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Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: A multi-channel near-infrared spectroscopy study

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ABSTRACT

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain activity. Previous NIRS studies indicated the oxy-hemoglobin (oxy-Hb) increase during a verbal fluency task (VFT) is attenuated in patients with major depressive disorder (MDD) as compared with healthy controls. However, the possible relationship between depression symptom severity and oxy-Hb change on NIRS has not yet been elucidated. To examine this relationship, we recruited 30 patients with MDD and 30 age-, gender- and intelligence quotient-matched controls. All underwent NIRS during VFT. As expected, the oxy-Hb increase during the task was significantly smaller in patients than in controls. After false discovery rate correction using 31 channels, the mean increase in oxy-Hb during the task showed a significant negative correlation with the total score of the Hamilton Rating Scale for Depression 21-item version (ch25: rho = −.56; FDR-corrected *p*: .001). When each item of the HAM-D21 was examined individually, insomnia early in 9 channels (rho = −.63 to −.46; FDR corrected *p*: .000–.014), work and activity in 2 channels (rho = −.61 to −.57; FDR corrected *p*: .001 to .003) and psychomotor retardation in 12 channels (rho = −.70 to −.44; FDR corrected *p*: .000–.018) showed significant negative correlations with the mean oxy-Hb increase in the right frontal temporal region. Although it is possible that our results were affected by medication, these data suggest reduced right frontal temporal activation on NIRS during VFT is related to the symptom severity of MDD.

1. Introduction

Major depressive disorder (MDD) is a severe and common psychiatric disorder with a lifetime prevalence of 6.7 per 100 (Waraich et al., 2004). Although depressive symptoms per se do not specifically appear in MDD but also in other psychiatric disorders including bipolar disorders, we do not have an objective diagnostic marker to obtain a clear-cut diagnosis for those patients. In Japan, a relatively new neuroimaging method, near-infrared spectroscopy (NIRS) has been approved by the Ministry of Health, Labor and Welfare as a highly advanced medical technology to help distinguish between schizophrenia, depression and bipolar disorders in 2009. Verbal fluency task (VFT) is recommended as an activation task because of a relatively rich store of data. VFT is an easy task to examine the executive function and frequently used in neuroimaging studies (Alvarez and Emory, 2006) and is known to activate prefrontal cortex (PFC) in healthy subjects (Frith et al., 1991; Schlösser et al., 1998). Numerous neuropsychological studies suggest that patients with MDD show executive dysfunction (Gohier et al., 2009; Rose and Ebmeier, 2006; Fossati et al., 2003; Porter et al., 2003; Degl'Innocenti et al., 1998).

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, restraint-free functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain

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function near the brain surface using near-infrared light (Strangman et al., 2002a; Boas et al., 2004). NIRS has enabled bedside measurement of the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) changes with a high time resolution (.1 s). The concentrations of oxy-Hb and deoxy-Hb are assumed to reflect the regional cerebral blood volume (rCBV) changes, which was supported by the simultaneous NIRS and PET study (Villringer et al., 1997; Ohmae et al., 2006).

In fact, numerous studies have demonstrated that the oxy-Hb increase in the fronto-temporal regions during a VFT is significantly smaller in patients with MDD than in those with bipolar disorder or healthy controls (Pu et al., 2008; Kameyama et al., 2006; Suto et al., 2004; Matsuo et al., 2002). Moreover, NIRS studies using VFT have also demonstrated frontal lobe dysfunction in schizophrenia (Suto et al., 2004; Takizawa et al., 2008), and panic disorder (Nishimura et al., 2007). However, the relationship between depression symptom severity at the time of examination and oxy-Hb change on NIRS has not yet been clarified.

In neuroimaging studies using other methodologies, focusing on cortex level that NIRS reflects, positron emission tomography (PET) studies found that abnormal reductions of cerebral blood flow (CBF) and metabolism in patients with MDD in PFC (Kimbrell et al., 2002; Bench et al., 1995; Mayberg et al., 1994; Baxter et al., 1989). As for the relationship between executive function and CBF or metabolism, Elliott et al. (1997) showed activation in PFC was significantly attenuated relative to controls during the Tower of London planning task in PET study. In a functional magnetic resonance imaging (fMRI) study, depressed patients showed significant decreased prefrontal activation during VFT (Okada et al., 2003).

As for the relationship between depression symptom severity and frontal lobe function, Brody et al. (1999) found a positive correlation between change in Hamilton Rating Scale for Depression (HAM-D) scores and change in normalized inferior frontal gyrus (IFG) and ventrolateral PFC (VLPFC) metabolism, which indicates that IFG metabolism increased and VLPFC metabolism decreased as depression symptoms became better. Other initial studies also suggest that abnormal functions in dorsolateral PFC (DLPFC) are mood state dependent, attenuated during the depressed mood and reversing during symptom remission (Bench et al., 1995; Mayberg et al., 1994). In contrast, Drevets et al. (2002) showed the persistence of abnormal metabolic deficits using PET measures in the dorsomedial/dorsal anterolateral PFC in MDD during treatment. According to a review by Drevets (2000), a complex relationship exists between depression symptom severity and metabolic activity in the orbital cortex and VLPFC.

Findings obtained by more recent studies investigating cross-sectional relationship between depression symptom severity and brain function assessed by basal regional CBF and metabolism are also inconsistent. For example, Périco et al. (2005) reported that depression symptom severity was negatively correlated with regional CBF (rCBF) in the left amygdala, lentiform nucleus, and parahippocampal gyrus, and positively correlated with rCBF in the right postero-lateral parietal cortex, whereas Milak et al. (2005) showed only positive correlations in bilateral mesiotemporal cortex, parts of the ventral subgenual basal forebrain, and most of the thalamus, hypothalamus, ventral striatum, and midbrain. Accordingly more studies are warranted to clarify the relationship between depression severity and brain activity including frontal lobe function.

