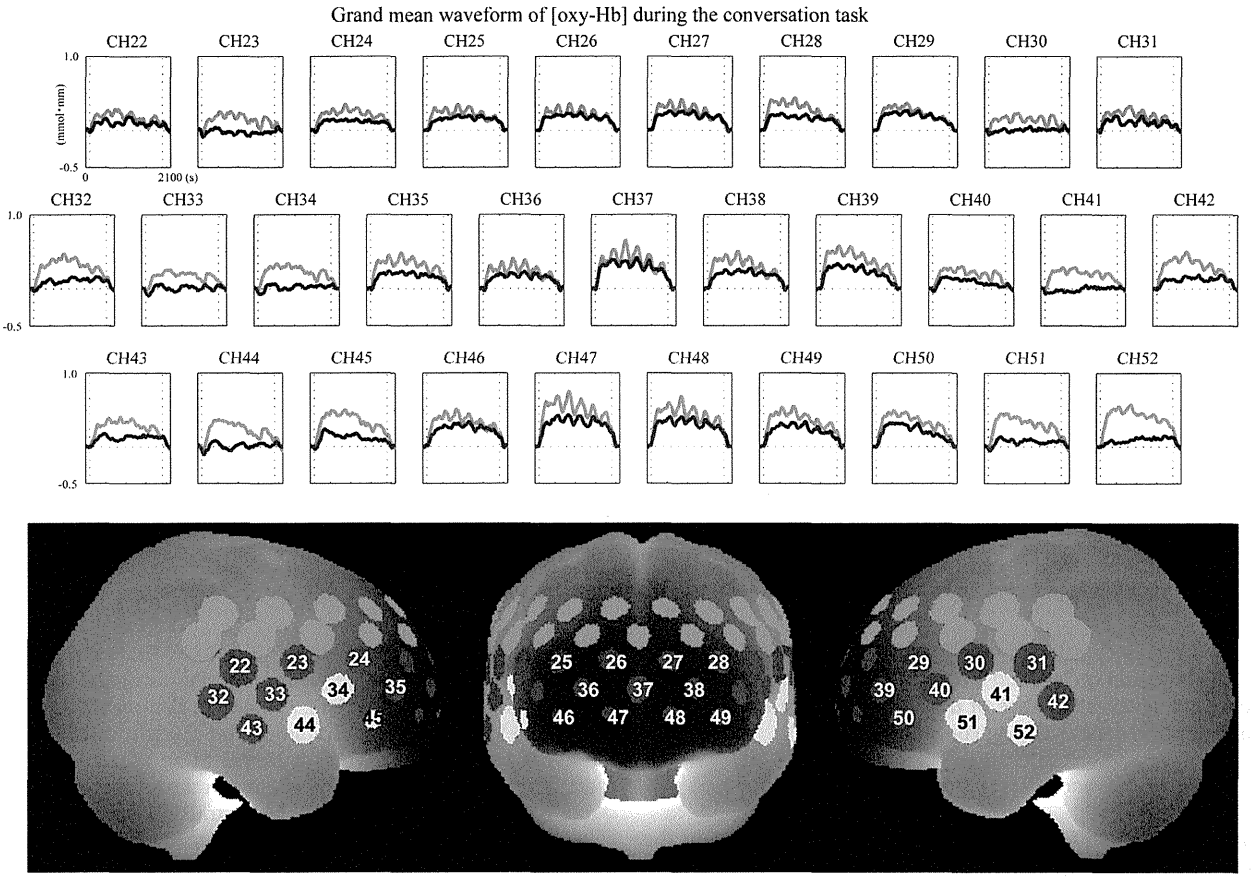

Fig. 3. Grand mean waveform of [oxy-Hb] during the conversation task. Upper 31 figures (Ch22–52): green line, control subject; red line, schizophrenic subject. The yellow channels of the upper figures show significant differences between groups, as assessed using the post-hoc *t* test. The 3 figures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

Please cite this article in press as: Takei Y, et al., Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.07.029

ARTICLE IN PRESS

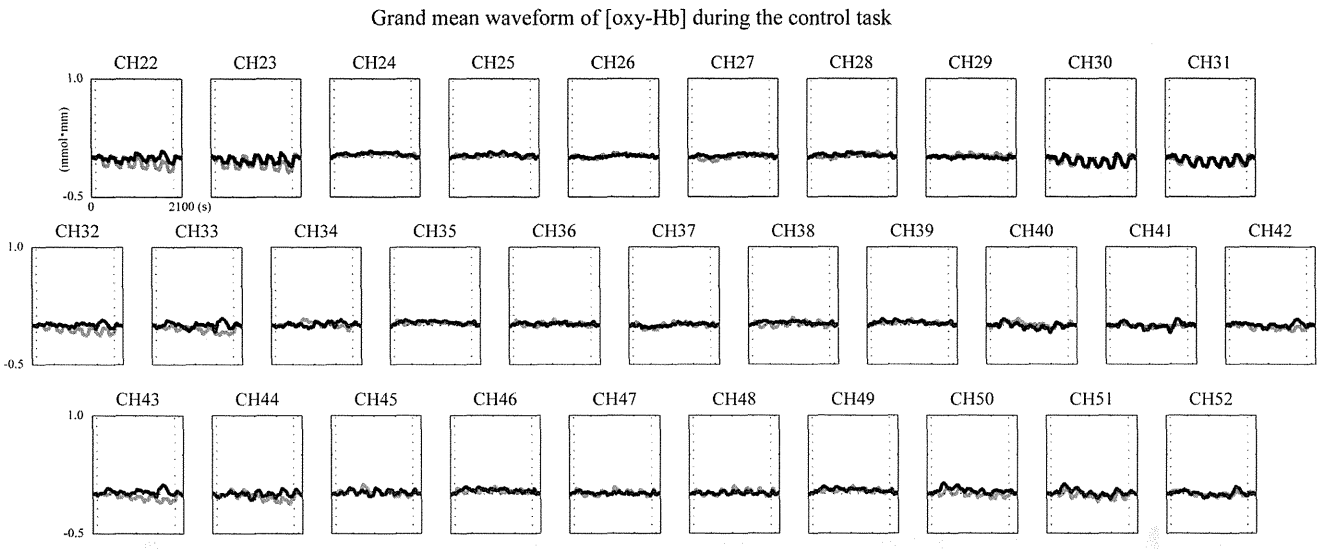

Fig. 4. Value of mean total changes in the waveform of [oxy-Hb] during the control task. Green line, normal controls; red line, schizophrenic subjects. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(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

Please cite this article in press as: Takei Y, et al., Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.07.029

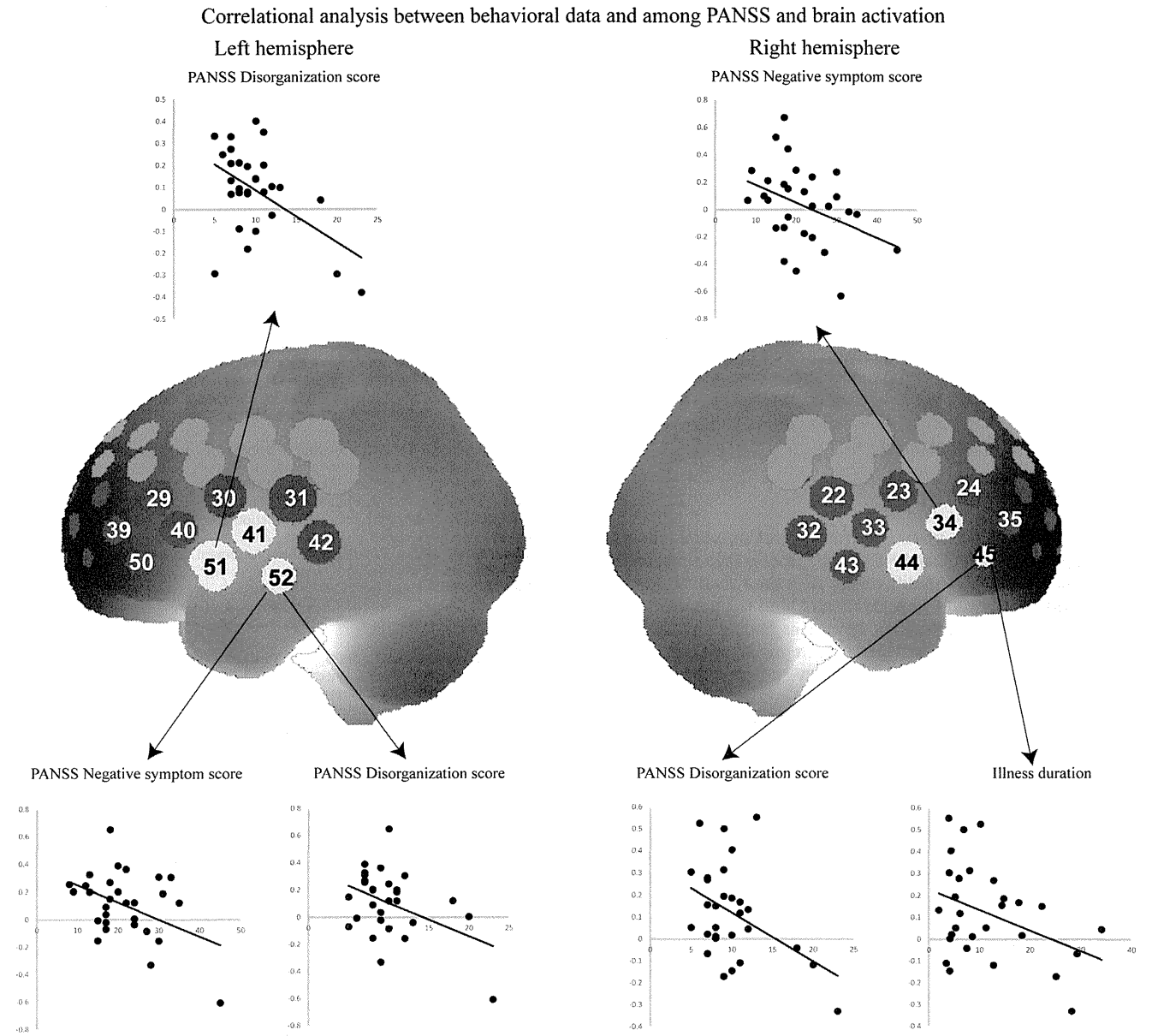

Fig. 5. Correlation analysis of behavioral data, PANSS subscores, and brain activation. Correlation analysis of illness duration and PANSS negative symptom and disorganization subscores and value of mean total changes in the waveform of oxygenated hemoglobin concentration ([oxy-Hb]) during the conversation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

Please cite this article in press as: Takei Y, et al., Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.07.029

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.

References

Abdel-Hamid M, Lehmkamper C, Sonntag C, Juckel G, Daum I, Brune M. Theory of mind in schizophrenia: the role of clinical symptomatology and neurocognition in understanding other people's thoughts and intentions. Psychiatry Research 2009;165:19–26.

Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE. Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. The American Journal of Psychiatry 1990;147:1457–62.

Benedetti F, Bernasconi A, Bosia M, Cavallaro R, Dallaspezia S, Falini A, et al. Functional and structural brain correlates of theory of mind and empathy deficits in schizophrenia. Schizophrenia Research 2009;114:154–60.

Brune M, Schaub D. Mental state attribution in schizophrenia: what distinguishes patients with "poor" from patients with "fair" mentalising skills? European Psychiatry 2012;27:358–64.

Brune M, Schaub D, Juckel G, Langdon R. Social skills and behavioral problems in schizophrenia: the role of mental state attribution, neurocognition and clinical symptomatology. Psychiatry Research 2011;190:9–17.

Callicott JH, Mattay VS, Verchinski BA, Marenco S, Egan MF, Weinberger DR. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. American Journal of Psychiatry 2003;160:2209–15.

Costantini M, Di Vacri A, Chiarelli AM, Ferri F, Romani GL, Merla A. Studying social cognition using near-infrared spectroscopy: the case of social Simon effect. Journal of Biomedical Optics 2013;18:25005.

Cui X, Bryant DM, Reiss AL. NIRS-based hyperscanning reveals increased interpersonal coherence in superior frontal cortex during cooperation. Neuroimage 2012;59:2430–7.

Frith CD. The social brain? Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences 2007;362:671–8.

Frith CD, Frith U. The neural basis of mentalizing. Neuron 2006;50:531–4.

Frith U. Mind blindness and the brain in autism. Neuron 2001;32:969–79.

Gallagher HL, Frith CD. Functional imaging of 'theory of mind'. Trends in Cognitive Sciences 2003;7:77–83.

Gur RE. Neuropsychiatric aspects of schizophrenia. CNS Neuroscience & Therapeutics 2011;17:45–51.

Hock C, Villringer K, Muller-Spahn F, Wenzel R, Heekeren H, Schuh-Hofer S, et al. Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS)—correlation with simultaneous rCBF-PET measurements. Brain Research 1997;755:293–303.

Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. The American Journal of Psychiatry 2005;162:2233–45.

Hooker CI, Bruce L, Lincoln SH, Fisher M, Vinogradov S. Theory of mind skills are related to gray matter volume in the ventromedial prefrontal cortex in schizophrenia. Biological Psychiatry 2011;70:1169–78.

Inagaki AI T. Dose equivalence of psychotropic drugs. Part XVIII: dose equivalence of psychotropic drugs: 2006 version. Rinsyo Seisin Yakuri 2006;9:1443–7.

Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 1987;13:261–76.

Konvalinka I, Roepstorff A. The two-brain approach: how can mutually interacting brains teach us something about social interaction? Frontiers in Human Neuroscience 2012;6:215.

Koutsouleris N, Gaser C, Jager M, Bottlender R, Frodl T, Holzinger S, et al. Structural correlates of psychopathological symptom dimensions in schizophrenia: a voxel-based morphometric study. Neuroimage 2008;39:1600–12.

Liddle PF. Functional imaging—schizophrenia. British Medical Bulletin 1996;52:486–94.

Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. Archives of General Psychiatry 1999;56:749–54.

Nenadic I, Smesny S, Schlosser RG, Sauer H, Gaser C. Auditory hallucinations and brain structure in schizophrenia: voxel-based morphometric study. The British Journal of Psychiatry: The Journal of Mental Science 2010;196:412–3.

Nestor PG, Shenton ME, McCarley RW, Haimson J, Smith RS, O'Donnell B, et al. Neuropsychological correlates of MRI temporal lobe abnormalities in schizophrenia. The American Journal of Psychiatry 1993;150:1849–55.

Okamoto M, Dan H, Sakamoto K, Takeo K, Shimizu K, Kohno S, et al. Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping. Neuroimage 2004;21:99–111.

Premkumar P, Fannon D, Kuipers E, Cooke MA, Simmons A, Kumari V. Association between a longer duration of illness, age and lower frontal lobe grey matter volume in schizophrenia. Behavioural Brain Research 2008;193:132–9.

Please cite this article in press as: Takei Y, et al., Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.07.029

Riley EM, McGovern D, Mockler D, Doku VC, OCeallaigh S, Fannon DG, et al. Neuropsychological functioning in first-episode psychosis—evidence of specific deficits. Schizophrenia Research 2000;43:47–55.

Shenton ME, Kikinis R, Jolesz FA, Pollak SD, Lemay M, Wible CG, et al. Abnormalities of the left temporal-lobe and thought-disorder in schizophrenia—a quantitative magnetic-resonance-imaging study. New England Journal of Medicine 1992;327:604–12.

Suda M, Takei Y, Aoyama Y, Narita K, Sakurai N, Fukuda M, et al. Autistic traits and brain activation during face-to-face conversations in typically developed adults. PloS One 2011;6:e20021.

Suda M, Takei Y, Aoyama Y, Narita K, Sato T, Fukuda M, et al. Frontopolar activation during face-to-face conversation: an in situ study using near-infrared spectroscopy. Neuropsychologia 2010;48:441–7.

Suga M, Yamasue H, Abe O, Yamasaki S, Yamada H, Inoue H, et al. Reduced gray matter volume of Brodmann's Area 45 is associated with severe psychotic symptoms in patients with schizophrenia. European Archives of Psychiatry and Clinical Neuroscience 2010;260:465–73.

Sugranyes G, Kyriakopoulos M, Corrigall R, Taylor E, Frangou S. Autism spectrum disorders and schizophrenia: meta-analysis of the neural correlates of social cognition. PloS One 2011;6:e25322.

Suto T, Fukuda M, Ito M, Uehara T, Mikuni M. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. Biological Psychiatry 2004;55:501–11.

Toronov V, Webb A, Choi JH, Wolf M, Michalos A, Gratton E, et al. Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. Medical Physics 2001;28:521–7.

Tsuzuki D, Jurcak V, Singh AK, Okamoto M, Watanabe E, Dan I. Virtual spatial registration of stand-alone fNIRS data to MNI space. Neuroimage 2007;34:1506–18.

van der Gaag M, Hoffman T, Remijsen M, Hijman R, de Haan L, van Meijel B, et al. The five-factor model of the Positive and Negative Syndrome Scale II: a ten-fold cross-validation of a revised model. Schizophrenia Research 2006;85:280–7.

Van Overwalle F, Baetens K. Understanding others' actions and goals by mirror and mentalizing systems: a meta-analysis. Neuroimage 2009;48:564–84.

Please cite this article in press as: Takei Y, et al., Temporal lobe and inferior frontal gyrus dysfunction in patients with schizophrenia during face-to-face conversation: A near-infrared spectroscopy study, Journal of Psychiatric Research (2013), http://dx.doi.org/10.1016/j.jpsychires.2013.07.029

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

Masaru Kinou [a,1], Ryu Takizawa [a,b,*,1], Kohei Marumo [a], Shingo Kawasaki [a,c], Yuki Kawakubo [d], Masato Fukuda [e], Kiyoto Kasai [a]

[a] Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, P080 De Crespigny Park, Denmark Hill, London SE5 8AF, United Kingdom
[c] Optical Topography Group, Application Development Office, Hitachi Medical Corporation, Shintoyofuta 2-1, Kashiwa, Chiba 277-0804, Japan
[d] Department of Child Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[e] Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

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.
© 2013 Elsevier B.V. All rights reserved.

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

* Corresponding author at: Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo & MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel.: +81 3 5800 9263; fax: +81 3 5800 6894.
E-mail address: takizawar-tky@umin.ac.jp (R. Takizawa).
[1] These authors contributed equally to this work.

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
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

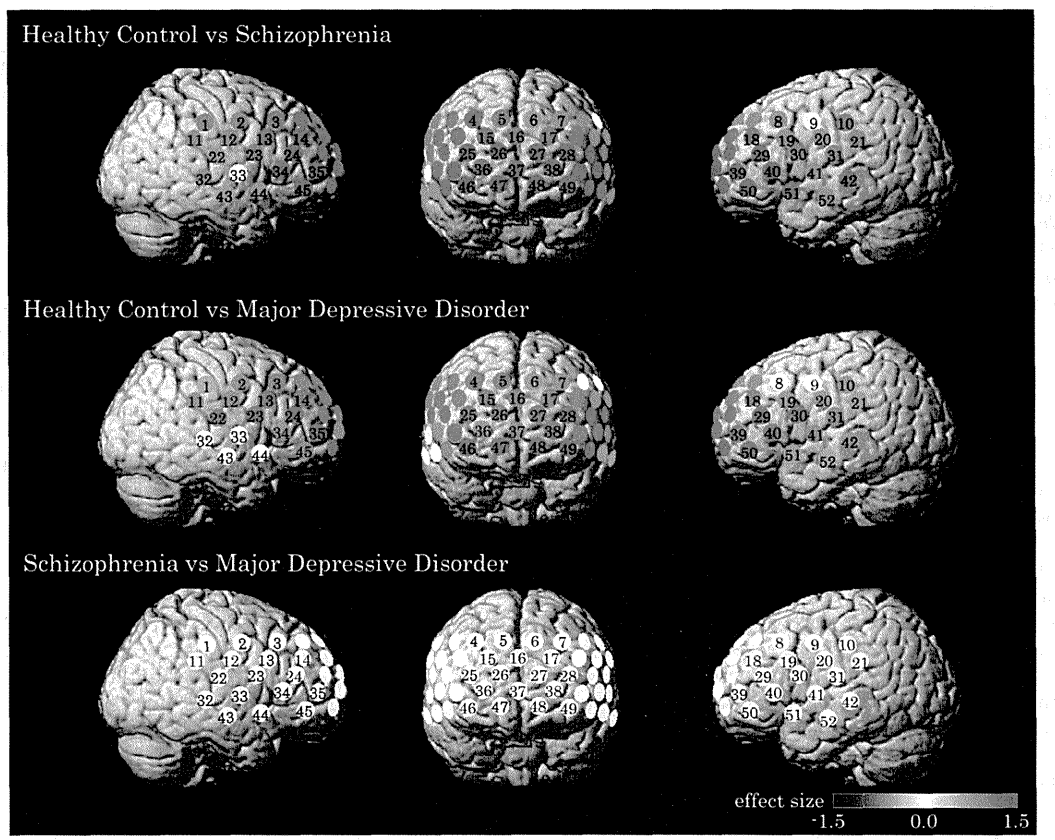

Fig. 1. Group differences in mean [oxy-Hb] increase during the task period. The effect sizes of the group differences are indicated by the color gradient. Channels that did not display significant differences among the 3 groups are colored in white.

analysis of variance (ANOVA); a correction for multiple comparisons was made using FDR.