In the present study, considering the consistent finding of attenuated oxy-Hb changes during VFT in the fronto-temporal regions in depression, we hypothesized that oxy-Hb changes during VFT in NIRS could be objective indicators of depressive symptom severity. Thus, we used multi-channel NIRS to investigate the relationship between oxy-Hb changes and symptom severity in patients with MDD. Because NIRS can be measured easily and noninvasively in a restraint-free environment over a short amount of time we expect that NIRS can be widely used to assess objectively depressive symptom severity as a clinical examination.

2. Materials and methods

2.1. Subjects

The subjects were 30 patients with MDD, and 30 healthy volunteers matched for age, gender and premorbid intelligence quotient (IQ). Premorbid IQ was estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). All subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native speakers of Japanese. All MDD subjects were outpatients of the National Center of Neurology and Psychiatry Hospital in Tokyo, Japan. They were diagnosed according to the Structured Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Disorders (SCID-I; First et al., 1995) by experienced psychiatrists. All patients were medicated with antidepressants. Twenty-seven out of 30 patients were prescribed with one or two antidepressants, 16 with SSRIs, 12 with tricyclics, 7 with milnacipran, 5 with tetracyclics, 2 with trazodone and 1 with mirtazapine. In addition, 20 patients were prescribed with anxiolytics, 16 with hypnotics, 7 with mood stabilizers and 9 with antipsychotics (Supplementary Table 1). Daily doses of all antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006) and anxiolytics/hypnotics to that of diazepam (Inagaki and Inada, 2006) for each patient. The controls were healthy volunteers recruited from the same geographical area through advertisements in free local magazines and our website announcement. They were interviewed using the SCID-I for MDD or SCID-NP for healthy volunteers and an unstructured interview for family history, and those individuals who had a current or past history of Axis I psychiatric disorder or a positive family history of Axis I psychiatric disorder within their first degree relatives were excluded. The exclusion criteria for both groups were previous head trauma, neurological illness, a history of electroconvulsive therapy, alcohol/substance abuse or addiction.

After the study procedures had been fully explained, written informed consent was obtained from every participant. This study was approved by the ethics committee of the National Center of Neurology and Psychiatry.

2.2. Clinical assessment

Depressive symptoms and the level of social functioning were evaluated by a single experienced psychiatrist using the GRID Hamilton Rating Scale for Depression 21-item version (GRID HAM-D21; Kalali et al., 2002) and Global Assessment of Functioning scores (GAF; American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data on the same day that the NIRS measurements were conducted. Sleepiness was evaluated as the score on the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973).

2.3. Activation task

The activation task was a letter version of VFT similar to that described by Takizawa et al. (2008). During the VFT, changes in oxy-Hb and deoxy-Hb were measured. The VFT consisted of a 30-sec pre-task baseline, a 60-sec VFT, and a 70-sec post-task baseline. The subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/ and /o/ during the pre-task and post-task baseline periods. For the VFT, the subjects were instructed to generate as many words as possible.

One of the three initial syllables (A; 0–20 s /a/, /to/, or /na/, B; 20–40 s /i/, /ki/, or /se/, C; 40–60 s /o/, /ta/, or /ha/) was randomly

presented on the computer display placed in front of the subjects, every 20 s during the 60-sec task. The number of possible combinations of syllables is 27 (A;3 × B;3 × C;3 = 27). We adopted 15 among the possible combinations. The number of correct words generated during the task was determined as a measure of task performance.

3. NIRS measurements

3.1. NIRS device

We used a 52-channels NIRS (ETG-4000 Optical Topography System; Hitachi Medical Co., Tokyo, Japan) which measures relative changes in oxy-Hb and deoxy-Hb using two wavelengths (695 nm and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). With this system, these Hb values include a differential pathlength factor (DPF). In the NIRS system, "hemoglobin concentration change*DPF" is calculated as a solution to the simultaneous equations based on the Beer–Lambert law, which cannot escape the effect of DPF. Although DPF varies among various brain regions Zhao et al., using a Monte Carlo simulation, reported the estimated DPF variation in the forehead region of adult humans was roughly homogeneous (Zhao et al., 2002).

The distance between a pair of source-detector probes was set at 3.0 cm and each area measured between a pair of source-detector probes was defined as a 'channel'. The NIRS device is considered to measure 'channels' at a 2–3 cm depth from the scalp, that is, at the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003, Toronov et al., 2001).

3.2. Probe positioning and measurement points

The NIRS probes were fixed with 3 × 11 thermoplastic shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. The probes can measure Hb values from bilateral prefrontal and temporal surface regions. The measuring points were labeled ch1 to ch52 from right-posterior to left-anterior (Fig. 1). The correspondence between these NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical cranio-cerebral correlations (Okamoto et al., 2004) and presented on the basis of results obtained by the virtual registration method (Tsuzuki et al., 2007).

3.3. Measurement parameters

The rate of data sampling was .1 second (s). The obtained data were analyzed using integral mode; the pre-task baseline was determined as the mean over a 10 s period just prior to the task period, and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was then applied to the data between these two baselines. The moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. Because we could not remove all artifacts in this way, we applied automatic rejection of data with artifacts separately for each channel (Takizawa et al., 2008).