Subsequently, as post-hoc analyses, we used Tukey's multiple comparison tests to compare the mean [Hb] changes during the task period for channels considered significant after ANOVA between each group (NC–SZ, NC–MDD, and SZ–MDD). A correction for multiple comparisons was made using FDR. To elucidate the spatiotemporal characteristics of NIRS signals, we calculated the effect size (Cohen, 1988) for each difference in these channels.

Next, we compared the time course of [Hb] changes. A previous NIRS study on difference between patients with SZ and MDD (Suto et al., 2004) did not mention statistical significance, but the figure included seemed to show an NIRS signal difference during the first period of the task in the frontopolar cortex area; therefore, we focused our attention on the initial slope of the task period as one of the parameters for the time-course change. To confirm the characteristics of the time course for each group, the initial 5-s slope of the task period was compared among the 3 groups for each channel, in a similar manner. In addition, we conducted similar analyses by using the other parameters for time-course change, which were introduced by Shimodera et al. (2012).

Finally, we analyzed the relationship between [Hb] changes and clinical characteristics, which included GAF, PANSS, and HRS-D scores, age, and dose of medication by calculating Pearson's correlation coefficients. Initially, we investigated the associations between mean NIRS signal change and the clinical characteristics. If any significant association was found, we confirmed the robustness of such associations by using the raw waveform data along the time course of the NIRS signal. According to the conservative method of Kameyama et al. (2006) and Marumo et al. (2009), in order to avoid multiple comparison errors, channels that yielded data with p values of <0.05 for more than 20 s consecutively (200 comparison time points in NIRS signals) during the measurement were considered to have a significant correlation.

Although we focused on [oxy-Hb] here, we have shown the analyses of [deoxy-Hb] data in Supplementary material (1). All data are expressed as means ± S.D. The significance level was set at alpha = 0.05. Statistical analyses were performed using the statistical packager for the Social Sciences ver. 20.0.0J (IBM, Corp., 2011, Chicago IL).

3. Results

3.1. Task performance

The mean number of correct words during the 60-s VFT was not significantly different among the 3 groups ($F[2, 93] = 1.11$, $p = 0.33$, Table 1).

3.2. NIRS [oxy-Hb] change during the VFT period

To assess the presence of significant activations, we compared the mean [oxy-Hb] change between the pre-task and 60-s task periods. HCs showed a significant increase in all channels of the PFC (FPPFC, DLPFC, and VLPFC) (channels 1–52; FDR $p < 0.05$, corrected for 52 channels). Patients with SZ exhibited a significant increase in the DLPFC and VLPFC (channels 24, 34, 35, 39, 41, 44, 45, 47, 49, 51, and 52; FDR $p < 0.05$, corrected for 52 channels), whereas patients with MDD showed a significant increase in the DLPFC, VLPFC, and part of the FPPFC (channels 1, 13, 14, 16–21, 24–29, and 32–52; FDR $p < 0.05$, corrected for 52 channels).

One-way ANOVA using group as a between-subject factor showed a significant main effect of group on the [oxy-Hb] increase during the 60-s task period in the following 50 channels: 1–8, 10–32, and 34–52 (FDR $p < 0.05$, corrected for 52 channels). An additional analysis was performed to compare the 3 groups within the above-mentioned 50 significant channels.

We found that in the widespread PFC, the [oxy-Hb] change in patients with SZ was significantly more reduced than that in HC (channels 1–8, 10–32, 34–52; FDR $p < 0.05$, corrected with 50 channels, Fig. 1).

Similarly, across the PFC, the [oxy-Hb] change was significantly more reduced in patients with MDD than in HCs (channels 1–7, 10–31, 34–42, and 45–52; FDR $p < 0.05$, corrected with 50 channels, Fig. 1).

Patients with SZ and MDD did not show significant difference in the mean [oxy-Hb] for any channel.

3.3. Time course of cognitive activation

The time-course patterns of [oxy-Hb] and [deoxy-Hb] changes in the left FPPFC (channel 38) vary according to diagnostic group (Fig. 2). The HC and MDD groups showed an immediate increase and regular decrease in [oxy-Hb] during the task. In contrast, the SZ group showed slow increase after the start of the task and immediate decrease after the end of the task period. In addition, this group showed a small increase in [oxy-Hb] during the post-task period.

One-way ANOVA using group as a between-subject factor showed a significant difference in the initial slope during the task period at 29 channels (channels 3, 8, 13–18, 20, 24–29, 34–40, and 45–51; FDR $p < 0.05$, corrected for 52 channels). Similar to the analysis of mean [oxy-Hb] change, an additional analysis to compare each group within these 29 significant channels was performed.

The initial slope for HCs was significantly steeper than that for patients with SZ at 26 channels (channels 3, 13–15, 17–18, 20, 24–29, 34–39, and 45–51; FDR $p < 0.05$, corrected for 27 channels, Fig. 3). However, the slope for patients with MDD was not significantly different from that for HCs at any channel (FDR $p > 0.05$, corrected for 27 channels, n.s.).

The slopes for patients with MDD were significantly steeper than those for patients with SZ at 15 channels located approximately in the FPPFC (channels 25–28, 35–40, 45–48 and 51; FDR $p < 0.05$, corrected for 27 channels, Fig. 3).

The comparisons of parameters between the 3 groups for channel 38 are summarized in Fig. 4.

In Supplementary material (2), we also show the results obtained using the indices that Shimodera et al. (2012) used. In brief, one of the

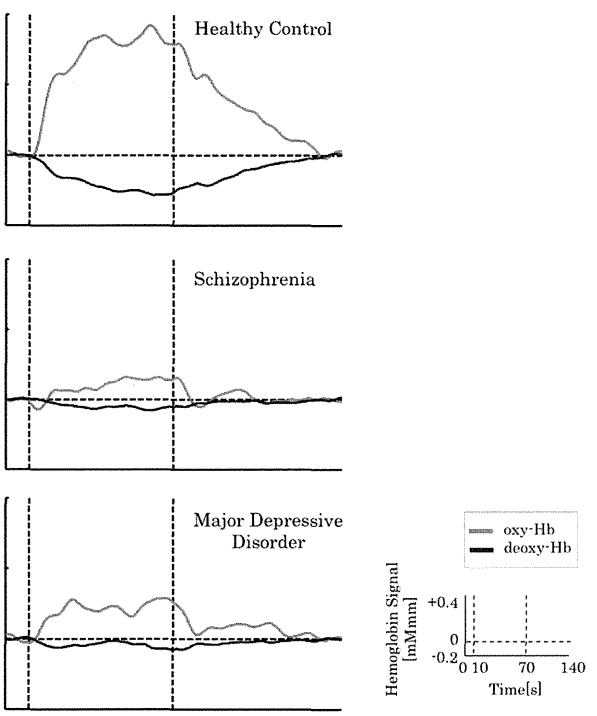

Fig. 2. Time course of [oxy-Hb] and [deoxy-Hb] changes in the FPPFC (channel 38).

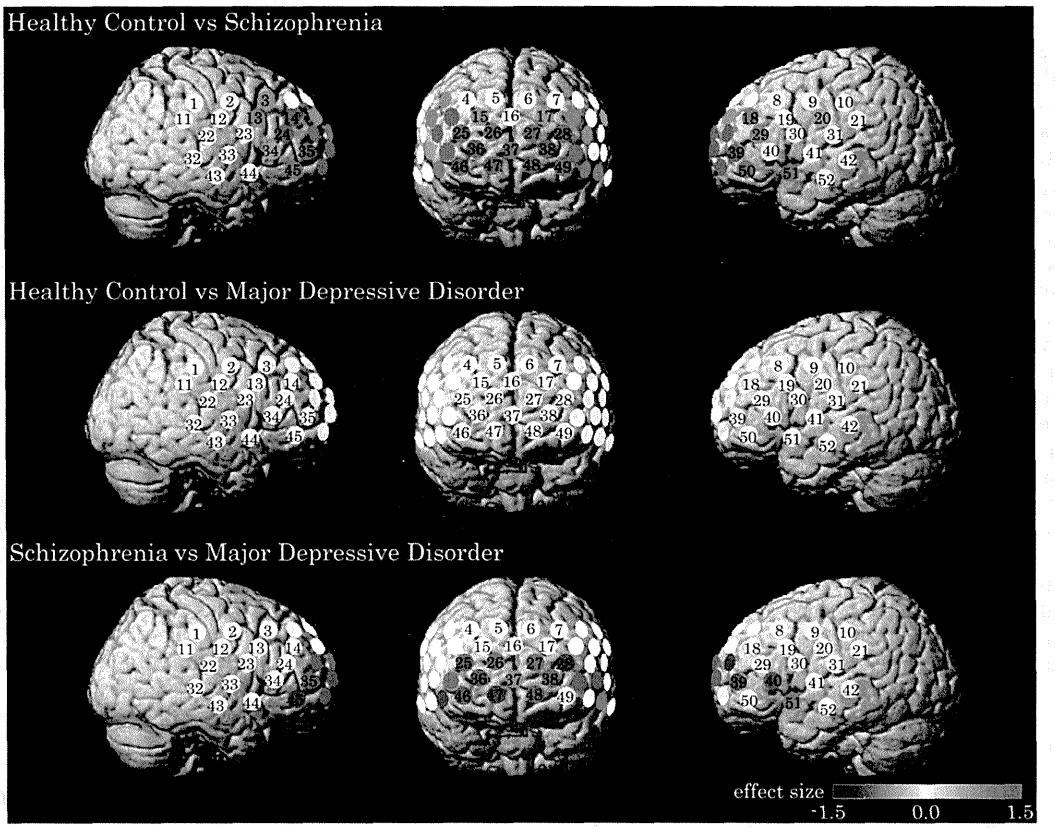

Fig. 3. Group differences in initial [oxy-Hb] slope. The effect sizes of the group differences are indicated by the color gradient. Channels that did not display significant differences among the 3 groups are colored in white.