According to the aforementioned measurement parameters for integral mode, the waveforms of oxy-Hb, deoxy-Hb and total-Hb

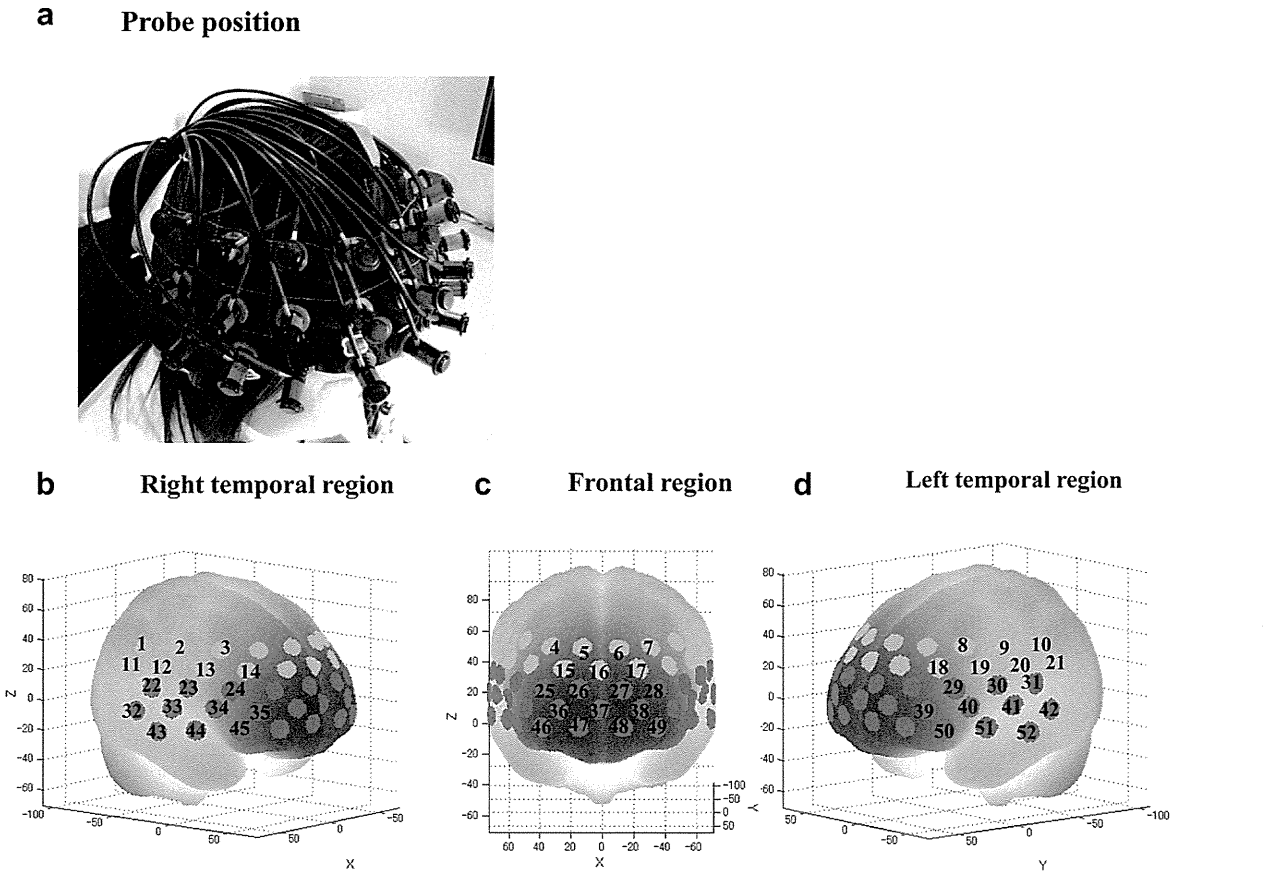

Fig. 1. Measurement points of 52 channels for near-infrared spectroscopy (NIRS) (a) Probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral frontal regions. (b–d) The 52 measuring positions of the NIRS device are superimposed on the 3D-reconstructed cerebral surface, based on magnetic resonance imaging. The 52 measuring positions are labeled ch1 to ch52, from the right posterior to the left posterior. The dimensional figures b, c and d indicate the right temporal, frontal and left temporal brain regions, respectively. Because acquired NIRS data from the 21 channels in the upper two rows (pink channels) clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ratio seemed to be low, they were excluded from statistical analyses.

changes were acquired from each subject in all 52 channels during VFT.

3.4. Measurement environment

The subjects sat on a comfortable chair in a silent and day-lit room. They were instructed to minimize motions such as head movements, strong biting and blinking during the NIRS measurement, to avoid artifacts.

Data clearly containing motion artifacts, based on both our observations and the NIRS recording, were excluded from further analyses.

4. Statistical analysis

Because acquired NIRS data from the 21 channels in the upper two rows clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ration seemed to be low, they were excluded from statistical analyses.

The χ^2 test or Student's *t*-test was used to compare proportions and means, respectively, between the MDD and control groups.

As for the analysis of the NIRS data, we focused on oxy-Hb data, since oxy-Hb change (task period − pre- and post-task baseline period) is assumed to more directly reflect cognitive activation than deoxy-Hb change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b). The mean oxy-Hb changes were compared between the two groups (MDD and control) for each channel using Student's *t*-test. To examine the relationships between oxy-Hb changes and HAM-D21 total scores, HAM-D21 subscale scores, GAF, or other clinical variables, Spearman's rhos were calculated for MDD patients.

All statistical analyses were performed using SPSS for Windows, version 18.0.0 software (SPSS Japan, Tokyo, Japan). A value of $p < .05$ (two-tailed) was considered to be statistically significant. We set the value of q specifying the maximum false discovery rate (FDR) at .05, such that the false positive rate was no more than 5% on average in treating the oxy-Hb data obtained from multiple channels (Singh and Dan, 2006).

5. Results

5.1. Demographic and clinical data of patients and controls

Table 1 summarizes demographic characteristics of the patients and controls. The two groups did not differ significantly in age, gender, handedness, estimated premorbid IQ or SSS.

5.2. Task performance

The number of words generated did not differ significantly among the 15 combinations employed (15 combinations: $F[1, 45] = 1.1$, $p = .39$; three initial syllables: $F[2, 90] = 1.2$, $p = .31$) in either group. The number of generated words during VFT did not differ significantly (patients: 12.3 ± 3.9; controls 13.9 ± 4.3, $t = 1.5$, df = 58, $p = .13$) between the MDD and control groups.