2 parameters that Shimodera et al. (2012) employed for time-course analysis was significantly different between the patient groups (MDD and SZ) and healthy controls, but not significantly different between the patients with MDD and SZ.

3.4. Correlation with clinical characteristics

For analyzing the correlation between PFC response and clinical characteristics, GAF scores were calculated and found to exhibit significant positive correlations with the mean [oxy-Hb] change of the 60-s task period in patients with SZ at 7 channels ($r = 0.377–0.487$) and in patients with MDD at 23 channels ($r = 0.451–0.610$) (SZ: channels 27–28, 36–39, and 46, located mainly in the FPPFC; MDD: channels 2, 10, 12, 13, 20, 24, 25, 30, 34–37, 39–41, 43, 44, 46–48, and 50–52, located mainly in the DLPFC and VLPFC), which means that the more severe the GAF scores were the more reduced the NIRS changes were (Fig. 5). Additionally, to confirm the robustness of such associations, the time-course analysis of the associations revealed that there were significant associations in the latter half of the time course of the NIRS measurement (SZ: channels 13, 17, 24, 26–28, 34–39, and 46–49, located mainly

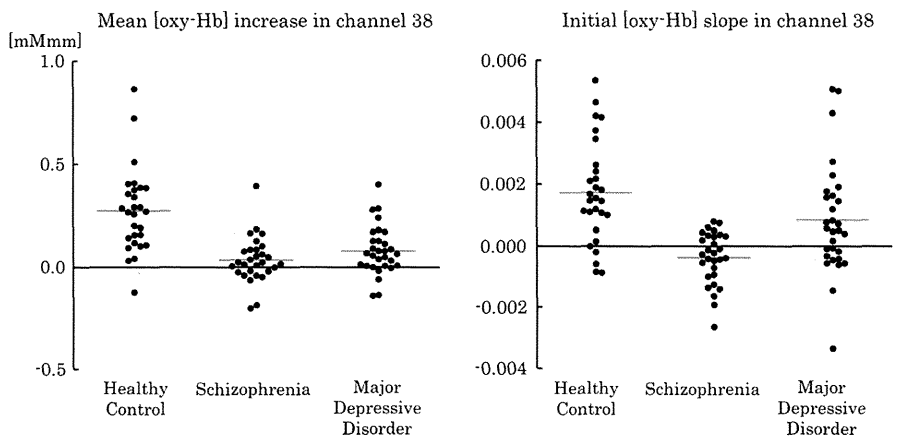

Fig. 4. Comparisons of mean [oxy-Hb] increase and initial [oxy-Hb] slope among the 3 groups. The bars indicate the mean ± 1 standard deviation.

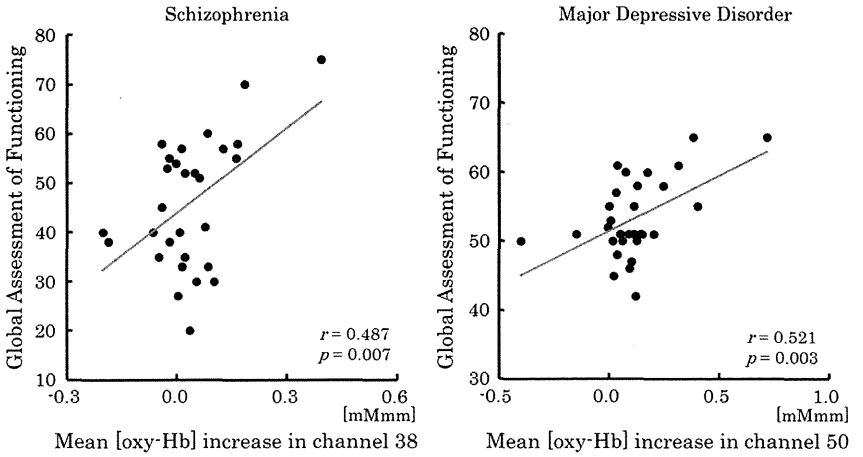

Fig. 5. Scatterplots for correlations between NIRS signal and GAF score in patients with schizophrenia and major depression.

in the FPPFC; MDD: channels 2, 10, 12–13, 20, 24, 29, 34–36, 39–44, 46–48, and 50–52, located mainly in the DLPFC and VLPFC) ($p < 0.05$, with 200 consecutive time points) (Fig. 6).

Other clinical characteristics, including age, dose of medication, and PANSS and HRS-D scores were not significantly correlated with mean [oxy-Hb] change in the 60-s task period at any channel in any group. Moreover, no clinical characteristic showed significant correlation with the initial [oxy-Hb] slope of the task period at any channel in any group.

4. Discussion

These results suggest the presence of a significant difference in the time-course patterns of prefrontal activations in a VFT among HCs, patients with SZ, and patients with MDD matched for age, sex, task performance, and education years. Compared to HCs, patients with SZ and those with MDD showed a significant task-associated reduction in mean [oxy-Hb]. In addition, the initial slope was significantly steeper for patients with MDD and HCs than for patients with SZ. Furthermore, in patients with SZ, the mean [oxy-Hb] change in the area approximately located in the FPPFC was significantly correlated with the GAF score; this is similar to our previous finding (Takizawa et al., 2008), whereas patients with MDD exhibited a significant correlation between mean [oxy-Hb] change and GAF scores in the areas approximately located in the DLPFC and VLPFC. These findings may help understand the differential brain pathophysiology of SZ and MDD better.

4.1. Functional prefrontal abnormality in patients with SZ and MDD

Compared with HCs, patients with SZ and those with MDD showed a reduced NIRS [oxy-Hb] increase in the 60-s task period at the PFC. This result agrees with those of previous NIRS studies (Kameyama et al., 2006; Suto et al., 2004; Takizawa et al., 2008) and other neuroimaging studies.

The 2 patient groups had an [oxy-Hb] reduction compared to that of HCs in FPPFC and DLPFC; however, patients with MDD showed no significant [oxy-Hb] reduction in VLPFC, whereas patients with SZ did, i.e., compared to patients with MDD, those with SZ had reduced NIRS signals in a wider area (Fig. 1). However, patients with SZ and MDD did not show significant difference in mean [oxy-Hb] change at all channels; this suggests that differentiating between these 2 disorders using only the mean change in NIRS signal is difficult.

The VFT recruits not only a single specific cognitive domain, but also some integrated cognitive dimensions, such as working memory,

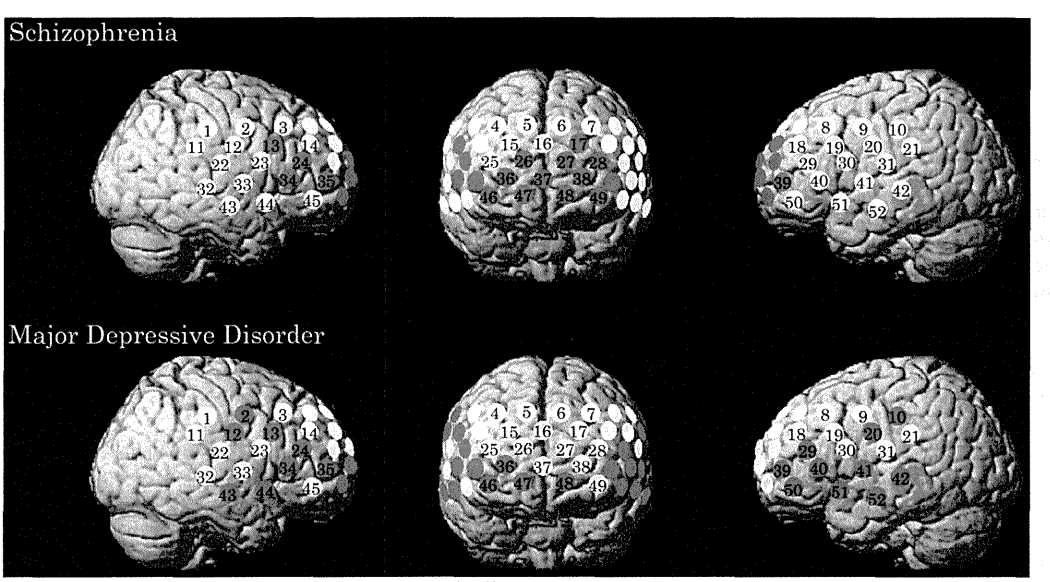

Fig. 6. Cerebral regions that exhibited a significant correlation between GAF score and mean [oxy-Hb] change.

selection of appropriate words, inhibition of inappropriate words, and maintenance of attention (Ruff et al., 1997). For this reason, our "hypofrontality" result during the VFT could not clarify the specific deficit of neural networks in each patient group. However, the difference in mean [oxy-Hb] change during the VFT between patients and HCs may reflect a common impairment, such as executive dysfunction. In addition, from the perspective of the area that showed a group difference (Fig. 1), the brain pathophysiology involving this impairment in SZ might be severer than that of MDD.

4.2. Differential spatiotemporal characteristics of prefrontal activation

The comparison of the time course of [oxy-Hb] signal between the 3 groups (Fig. 2) revealed that the SZ group showed a more gradual slope than the MDD or NC groups, whereas the MDD and HC groups showed no significant difference in the initial slope, immediately after the task started.

Despite the fact that the 2 patient groups had a similar reduced [oxy-Hb] change, there was a difference in the time course of NIRS [oxy-Hb] signal between them. Several previous functional neuroimaging studies based on fMRI also reported a difference in cognitive activation, and the possibilities of qualitative changes, between patients with SZ and MDD (Holmes et al., 2005; Hugdahl et al., 2004). In our study, we replicated this qualitative difference between the disorders based not only on the activation of the PFC region, but also on the comparison of the time course of frontal activation. These findings suggest that the brain pathophysiology of SZ might be severer than that of MDD.

Furthermore, the initial rise rate of the prefrontal hemodynamic response to the task stimulus in patients with MDD was similar to that of HCs, but the response did not continue to increase throughout the task period (Fig. 2), which means that, despite the fact that the load of the task continued, the prefrontal hemodynamic response in these patients did not follow. This discontinuance in the frontal hemodynamic response may reflect symptoms of depression, such as impaired concentration and psychomotor slowing (Hickie et al., 2007). Conversely, patients with SZ appeared to have an inefficient small reactivation or a delay of baseline reversion after the task period (Fig. 2), similar to the results of previous NIRS studies (Suto et al., 2004; Takizawa et al., 2008). As was also discussed for the abnormal time course of patients with SZ observed in a recent NIRS study (Shimodera et al., 2012), only its reduced mean signal change does not seem to represent their functional dysfunctions. The time-course analyses of cognitive activation according to patient groups need to be replicated in future NIRS studies.

4.3. Association between functional impairment and PFC subregions

In this study, we found a significant correlation between the mean [oxy-Hb] change of the task period in specific cerebral regions and the GAF score. However, the correlated cerebral regions were spatially different between patients with SZ (mainly in the FPPFC) and patients with MDD (mainly in the VLPFC/DLPFC) (Fig. 6).

Recent neuroimaging studies reported that the regions activated in patients with SZ were different from those activated in patients with MDD for the same cognitive task, suggesting that the abnormal neural correlates and compensatory mechanisms might be different between patients with SZ and MDD (Barch et al., 2003; Holmes et al., 2005; Hugdahl et al., 2004). Thus, in the present study, the activated regions that correlated to GAF might be variable in each patient group.

Our previous study (Takizawa et al., 2008) was replicated regarding the relationship between GAF score and NIRS [oxy-Hb] increase in the FPPFC and DLPFC. As was discussed in Takizawa et al. (2008), this relationship suggests that reduced frontopolar cortical activations may be associated with functional impairment in patients with SZ.

Regarding patients with MDD, a previous NIRS study using the same VFT (Pu et al., 2008) showed that the mean [oxy-Hb] change in the right DLPFC was significantly associated with scores on the Social Adaptation Self-Evaluation Scale, which evaluates social motivation and behavior (Bosc et al., 1997). This measure should be strongly related with global social functioning, which is similar to what was measured by the GAF scale in the current study. Therefore, here we replicated part of the Pu et al. (2008) regarding the correlations between the DLPFC signal and the generalized scores of social functioning in patients with MDD.

Studies based on nonhuman primates reported that the VLPFC receives projections from the orbitofrontal cortex and subcortical areas, such as the midbrain and amygdala, which are involved in processing motivational and emotional information. The VLPFC might integrate cognitive and motivational information to guide flexible goal-directed behavior (Sakagami and Pan, 2007). In mood disorders, a deficit in the VLPFC observed in emotion tasks reflected the impairment in processing motivational and emotional information in this area (Johnstone et al., 2007; Taylor Tavares et al., 2008). These VLPFC functions may be factors that influence the extent of social functioning in patients with depression. Thus, our results of increasing severity in functional impairments with the reduction of VLPFC signals might be justified. However, the global role of the VLPFC and its relation to social impairment in patients with MDD remains to be elucidated. Our results regarding the VLPFC warrant further investigation.

The correlation between lateral PFC activation and GAF score in patients with MDD suggests that this region plays a key role in maintaining social function in these patients; however, these PFC areas seemed to be different from those observed in patients with SZ, for some reason (e.g., compensatory or abnormal mechanisms). These findings suggest not only differential brain pathophysiology, but also differential symptomatology between patients with MDD and SZ. Further detailed investigations need to be performed in the future.

4.4. Limitations

Some methodological limitations need to be addressed. First, all patients were taking medication at the time of NIRS measurement. Some authors have mentioned an absence of significant effects of psychotropic medications on abnormal structural and functional neuroimaging measures (Phillips et al., 2008). Moreover, similar to what was observed in previous NIRS studies (Shimodera et al., 2012; Takizawa et al., 2008), psychotropic medication dose was not related to [oxy-Hb] change at any channels in the present study. However, the effect of antidepressants or antipsychotics on neuroimaging studies could not be entirely ruled out. In addition, we confirmed that the significant findings were unchanged if either or medication or task performance was included as a covariate in the analyses. Second, in the current study, NIRS measurements were made once throughout the stages of the disease. To repeat the NIRS measurements during the treatment of patients, the actual state of activation patterns throughout the process of recovery may become clear (Walsh et al., 2007). A longitudinal study is needed to replicate our findings. Third, NIRS has a low spatial resolution, and its accuracy in the estimation of measurement positions is limited. According to the virtual registration method (Tsuzuki et al., 2007; Tzourio-Mazoyer et al., 2002), which estimates the cortical localization of each channel. We interpreted that the correlated cerebral area (including channel 24 or 29, and more lateral channels) in patients with MDD was located mainly in the bilateral VLPFC and right DLPFC (Fig. 6).

4.5. Conclusions and future implications

In conclusion, we investigated the hemodynamic changes using the LFT in patients with MDD and SZ and in HCs by using 52-channel NIRS with a wide coverage over the prefrontal cortical surface area. The comparison between patients with SZ and MDD revealed a difference in the time course of the NIRS signal. We also observed a correlation between the GAF score and the mean [oxy-Hb] change at the FPPFC in patients with SZ, and at the DLPFC and VLPFC in patients with MDD. These

results suggest the presence of differential prefrontal abnormalities in each disease, despite a similar reduction in the magnitude of hemodynamic activations between them. These findings may lead to a better understanding of the different brain pathophysiology of SZ and MDD. Finally, these results, if replicated using large-scale or longitudinal studies, suggest that NIRS could potentially be used as an aid for the diagnosis and clinical evaluation of SZ and MDD.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.08.026.

Role of funding source

This work was supported in part by Grants-in-Aid for Scientific Research (Innovative areas No. 23118001 & 23118004 [Adolescent Mind & Self-Regulation] to KK; No. 23791309 to RT) and a grant from the "Development of Biomarker Candidates for Social Behavior" study carried out under the Strategic Research Program for Brain Sciences (to KK) of the MEXT. This study was also supported in part by the Health and Labor Sciences Research Grants for Comprehensive Research on Disability Health and Welfare (H23-seishin-ippan-002 to RT); an Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP (No. 23-10 to RT); and by the Japan Research Foundation for Clinical Pharmacology (to RT). The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in this study, and had the final responsibility in the decision to submit this work for publication.

Contributors

Masato Fukuda, Ryu Takizawa, and Kiyoto Kasai designed the study and wrote the protocol. Ryu Takizawa, Masaru Kinou, and Shingo Kawasaki performed the statistical analysis. Masaru Kinou, Ryu Takizawa, Marumo Kohei, and Yuki Kawakubo carried out data acquisition. Ryu Takizawa and Masaru Kinou wrote the first draft of the manuscript, and the other authors revised it critically for important intellectual content. All authors have approved the final version of the manuscript.

Conflict of interest

Regarding financial and material support for the present study, Dr. Kasai has a potential conflict of interest (see below for details). All other authors have no relevant conflicts of interest.

Beginning July 31, 2003, and continuing to the present, the University of Tokyo and the Hitachi Group (Advanced Research Laboratory, Hitachi Ltd. and The Research and Developmental Center, Hitachi Medical Corporation) have had an official contract for a collaborative study on the clinical applications of near-infrared spectroscopy (NIRS) in psychiatric disorders, which has been approved by the Research Promotion Office, University of Tokyo Hospital. The principal investigator of this study is Kiyoto Kasai. For this study, the Hitachi Medical Corporation provided a project grant (JPY 300,000 per year) and material support (temporary rental of a near-infrared spectroscopy machine (ETG-4000, Optical Topography)).

Acknowledgments

The authors thank all the participants in this study. This study is based in part on the Ph.D. thesis of Dr. Kinou, which was submitted to the University of Tokyo.

References

Audenaert, K., Brans, B., Van Laere, K., Lahorte, P., Versijpt, J., van Heeringen, K., Dierckx, R., 2000. Verbal fluency as a prefrontal activation probe: a validation study using 99mTc-ECD brain SPET. Eur. J. Nucl. Med. 27 (12), 1800–1808.

Barch, D.M., Sheline, Y.I., Csernansky, J.G., Snyder, A.Z., 2003. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol. Psychiatry 53 (5), 376–384.

Berman, K.F., Doran, A.R., Pickar, D., Weinberger, D.R., 1993. Is the mechanism of prefrontal hypofunction in depression the same as in schizophrenia? Regional cerebral blood flow during cognitive activation. Br. J. Psychiatry 162, 183–192.

Bosc, M., Dubini, A., Polin, V., 1997. Development and validation of a social functioning scale, the social adaptation self-evaluation scale. Eur. Neuropsychopharmacol. 7 (Suppl. 1), S57–70 (discussion S71-53).

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Erlbaum, Hillsdale, NJ.

Driesen, N.R., Leung, H.C., Calhoun, V.D., Constable, R.T., Gueorguieva, R., Hoffman, R., Skudlarski, P., Goldman-Rakic, P.S., Krystal, J.H., 2008. Impairment of working memory maintenance and response in schizophrenia: functional magnetic resonance imaging evidence. Biol. Psychiatry 64 (12), 1026–1034.

Ferrari, M., Quaresima, V., 2012. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage 63 (2), 921–935.

Frank, E., Prien, R.F., Jarrett, R.B., Keller, M.B., Kupfer, D.J., Lavori, P.W., Rush, A.J., Weissman, M.M., 1991. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch. Gen. Psychiatry 48 (9), 851–855.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.