5.3. Group comparison

As shown in Fig. 2, the MDD group had significantly smaller oxy-Hb increases than the control group in 22 channels (ch22–29, ch32–33, ch35–39 and ch44-50; FDR-corrected *p*: .000–.024) during VFT.

5.4. Relationship with symptom severity at the time of examination

As shown in Fig. 2, there were significant negative correlations between mean oxy-Hb changes during the task and HAM-D21 total scores in one channel (ch25: rho = −.56; FDR-corrected *p*: .001). Mean oxy-Hb changes during the task period showed significant negative correlations with three individual items of the HAM-D21 subscale scores (Fig. 3); insomnia early in 9 channels (ch23, ch25–27, ch36–37 and ch46–48: rho = −.63 to −.46; FDR corrected *p*: .000–.014), work and activity in 2 channels (ch44 and ch45: rho = −.61 to −.57; FDR corrected *p*: .001 to .003), and psychomotor retardation in 12 channels (ch22–24, ch32, ch35–36, ch41, ch43–ch45, ch47 and ch51: rho = −.70 to −.44; FDR corrected *p*: .000–.018). Mean oxy-Hb changes showed no significant correlations with the remaining HAM-D21 subscale scores (i.e., depressed mood, guilt, insomnia middle, insomnia late, psychomotor agitation, anxiety psychic, anxiety somatic, loss of appetite, somatic symptoms general, sexual interest, hypochondriasis, loss of weight, insight, diurnal variation, and obsessional symptoms;) (Fig. 4).

Furthermore, mean oxy-Hb changes showed no significant correlation with task performance during VFT or other clinical variables, such as age, duration of illness, and sleepiness (data not shown).

5.5. Relationships with medication

There were no significant correlations between the HAM-D21 total score and doses of antidepressants (rho = −.23, $p = .22$) or anxiolytics (rho = .25, $p = .18$). There were significant negative correlations between mean oxy-Hb changes during the task and doses of antidepressants in 6 channels (ch31, ch40–41, ch45, ch50–51: rho = −.57

Table 1
Demographic and clinical data of patients with major depressive disorder and controls.

Demographics	Patients with depression ($n = 30$)	Healthy controls ($n = 30$)	Group difference *p*-value
Age (years)	36.7 ± 11.6	35.1 ± 9.4	.871
Gender (female/male)	16/14	16/14	1.000
Edinburgh handedness inventory (%)	92.9 ± 9.7	92.0 ± 11.5	.753
Age at onset (years)	30.9 ± 10.8	–	–
Duration of illness (years)	5.8 ± 4.1	–	–
Duration of medication (years)	5.0 ± 3.6	–	–
GRID HAM-D21 total score	16.7 ± 4.8	–	–
Estimated premorbid IQ	105.7 ± 9.5	105.9 ± 8.3	.953
Sleepiness	3.3 ± 1.1	2.9 ± .9	.104
GAF	57.6 ± 9.3		
Medication			
Imipramine equivalent dose (mg/day)	141.9 ± 127.6	–	–
Diazepam equivalent dose (mg/day)	8.5 ± 11.6	–	–

The χ^2 test or *t*-test was used to compare these variables between patients and controls. GAF, Global Assessment of Functioning; GRID HAM-D21, GRID Hamilton Rating Scale for Depression 21 item; IQ, Intelligence Quotient.

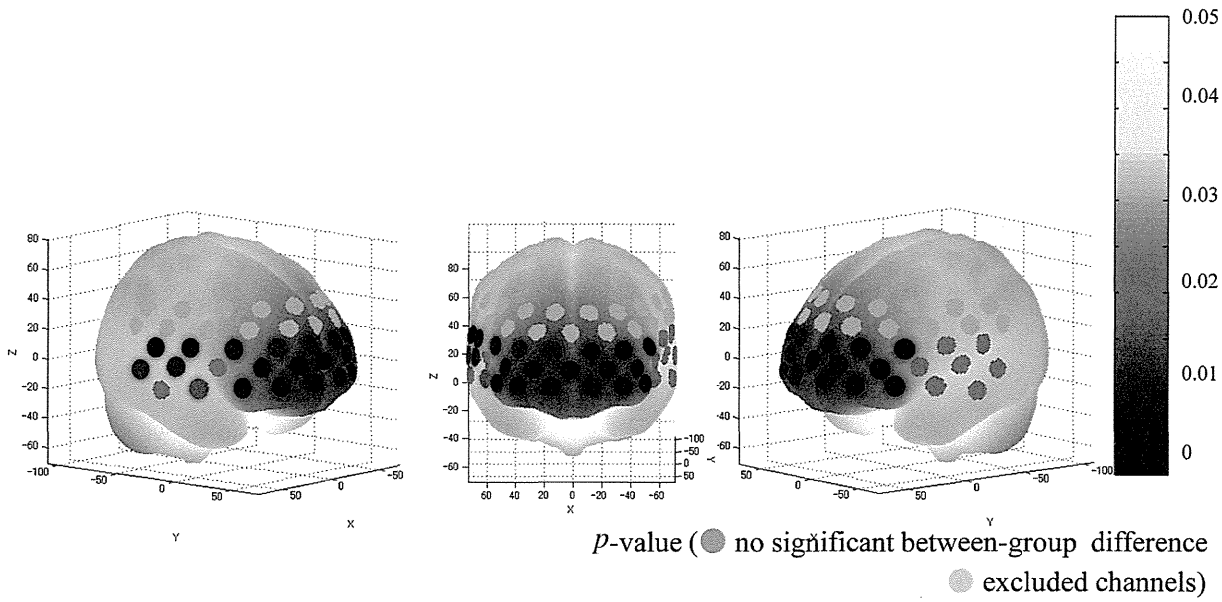

Fig. 2. *p*-value significance map of *t*-tests for oxy-Hb increases in patients with MDD compared with healthy controls during VFT using FDR correction. The warm colored circles represent significantly smaller oxy-Hb increases than in the control group at the channels indicated. There were 22 channels (ch22–29, ch32–33, ch35–39 and ch44–50; FDR-corrected *p*: 000–.024).

to −.48; FDR-corrected *p*: .002 to .007). Mean oxy-Hb changes showed no significant correlations with doses of anxiolytics.