Harvey, P.O., Fossati, P., Pochon, J.B., Levy, R., Lebastard, G., Lehericy, S., Allilaire, J.F., Dubois, B., 2005. Cognitive control and brain resources in major depression: an fMRI study using the n-back task. NeuroImage 26 (3), 860–869.

Herrmann, M.J., Walter, A., Ehlis, A.C., Fallgatter, A.J., 2006. Cerebral oxygenation changes in the prefrontal cortex: effects of age and gender. Neurobiol. Aging 27 (6), 888–894.

Hickie, I.B., Naismith, S.L., Ward, P.B., Little, C.L., Pearson, M., Scott, E.M., Mitchell, P., Wilhelm, K., Parker, G., 2007. Psychomotor slowing in older patients with major depression: relationships with blood flow in the caudate nucleus and white matter lesions. Psychiatry Res. 155 (3), 211–220.

Holmes, A.J., MacDonald III, A., Carter, C.S., Barch, D.M., Andrew Stenger, V., Cohen, J.D., 2005. Prefrontal functioning during context processing in schizophrenia and major depression: an event-related fMRI study. Schizophr. Res. 76 (2–3), 199–206.

Hugdahl, K., Rund, B.R., Lund, A., Asbjornsen, A., Egeland, J., Ersland, L., Landro, N.I., Roness, A., Stordal, K.I., Sundet, K., Thomsen, T., 2004. Brain activation measured with fMRI during a mental arithmetic task in schizophrenia and major depression. Am. J. Psychiatry 161 (2), 286–293.

Irani, F., Platek, S.M., Bunce, S., Ruocco, A.C., Chute, D., 2007. Functional near infrared spectroscopy (fNIRS): an emerging neuroimaging technology with important applications for the study of brain disorders. Clin. Neuropsychol. 21 (1), 9–37.

Jobsis, F.F., 1977. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science 198 (4323), 1264–1267.

Johnstone, T., van Reekum, C.M., Urry, H.L., Kalin, N.H., Davidson, R.J., 2007. Failure to regulate: counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J. Neurosci. 27 (33), 8877–8884.

Kakimoto, Y., Nishimura, Y., Hara, N., Okada, M., Tanii, H., Okazaki, Y., 2009. Intrasubject reproducibility of prefrontal cortex activities during a verbal fluency task over two repeated sessions using multi-channel near-infrared spectroscopy. Psychiatry Clin. Neurosci. 63 (4), 491–499.

Kameyama, M., Fukuda, M., Uehara, T., Mikuni, M., 2004. Sex and age dependencies of cerebral blood volume changes during cognitive activation: a multichannel near-infrared spectroscopy study. NeuroImage 22 (4), 1715–1721.

Kameyama, M., Fukuda, M., Yamagishi, Y., Sato, T., Uehara, T., Ito, M., Suto, T., Mikuni, M., 2006. Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. NeuroImage 29 (1), 172–184.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Koizumi, H., Yamashita, Y., Maki, A., Yamamoto, T., Ito, Y., Itagaki, H., Kennan, R., 1999. Higher-order brain function analysis by trans-cranial dynamic near-infrared spectroscopy imaging. J. Biomed. Opt. 4 (4), 403–413.

Kono, T., Matsuo, K., Tsunashima, K., Kasai, K., Takizawa, R., Rogers, M.A., Yamasue, H., Yano, T., Taketani, Y., Kato, N., 2007. Multiple-time replicability of near-infrared spectroscopy recording during prefrontal activation task in healthy men. Neurosci. Res. 57 (4), 504–512.

Liotti, M., Mayberg, H.S., 2001. The role of functional neuroimaging in the neuropsychology of depression. J. Clin. Exp. Neuropsychol. 23 (1), 121–136.

Manoach, D.S., Press, D.Z., Thangaraj, V., Searl, M.M., Goff, D.C., Halpern, E., Saper, C.B., Warach, S., 1999. Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. Biol. Psychiatry 45 (9), 1128–1137.

Marumo, K., Takizawa, R., Kawakubo, Y., Onitsuka, T., Kasai, K., 2009. Gender difference in right lateral prefrontal hemodynamic response while viewing fearful faces: a multichannel near-infrared spectroscopy study. Neurosci. Res. 63 (2), 89–94.

Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, S., Mahurin, R.K., Jerabek, P.A., Silva, J.A., Tekell, J.L., Martin, C.C., Lancaster, J.L., Fox, P.T., 1999. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am. J. Psychiatry 156 (5), 675–682.

Okada, G., Okamoto, Y., Morinobu, S., Yamawaki, S., Yokota, N., 2003. Attenuated left prefrontal activation during a verbal fluency task in patients with depression. Neuropsychobiology 47 (1), 21–26.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9 (1), 97–113.

Phillips, M.L., Travis, M.J., Fagiolini, A., Kupfer, D.J., 2008. Medication effects in neuroimaging studies of bipolar disorder. Am. J. Psychiatry 165 (3), 313–320.

Pu, S., Matsumura, H., Yamada, T., Ikezawa, S., Mitani, H., Adachi, A., Nakagome, K., 2008. Reduced frontopolar activation during verbal fluency task associated with poor social functioning in late-onset major depression: multi-channel near-infrared spectroscopy study. Psychiatry Clin. Neurosci. 62 (6), 728–737.

Ragland, J.D., Moelter, S.T., Bhati, M.T., Valdez, J.N., Kohler, C.G., Siegel, S.J., Gur, R.C., Gur, R.E., 2008. Effect of retrieval effort and switching demand on fMRI activation during semantic word generation in schizophrenia. Schizophr. Res. 99 (1–3), 312–323.

Ruff, R.M., Light, R.H., Parker, S.B., Levin, H.S., 1997. The psychological construct of word fluency. Brain lang. 57 (3), 394–405.

Sakagami, M., Pan, X., 2007. Functional role of the ventrolateral prefrontal cortex in decision making. Curr. Opin. Neurobiol. 17 (2), 228–233.

Schecklmann, M., Ehlis, A.C., Plichta, M.M., Fallgatter, A.J., 2008. Functional near-infrared spectroscopy: a long-term reliable tool for measuring brain activity during verbal fluency. NeuroImage 43 (1), 147–155.

Shimodera, S., Imai, Y., Kamimura, N., Morokuma, I., Fujita, H., Inoue, S., Furukawa, T.A., 2012. Mapping hypofrontality during letter fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study. Schizophr. Res. 136 (1–3), 63–69.

Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., Thase, M.E., 2007. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biol. Psychiatry 61 (2), 198–209.

Singh, A.K., Dan, I., 2006. Exploring the false discovery rate in multichannel NIRS. NeuroImage 33 (2), 542–549.

Suto, T., Fukuda, M., Ito, M., Uehara, T., Mikuni, M., 2004. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. Biol. Psychiatry 55 (5), 501–511.
Takizawa, R., Kasai, K., Kawakubo, Y., Marumo, K., Kawasaki, S., Yamasue, H., Fukuda, M., 2008. Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study. Schizophr. Res. 99 (1–3), 250–262.
Takizawa, R., Hashimoto, K., Tochigi, M., Kawakubo, Y., Marumo, K., Sasaki, T., Fukuda, M., Kasai, K., 2009. Association between sigma-1 receptor gene polymorphism and prefrontal hemodynamic response induced by cognitive activation in schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 33 (3), 491–498.
Taylor Tavares, J.V., Clark, L., Furey, M.L., Williams, G.B., Sahakian, B.J., Drevets, W.C., 2008. Neural basis of abnormal response to negative feedback in unmedicated mood disorders. NeuroImage 42 (3), 1118–1126.
Tess, A.V., Smetana, G.W., 2009. Medical evaluation of patients undergoing electroconvulsive therapy. N. Engl. J. Med. 360 (14), 1437–1444.
Tsuzuki, D., Jurcak, V., Singh, A.K., Okamoto, M., Watanabe, E., Dan, I., 2007. Virtual spatial registration of stand-alone fNIRS data to MNI space. NeuroImage 34 (4), 1506–1518.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289.
Videbech, P., Ravnkilde, B., Kristensen, S., Egander, A., Clemmensen, K., Rasmussen, N.A., Gjedde, A., Rosenberg, R., 2003. The Danish PET/depression project: poor verbal fluency performance despite normal prefrontal activation in patients with major depression. Psychiatry Res. 123 (1), 49–63.
Walsh, N.D., Williams, S.C.R., Brammer, M.J., Bullmore, E.T., Kim, J., Suckling, J., Mitterschiffthaler, M.T., Cleare, A.J., Pich, E.M., Mehta, M.A., Fu, C.H.Y., 2007. A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. Biol. Psychiatry 62 (11), 1236.
Walter, H., Vasic, N., Hose, A., Spitzer, M., Wolf, R.C., 2007. Working memory dysfunction in schizophrenia compared to healthy controls and patients with depression: evidence from event-related fMRI. NeuroImage 35 (4), 1551–1561.
Yamashita, Y., Maki, A., Koizumi, H., 1999. Measurement system for noninvasive dynamic optical topography. J. Biomed. Opt. 4 (4), 414–417.
Yurgelun-Todd, D.A., Waternaux, C.M., Cohen, B.M., Gruber, S.A., English, C.D., Renshaw, P.F., 1996. Functional magnetic resonance imaging of schizophrenic patients and comparison subjects during word production. Am. J. Psychiatry 153 (2), 200–205.