6. Discussion

6.1. Task performance

The number of words generated during the VFT did not differ significantly between patients and controls, which is consistent with the majority of previous studies (Matsuo et al., 2002; Fossati et al., 2003; Suto et al., 2004; Kameyama et al., 2006). Previous studies reported impairment on semantic fluency tasks in depression (Calev et al., 1989; Tarbuck and Paykel, 1995). However, on phonemic fluency task conflicting results patients showing normal or impairment performance in depression (Albus et al., 1996; Degl'Innocenti et al., 1998). Type of psychiatric disorder and task time setting may reflect the discrepancies (Fossati et al., 2003). In the present study, the time setting of VFT was three phonemes within 60 s, that is, 20 s for each phoneme, which differs from the standard VFT usually using 60 s for one phoneme. The time setting condition was designed as it is, so that the subjects were able to keep generating words regularly within the task period to avoid the effect of "not speaking". It is possible that the time setting condition in the present study caused the lack of significant between group-difference in task performance.

6.2. Between-group comparison of oxy-Hb activation

The present study showed oxy-Hb activation during VFT to be significantly smaller in the MDD group than in age-, gender- and IQ-matched healthy controls. This result is essentially consistent with those obtained using NIRS (Matsuo et al., 2002; Herrmann et al., 2004; Suto et al., 2004; Kameyama et al., 2006; Pu et al., 2008), single photon emission computed tomography (SPECT) (Mayberg et al., 1994) or functional magnetic resonance imaging (fMRI) (Okada et al., 2003).

6.3. Relationships with symptom severity at the time of examination

Mean oxy-Hb changes during the task period showed a significantly negative correlation with HAM-D21 total score at ch25. Ch25 is located approximately in the right DLPFC. The finding is in line with some initial studies (Bench et al., 1995; Mayberg et al., 1994) which suggest that abnormal functions in DLPFC are mood dependent. However, other more recent studies investigating cross-sectional relationship between depression psychopathology and brain function do not coincide with our result (Périco et al., 2005; Milak et al., 2005). One of the reasons for the discrepancy may arise from the different methodologies; in the present study we adopted VFT for activation whereas the previous studies observed the basal activity with no activation task. Although speculative as it is, the activation of PFC by VFT may have led to the significant relationship between oxy-Hb changes and depression symptom severity in the right DLPFC.

More interestingly, mean oxy-Hb changes during the task period showed significant negative correlations with three individual HAM-D21 items in a wider area than they showed with HAM-D21 total scores; insomnia early in nine, work and activity in two and psychomotor retardation in twelve channels. The nine channels correlating with "insomnia early" were located approximately in the right pre-motor area, DLPFC and frontopolar and orbitofrontal areas. The two channels correlating with "work and activity" were located approximately in the right DLPFC and temporopolar area. The twelve channels correlating with "psychomotor retardation" were located broadly in the fronto-temporal areas with right hemispheric dominance. Although these findings should be treated with care given the exploratory nature of multiple analyses, it is noteworthy that at least some subscale scores of HAM-D21 appeared to show stronger relationship with oxy-Hb changes than HAM-D21 total scores. It has been pointed out that HAM-D17 and/or HAM-D21 are not necessarily unidimensional, and thus not adequate to assess depression severity (Bagby et al., 2004). Licht et al. (2005) showed that a set of the HAM-D containing six subscales constitute a unidimensional scale measuring severity of