NeuroImage: Clinical 4 (2014) 481–487

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Depressive symptoms and neuroanatomical structures in community-dwelling women: A combined voxel-based morphometry and diffusion tensor imaging study with tract-based spatial statistics

Yayoi K. Hayakawa[a,c,1,*], Hiroki Sasaki[a], Hidemasa Takao[a], Naoto Hayashi[b], Akira Kunimatsu[a], Kuni Ohtomo[a], Shigeki Aoki[c]

[a] Department of Radiology, University of Tokyo Hospital, Tokyo, Japan
[b] Department of Computational Diagnostic Radiology and Preventive Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
[c] Department of Radiology, Juntendo University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 29 November 2013
Received in revised form 5 March 2014
Accepted 5 March 2014

Keywords:
Anterior cingulate gyrus
Voxel-based morphometry
Diffusion tensor imaging
Tract-based spatial statistics
Subclinical depression

ABSTRACT

Depressive symptoms, even at a subclinical level, have been associated with structural brain abnormalities. However, previous studies have used regions of interest or small sample sizes, limiting the ability to generalize the results. In this study, we examined neuroanatomical structures of both gray matter and white matter associated with depressive symptoms across the whole brain in a large sample. A total of 810 community-dwelling adult participants underwent measurement of depressive symptoms with the Center for Epidemiologic Studies Depression Scale (CES-D). The participants were not demented and had no neurological or psychiatric history. To examine the gray and white matter volume, we used structural MRI scans and voxel-based morphometry (VBM); to examine the white matter integrity, we used diffusion tensor imaging with tract-based spatial statistics (TBSS). In female participants, VBM revealed a negative correlation between bilateral anterior cingulate gray matter volume and the CES-D score. TBSS showed a CES-D-related decrease in fractional anisotropy and increase in radial and mean diffusivity in several white matter regions, including the right anterior cingulum. In male participants, there was no significant correlation between gray or white matter volume or white matter integrity and the CES-D score. Our results indicate that the reduction in gray matter volume and differences in white matter integrity in specific brain regions, including the anterior cingulate, are associated with depressive symptoms in women.

© 2014 The Authors. Published by Elsevier Inc.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

Major depressive disorder is associated with decreased brain volume or changes in white matter integrity, particularly in frontal areas (Abe et al., 2010; Bremner et al., 2002; Egger et al., 2008; Kieseppä et al., 2010; Shimony et al., 2009) and in medial temporal areas such as the hippocampus (Abe et al., 2010; Campbell et al., 2004; Videbech and Ravnkilde, 2004). Recently, depressive symptoms that do not meet the criteria for major depression have received increased attention. Understanding this preclinical state precisely is important for preventing major depressive disorder (Cuijpers et al., 2004). Several previous reports have suggested that depressive symptoms at a subclinical level have some of the same neural correlates as those in major depression (Hayakawa et al., 2013; Lavretsky and Kumar, 2002; Lyness et al., 1999). However, most previous studies on this issue have been based on regions of interest or small sample sizes, limiting the ability to draw firm conclusions from them.

The purpose of this study was to investigate brain structures associated with depressive symptoms in gray and white matter across the whole brain in a large sample. We used voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS). Both VBM and TBSS enable the global analysis of brain volume or white matter integrity without a priori identification of a region of interest. White matter integrity was represented by four DTI measures: fractional anisotropy (FA), mean diffusivity

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; TBSS, tract-based spatial statistics; VBM, voxel-based morphometry.

[1] Present address: Department of Radiology, New Tokyo Hospital, 473-1, Nemoto, Matsudo City, Chiba 271-0077, Japan.

* Corresponding author at: Department of Radiology, Graduate School of Medicine, University of Tokyo 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail address: yayoi-kan@umin.ac.jp (Y.K. Hayakawa).

2213-1582/$ - see front matter © 2014 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).
http://dx.doi.org/10.1016/j.nicl.2014.03.002

(MD), axial diffusivity (AD), and radial diffusivity (RD). The diffusivity of water molecules in white matter is more limited in the direction of neuronal fibers. Although the histological reasons for this limitation are not well understood, FA is believed to reflect the degree of myelination and axonal density (Arfanakis et al., 2002; Harsan et al., 2006;Song et al., 2002, 2003). Recently, more discrete analysis of the AD and RD has provided potential measures of the mechanisms that underlie white matter pathology and disease processes (Song et al., 2002; Wozniak and Lim, 2006). AD reflects diffusivity parallel to axonal fibers. Increases in AD are thought to reflect pathology of the axon itself, such as from trauma or ischemic changes (Song et al., 2003). RD reflects diffusivity perpendicular to axonal fibers and appears to be more strongly correlated with myelin abnormalities—either dysmyelination or demyelination—such as in multiple sclerosis (Song et al., 2005). All analyses were performed not only for all participants combined but also for each sex separately, because there is evidence that the brains of males and females with major depression have structural differences (Lorenzetti et al., 2009), suggesting that the sex difference may be present even at the subclinical level. In support of this hypothesis, in our preliminary study of 21 community-dwelling adults (Hayakawa et al., 2013), we found brain structural differences between subjects with subclinical depression and controls only in females.

2. Materials and methods

2.1. Participants

The participants were 1148 volunteers who underwent private health screening at the University of Tokyo hospital from 2008 to 2009. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) during a visit to screen for depression. The CES-D (range, 0–60) is a widely used 20-item self-report inventory that assesses the frequency and severity of depressive symptoms experienced in the past week. Adequate validity of the CES-D in elderly community-dwelling adults has been demonstrated (Haringsma et al., 2004).

The exclusion criteria were missing data from the CES-D or mini-mental state examination (MMSE); past or current history of neuropsychiatric disorders, including major depression diagnosed with the Diagnostic and Statistical Manual for Mental Disorders IV criteria; central nervous system disease; serious head trauma; or medication with antipsychotic drugs. Two trained neuroradiologists (one with 4 years, and the other with 10 years of experience) reviewed all scans (including T2-weighted, fluid-attenuated inversion recovery images and magnetic resonance angiography) and excluded participants who had gross abnormalities such as infarct, hemorrhage, brain tumor, or aneurysm. Participants with a Fazekas score of 3 (irregular periventricular hyperintensity extending into the deep white matter) were also excluded (Fazekas et al., 1987).

The ethical committee of our institute approved this study. After a complete explanation of the study was provided to each participant, written informed consent was obtained.

2.2. Image acquisition

MRI data were obtained on two 3 T Signa HDx scanners (GE Medical Systems, Milwaukee, WI, USA) of the exact same model with an 8-channel brain phased-array coil. For the VBM analysis, T1-weighted images were acquired by using three-dimensional spoiled-gradient recalled acquisition in the steady state (3D SPGR) in 124 axial slices (repetition time: 6.4 ms; echo time: 2.0 ms; flip angle: 151; field of view: 250 mm; slice thickness: 1 mm with no gap; acquisition matrix: 256 × 256; number of excitations: 0.5). The voxel dimensions were 0.977 × 0.977 × 1.0 mm. For the DTI analysis, diffusion tensor images were acquired by using a single-shot spin-echo echo-planar sequence in 50 axial sections (repetition time: 13,200 ms; echo time: 62 ms; field of view: 288 mm; slice thickness: 3 mm with no gap; acquisition matrix: 96 × 96; number of excitations: 1). Diffusion weighting was applied along 13 noncollinear directions with a b-value of 1000 s/mm^2, and a single volume was collected with no diffusion gradients applied (b = 0). The reconstructed voxel dimensions were 1.125 × 1.125 × 3.0 mm. Parallel imaging (array spatial sensitivity encoding technique) was used with an acceleration factor of 2.0.

2.3. Image processing

2.3.1. VBM analysis

All 3D SPGR images were processed and examined using the Statistical Parametric Mapping version 8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), where we applied VBM implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters in MATLAB 7.7.0.471 (The MathWorks, Natick, MA, U.S.A.) running on a Windows computer. A 'nonlinear only' modulation was performed on all images during spatial normalization so that values in resultant images are expressed as volume corrected for brain size. The resultant modulated images were smoothed with a Gaussian kernel of 8 mm (full width at half maximum).

2.3.2. DTI analysis

We performed an unbiased whole-brain TBSS analysis (Smith et al., 2006), which is part of FSL (FMRIB software library) 4.1 (http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). First, the raw diffusion data were corrected for eddy current distortion and head motion by using FDT (FMRIB's Diffusion Toolbox) 2.0 (Smith et al., 2004) and corrected for spatial distortion due to gradient nonlinearity by using grad_unwarp (Jovicich et al., 2006). Following brain extraction by using BET2.1 (Smith, 2002), FA, MD, AD, and RD maps were created by fitting a tensor model to the diffusion data by using FDT. The FA data of all participants were then aligned into Montreal Neurological Institute (MNI) 152 space by using FNIRT 1.0 (Smith et al., 2004), which uses a b-spline representation of the registration warp field. The FMRIB58_FA standard-space image was used as the target. Next, a mean FA image was generated and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. The mean FA skeleton image was thresholded at an FA value of 0.2 to prevent inclusion of nonskeleton voxels. The aligned FA data of each participant were then projected onto this skeleton. The MD, AD, and RD data were also aligned into MNI 152 space and projected onto the mean FA skeleton by using the FA data to find the projection vectors.

2.4. Statistical analysis

Relationships between four variables, CES-D, sex, age, and MMSE score, were tested by Pearson product moment correlation for all participants in the VBM analysis group and all participants in the TBSS analysis group.

2.4.1. VBM analysis

We performed voxel-wise correlation analyses by using the multiple regression function of SPM8 for all participants combined and for each sex separately. The CES-D score was treated as a covariate of interest. As nuisance variables, individual values for sex, age, and MMSE score were included for analysis of all participants combined, and age and MMSE for analysis of each sex. Two linear contrasts (1, −1) were made for positive and negative correlations, respectively. The significance level was set at family-wise error (FWE)-corrected $P < 0.05$.

Table 1
Participant characteristics.

	All			Men			Women			P
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
Participants in the VBM analysis										
N	792			523			269			
Age	55.3	9.8	23–84	55.3	9.7	23–84	55.2	9.9	24–81	n.s.
MMSE	29.1	1.1	24–30	29.1	1.1	24–30	29.2	1.0	24–30	n.s.
CES-D	4.2	5.1	0–48	3.8	4.7	0–48	5.1	5.7	0–44	<0.01
Participants in the TBSS analysis										
N	806			535			271			
Age	55.3	9.9	23–84	55.4	9.9	23–84	55.3	10.0	24–81	n.s.
MMSE	29.1	1.1	24–30	29.1	1.1	24–30	29.2	1.0	24–30	n.s.
CES-D	4.3	5.1	0–48	3.8	4.8	0–48	5.1	5.7	0–44	<0.01

MMSE: mini-mental state examination; CES-D: Center for Epidemiologic Studies Depression Scale. n.s., not significant; *P*: two-sample *t*-test for men vs. women.