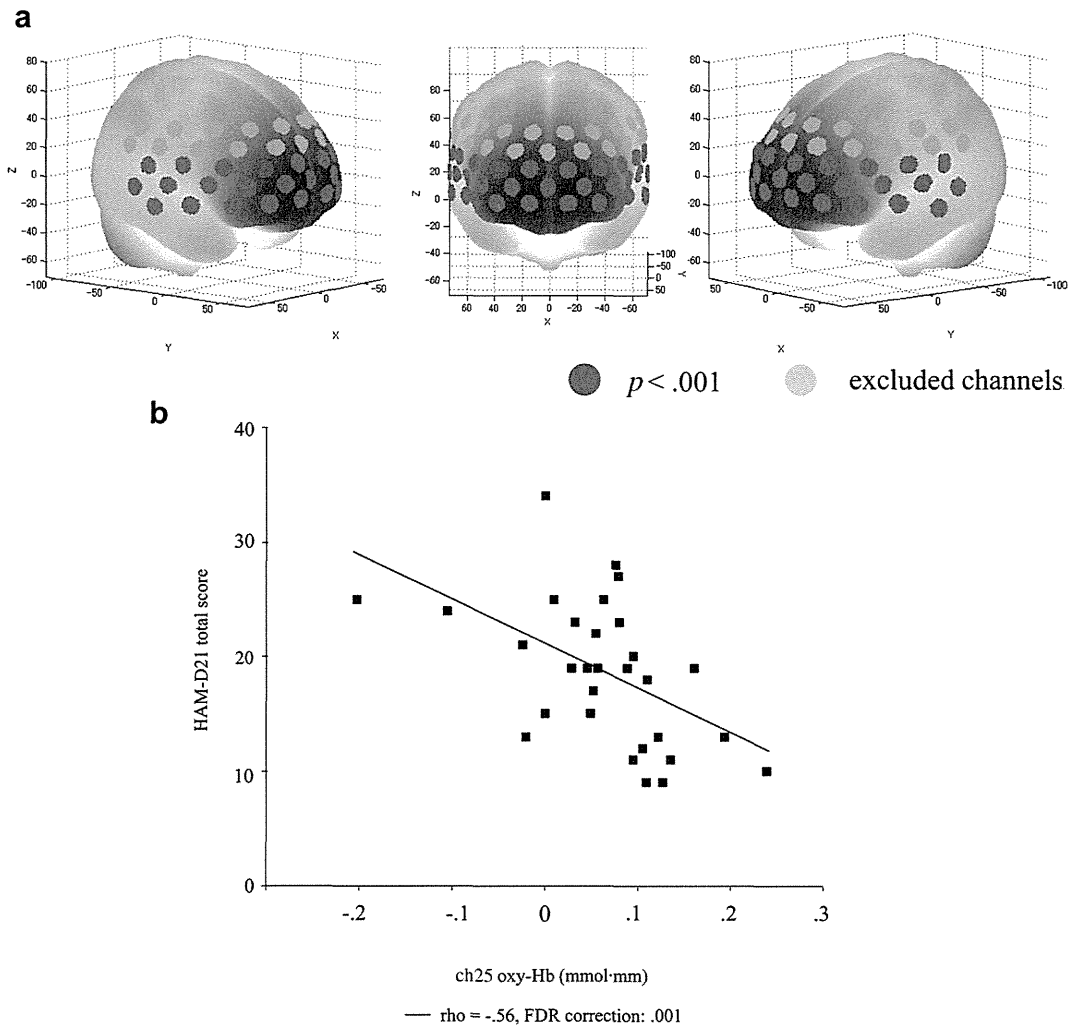

Fig. 3. (a) The channels with a significant correlation between oxy-Hb changes and HAM-D21 total score after FDR correction. (b) Scatter graph showing the relationship between HAM-D21 total scores and oxy-Hb activation in ch25.

depression, whereas the remaining items covering neurovegetative symptoms showed a problematic response somewhat insensitive to depression severity. In fact, the multidimensionality was highlighted in the unstable factor structure, which was demonstrated by a failure to replicate a single unifying structure across studies (Bagby et al., 2004). The relatively strong relationship indicated between HAM-D21 subscale scores and oxy-Hb changes in divergent areas, compared to HAM-D21 total scores may be due to the multidimensional properties of HAM-D21. Graff-Guerrero et al. (2004) also demonstrated that each HAM-D subscale score showed a significant correlation with the basal CBF in variant areas, in some cases showing positive correlation and others negative.

6.4. Relationships with medications

As all patients were taking antidepressants at the time of evaluation, the medication effect could not be ignored. Yet, there was no significant relationship between daily dose levels of antidepressants and the HAM-D21 total score. Although daily dose levels of antidepressants showed significant negative correlations with oxy-Hb changes in six channels, ch25, where a significant correlation between oxy-Hb changes and HAM-D21 total scores was observed, was not included in the six channels. Therefore, we suspect that the effect was small, if at all.

PET has been used to demonstrate that antidepressant medication normalizes both over-activity and under-activity in the frontal cortex (Kennedy et al., 2001, 2007; Mayberg et al., 2000; Goldapple et al., 2004). Unfortunately, our results could not clarify the relationship between medication and brain activation because our analysis was based on cross-sectional data. Although our data may reflect the more restraint-free, natural setting than those using fMRI or PET, further studies in drug-naïve patients are required to draw any conclusions as to the possible effects of medication on brain activation as measured by NIRS. Longitudinal studies investigating the relationship between the change in oxy-Hb data and symptom severity scores with a larger sample size are warranted to reach a conclusion on this matter.

The results of this study must be interpreted with caution due to certain limitations. First, because the analysis was based on cross-sectional data, causality cannot be determined. Longitudinal studies are needed to assess cause-and-effect relationships. Second, our sample size was not large, and is thus subject to type II error. Further studies with larger numbers of MDD patients are required. Finally, owing to the multidimensional properties of HAM-D21, assessment of depression symptom severity using HAM-D21 total scores may not be adequate, and thus, other scales such as Montgomery Asberg Depression Rating Scale (MADRS) or Beck Depression Inventory (BDI) should be tested in the future study.