2.4.2. DTI analysis

Voxel-wise analyses of the skeletonized data were performed by using permutation-based, voxel-wise nonparametric testing as implemented in the randomize tool of FSL (Nichols et al., 2002). We identified areas in which FA, MD, AD, or RD was significantly correlated with the CES-D score. Sex and age were included as covariates for analysis of all participants combined, and age for analysis of each sex. Both positive and negative contrasts were tested with 5000 permutations. We used threshold-free cluster enhancement (Smith et al., 2009) as implemented within randomize, which provides the ability to perform cluster-based inferences without setting an arbitrary cluster-forming threshold. Voxel-wise statistical inference was made on the resulting statistical image, and the significance level was set at $P< 0.05$, corrected for the FWE rate.

Table 2
Pearson product moment correlations between variables.

	CES-D	Sex	Age
In the VBM analysis group (792 participants)			
Sex	−0.123*		
Age	−0.103*	0.006	
MMSE	−0.009	−0.051	−0.279*
In the TBSS analysis group (806 participants)			
Sex	−0.117*		
Age	−0.119*	0.001	
MMSE	−0.013	−0.052	−0.279*

MMSE: mini-mental state examination; CES-D: Center for Epidemiologic Studies Depression Scale.
Sex is a dummy variable (female = 0, male = 1).
*$P < 0.01$.

3. Results

3.1. Participants

Of the 1148 volunteers who were screened, 338 met the exclusion criteria. Among the images from the resulting 810 participants, 18 3D SPGR images and 4 diffusion tensor images were excluded because of poor quality or artifacts. Images were therefore analyzed with VBM for 792 participants and with TBSS for 806 participants. There were no sex differences in age or MMSE in either group (Table 1). However, the CES-D score was significantly different between males and females in both analysis groups, and females were more depressed than males.

3.2. Relationships between CES-D and sex, age, and MMSE score

Table 2 shows Pearson product moment correlations between variables in each analysis group. The CES-D score was negatively correlated with sex and age. The sex is a dummy variable (female = 0, male = 1), so the negative correlation indicates that female participants tend to have higher CES-D scores. We found no correlation between CES-D and MMSE score. We found a negative correlation between the age and MMSE score.

3.3. VBM analysis of gray and white matter volume associated with CES-D

There was no significant correlation between gray matter volume and CES-D score for all participants combined. In the separate analysis of each sex, significant negative correlations between gray matter volume and the CES-D score were seen in the right rostral anterior cingulate gyrus and bilaterally in the dorsal anterior cingulate gyri in female participants after adjusting for age and MMSE score (Table 3). Fig. 1 shows the extent of gray matter regions that had a volume reduction correlated with the CES-D score in female participants. There was no significant correlation between gray matter volume and the CES-D score in male participants. We observed no significant correlation between white matter volume and the CES-D score.

3.4. DTI analysis of white matter integrity associated with CES-D

In the analysis of all participants combined, there were no significant correlations between DTI measures and CES-D score. In the separate analysis of each sex, TBSS showed clusters of significant FA reduction, MD increase, and RD increase that correlated with the CES-D score in female participants (Fig. 2). 10.3% of all skeleton voxels showed significant negative associations between FA and CES-D, and 16.5% and 20.2% showed positive associations with RD and MD, respectively. The clusters of FA reduction included deep white matter in the bilateral frontal, temporal, and occipital lobes, external capsule, a large portion of the corpus callosum, right anterior cingulate, left fornix, and left uncinate. The clusters of RD increase were in almost the same structures as the clusters of FA reduction. The clusters of MD increase included deep white matter in the bilateral frontal, temporal, occipital, and parietal lobes, external capsule, superior longitudinal fasciculus, a large portion of the corpus callosum, right anterior limb of the internal capsule, left anterior cingulate, left fornix, and left uncinate. The cluster tool in FSL revealed that a largest cluster including the right dorsal anterior cingulum (Fig. 3) showed a significant reduction in FA (*P*-value at the peak voxel = 0.003, cluster size = 14,170) and an increase in RD (*P*-value at the peak voxel = 0.002, cluster size = 20,391) in association with the CES-D score. There were no significant clusters of increased FA, reduced MD, or reduced RD. AD showed no significant correlation with the CES-D score. There was no significant correlation between DTI measures and the CES-D score in male participants.

Table 3.
Areas with significant gray matter volume reduction that correlated with depressive symptoms in female participants.

Anatomical location	Talairach coordinates			*P*	Cluster size
	x	y	z	(FWE corrected)	
Right rostral anterior cingulate gyrus	1	31	22	0.029	846
	15	32	21		
	10	28	15		
Left dorsal anterior cingulate gyrus	−1	4	34	0.037	785
Right dorsal anterior cingulate gyrus	7	0	34		

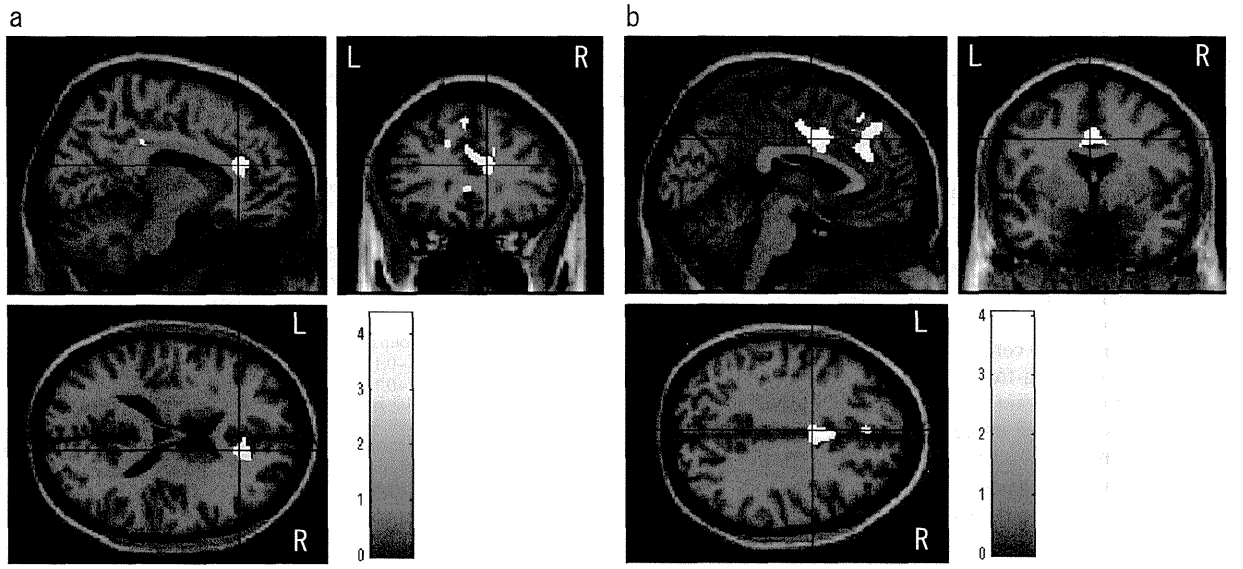

Fig. 1. Results from multiple regression in female participants with a threshold of $P < 0.001$ (uncorrected data). Gray matter volumes in the right rostral anterior cingulate gyrus (a) and bilateral dorsal anterior cingulate gyri (b) were negatively correlated with depressive symptoms ($P < 0.05$, FWE-corrected, cluster level). Cluster locations, sizes, and significance values are shown in Table 2. R and L indicate right and left, respectively. Color scale (0–4) represents *t* values.

4. Discussion

To our knowledge, this is the first report to simultaneously study brain volume and white matter integrity associated with depressive symptoms in a large sample. We found statistically significant results only in the analysis of female participants and not in all participants combined or in male participants. The gray matter volume in the right rostral anterior cingulate and bilateral dorsal anterior cingulate gyrus decreased in association with increased depressive symptoms. There were white matter regions in which FA was negatively correlated with depressive symptoms. The CES-D score in most of the regions showed significant positive correlations with RD and MD.

4.1. The anterior cingulate gyrus and depressive symptoms

Volume reduction in the anterior cingulate gyrus has been reported in major depression (Botteron et al., 2002; Caetano et al., 2006; Lorenzetti et al., 2009). Several studies of community-dwelling populations revealed regional brain volume reductions in the anterior cingulate gyrus associated with depressive symptoms (Boes et al., 2008; Dotson et al., 2009). Boes et al. (2008) revealed volume reduction in the rostral anterior cingulate cortex of boys (but not girls) with subclinical depressive symptoms, suggesting that the rostral anterior cingulate cortex may act as a biological marker of vulnerability to, or as a trait marker of, depression. Moreover, some personality traits, such as harm avoidance, are known to be risk markers for major depression and have relationships with anterior cingulate volume (Grucza et al., 2003; Pujol et al., 2002). The present study, along with the previous reports, indicates that anterior cingulate volume reduction is associated with subclinical depressive symptoms. This is consistent with the hypothesis that this area is associated with vulnerability or future progression to major depression.

In addition, using TBSS, we discovered a negative correlation between FA and the CES-D score, and a positive correlation between RD and the CES-D score, in the right anterior cingulum in female participants. Increased RD reflects demyelination of axons in animal studies (Song et al., 2005). Although the anatomical underpinnings of RD in humans are not fully understood, when the TBSS results are combined with the VBM results, this study suggests that the volume reduction seen in the right anterior cingulate gyrus is the result of demyelination and/or abnormal myelination of the underlying white matter. In the left anterior cingulum, there was a positive correlation between MD and depressive symptoms. By definition, the difference between MD and RD depends on AD. In this study, although AD showed no significant correlation with depressive symptoms, the slight but non-significant variance of AD may have influenced the difference between RD and MD.

4.2. The white matter integrity and depressive symptoms

Disruption of integrity in some white matter regions has recently been reported in major depression (Abe et al., 2010; Kieseppä et al., 2010; Shimony et al., 2009). Kieseppä et al. (2010), using TBSS, suggested that FA is decreased in the left sagittal stratum, right cingulate gyrus, and posterior body of the corpus callosum in major depression. Fewer studies have focused on white matter integrity and subclinical depressive symptoms in healthy participants. As for individuals