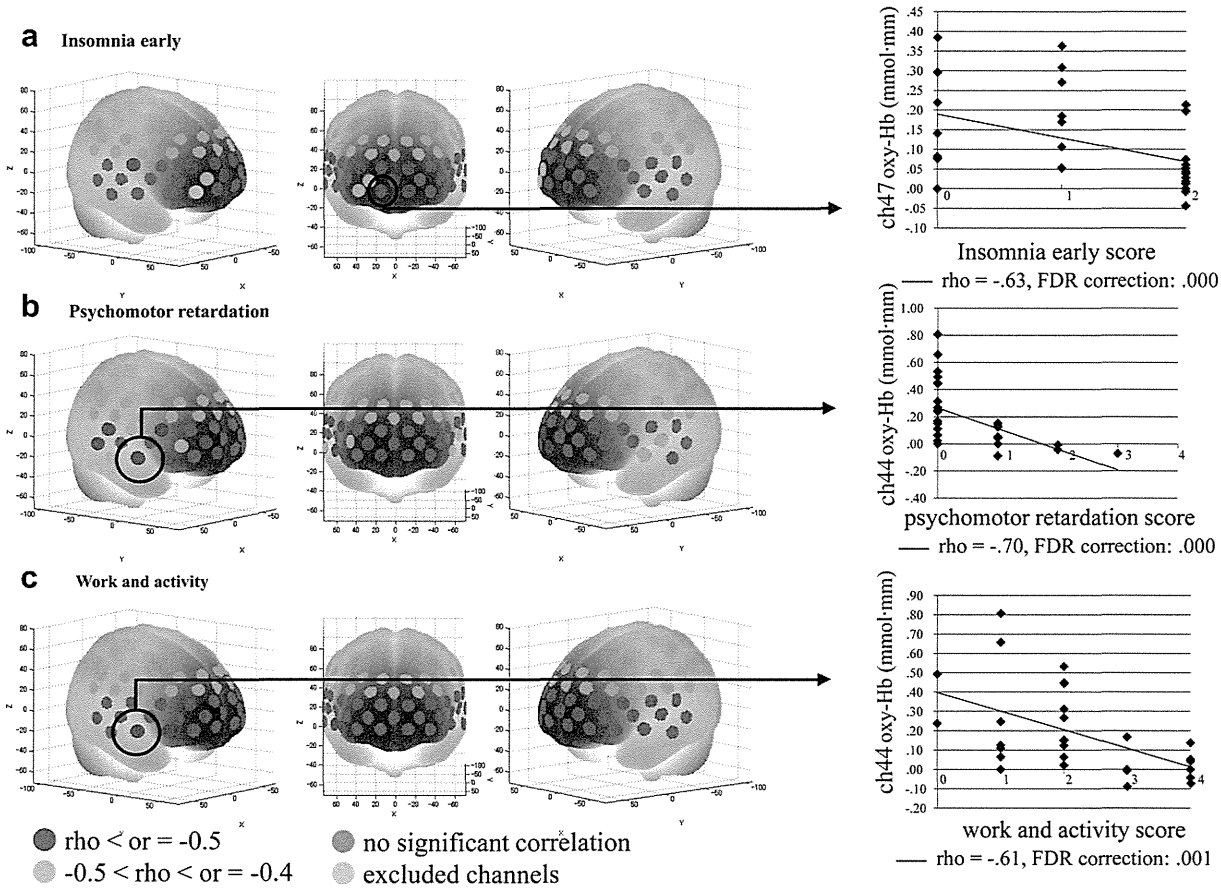

Fig. 4. rho-value map for the correlation between oxy-Hb activation in MDD patients and three individual HAM-D21 subscale scores after FDR correction. (a) insomnia early, (b) psychomotor retardation, and (c) work and activity.

7. Conclusion

In this study, we confirmed that the increase in oxy-Hb during a VFT task is significantly smaller in MDD than in age- and gender-matched healthy subjects. This difference could not be explained by a difference in task performance or premorbid IQ. The blunted increase in right DLPFC was associated with the symptom severity of MDD and therefore oxy-Hb changes during VFT in this region may be a state-dependent marker of depression.

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Contributors

T. Noda designed the study, wrote the protocol, assessment of depression severity, literature searches, statistically analyzed the data, and wrote the first draft of the manuscript. T. Matsuda was involved in patient recruitment and assessment of depression severity. H. Kunugi and S. Yoshida wrote the final version of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest with respect to this study or its publication.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2012.04.001.

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Different hemodynamic response patterns in the prefrontal cortical sub-regions according to the clinical stages of psychosis

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ABSTRACT

Background: Symptomatic and functional outcomes in schizophrenia are associated with the duration of untreated psychosis. However, no candidate biomarkers have been adopted in clinical settings. Multichannel near-infrared spectroscopy (NIRS), which can easily and noninvasively measure hemodynamics over the prefrontal cortex, is a candidate instrument for clinical use.
Aims: We intended to explore prefrontal dysfunction among individuals at different clinical stages, including ultra-high-risk (UHR), first-episode psychosis (FEP), and chronic schizophrenia (ChSZ), compared to healthy subjects.
Method: Twenty-two UHR subjects, 27 patients with FEP, 38 patients with ChSZ, and 30 healthy subjects participated. We measured hemodynamic changes during a block-designed letter fluency task using multichannel NIRS instruments.
Results: We found that the activations of the bilateral ventrolateral prefrontal cortex, and the fronto-polar and anterior parts of the temporal cortical regions in the UHR group were lower than those of the controls, but similar to those of the FEP and ChSZ groups. However, the activations in the bilateral dorsolateral prefrontal cortex regions decrease with advancing clinical stage.
Conclusions: To the best of our knowledge, this is the first study directly comparing differences in hemodynamic changes with respect to the 3 clinical stages of psychosis. Furthermore, this study also demonstrates different patterns of impairment according to the progression of clinical stages using NIRS instruments. NIRS measurements for UHR and FEP individuals may be candidate biomarkers for the early detection of the clinical stages of psychosis.

1. Introduction

Retrospective studies suggest that patients with schizophrenia have prodromal symptoms before psychotic symptoms such as depression, anxiety, attenuated psychotic symptoms, and functional decline fully emerge (Yung et al., 1998; Hafner, 2000; Klosterkotter et al., 2001). A recent review suggests that patients with short durations of untreated psychosis (DUP) have better symptomatic and functional outcomes throughout their lives (Perkins et al., 2005). Therefore, supportive services and programs have been developed toward early detection and intervention for people exhibiting prodromal symptoms to reduce DUP and prevent the transition to psychosis (French et al., 2007; Yung and McGorry, 2007; Joa et al., 2008). To screen for high-risk individuals before developing psychosis, called ultra-high-risk (UHR) individuals, various clinical diagnostic tools have been developed in the last 20 years (Yung et al., 1998; Miller et al., 1999; Klosterkotter et al., 2001; Yung et al., 2004; Yung and McGorry, 2007; Cannon et al., 2008). The rate of transition to psychosis is about 20–30% per year for help seekers who meet the UHR criteria according to these assessment tools (Yung et al., 2004; Cannon et al., 2008). These clinical assessments are helpful but insufficient for early detection and intervention; therefore, more objective tools for detection are needed to help high-risk individuals. Several possible biomarkers for improving the predictive value for developing psychosis are reported in structural MRI studies (Fornito et al., 2008; Koutsouleris et al., 2009); however, no candidate biomarkers have been adopted in clinical settings. MRI instruments have an advantage in spatial resolution; this advantage has substantially contributed to the anatomical and functional clarification of psychiatric disorders. However, routine and repetitive MRI use for patients with psychiatric disorders presents difficulties due to increased costs, greater noise, and the restricted position required during testing.

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Near-infrared spectroscopy (NIRS), which can easily and noninvasively measure hemodynamics over the surface of the prefrontal cortex, is a candidate instrument for clinical use. NIRS instruments are also small and convenient such that they can be easily moved almost everywhere, including schools and care units. Our previous NIRS studies suggest that patients with chronic schizophrenia (ChSZ) have impaired activity and characteristic waveform patterns over the prefrontal cortical regions during a letter fluency task (LFT) (Suto et al., 2004; Takizawa et al., 2008). On the basis of these results, the Health, Labour, and Welfare Ministry in Japan approved the NIRS instrument as a diagnostic support system for patients with schizophrenia, major depression, and bipolar disorder. However, little is known about how the NIRS signals of pre- and postpsychotic individuals change; thus, we assumed that the activities in the prefrontal cortex might be different at each clinical stage. If we identify these differences, the NIRS system may be a potential candidate biomarker for objectively detecting and evaluating young people experiencing various symptoms and impaired functions.

The aim of this study is to explore the prefrontal dysfunction of UHR help seekers and patients with first-episode psychosis (FEP) compared to controls during a block-designed LFT, using multichannel NIRS instruments. In addition, if we succeed in early detection and intervention for young patients, they would be able to preserve their functions during the chronic phase. Therefore, we compared patients with ChSZ matched for age-at-onset and DUP to patients with FEP.

2. Method and materials

2.1. Participants

A total of 117 Japanese individuals participated in this study: 22 subjects who fulfilled the UHR criteria, 27 patients with FEP, 38 patients with ChSZ, and 30 healthy subjects (HC group) as controls (Table 1). All participants were recruited from the University of Tokyo Hospital and the Tokyo Metropolitan Matsuzawa Hospital. All UHR individuals and most patients with FEP were help seekers registered at the outpatient unit specialized for early intervention in the University of Tokyo Hospital. The route of participation was via internet homepage (http://plaza.umin.ac.jp/arms-ut), usual outpatient and inpatient units, the University of Tokyo Health Service Center, and introductions from other psychiatry clinics. All subjects gave written informed consent to the ethical committee of the Faculty of Medicine, University of Tokyo (approval No. 630-5, 2226-1), and the ethical committee of the Tokyo Metropolitan Matsuzawa Hospital (approval No. 20) after a complete explanation of this study and in accordance with the Declaration of Helsinki.

Upon entry, the UHR individuals were between 15 and 30 years of age. We used the Structured Interview for Prodromal Symptoms (SIPS) as the UHR criteria, which consists of 3 criteria: attenuated psychotic symptoms (APS), brief intermittent psychotic symptoms (BIPS), or genetic risk and deterioration (GRD) (Miller et al., 1999; Kobayashi et al., 2007). APS correspond to individuals who exhibited onset or worsened subthreshold psychotic symptoms within 12 months but not psychotic severity. BIPS correspond to individuals who had psychotic symptoms within 3 months but with a limited duration and frequency such that they were not at all or only slightly influenced by their symptoms and did not meet the psychotic episode criteria according to the DSM-IV criteria (American Psychiatric Association, 1997). GRD corresponds to individuals whose functioning had deteriorated in the previous 12 months as defined by a 30% or more decrease in the GAF score (American Psychiatric Association, 1994) as well as those who also had one or more first-degree relatives diagnosed with psychosis and/or schizotypal personality disorder according to the DSM-IV criteria.

We defined the first episode as follows: age 15–40 years, no history of antipsychotic drug treatments for more than 16 cumulative weeks, and continuous psychotic symptoms within the past 60 months. The exclusion criteria for all 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, low premorbid IQ (below 70), and previous alcohol abuse or addiction. For the HC group, we used the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) to rule out psychiatric disorders and also excluded participants with first-degree relative(s) with psychotic disorders.

The problem of the use of illegal substances (e.g., cannabis) among young people shows that there are still a small number of young individuals who have experienced using such drugs in Japan. Therefore, we adopted previous continuous substance use as an exclusion criterion in this study. Other research in various domains suggests a relationship between schizophrenia and pervasive developmental disorder. Therefore, we also intended to develop biomarkers related to early detection and prediction for psychosis and focused on the pathophysiological differences between these disorders. Although the basis of pervasive developmental disorder comprises a spectrum from normality to disorder and because some cases are hard to diagnose, we also excluded

Table 1
Demographic characteristics of study participants.

	Controls		UHR		FEP		ChSZ		*p* value	*F* value
		SD		SD		SD		SD		
n (male:female)[a]	30 (17:13)		22 (13:9)		27 (18:9)		38 (22:16)		=0.815	
Age (y) [b]	24.3	4.8	21.6	3.7	25.2	7.0	31.3	6.1	<0.001[c]	17.0
Premorbid IQ[b]	107.6	8.6	106.6	10.1	106.5	9.5	103.4	10.6	=0.311	1.20
Letter numbers[b]	16.2	4.8	14.6	6.1	12.7	5.2	14.3	4.1	=0.083	2.28
PANSS Positive[b]	N.A.	N.A.	14.8	3.8	15.3	4.7	14.8	5.2	=0.891	0.116
Negative[b]	N.A.	N.A.	19.3	6.5	19.8	6.1	18.7	6.3	=0.777	0.253
General[b]	N.A.	N.A.	35.8	9.0	33.4	8.7	35.8	7.8	=0.494	0.711
GAF[b]	N.A.	N.A.	44.9	12.2	41.3	12.4	49.1	11.0	=0.034[d]	3.52
Age at onset (y)	N.A.	N.A.	N.A.	N.A.	24.4	6.2	23.5	6.4	=0.906	
DUP (w)	N.A.	N.A.	N.A.	N.A.	28.9	52.4	27.0	41.1	=0.794	
DOM (m)	N.A.	N.A.	N.A.	N.A.	1.8	1.2	94.6	60.2	<0.001[d]	
CP (mg)[b]	N.A.	N.A.	77	179	630	501	667	563	<0.001[e]	12.1
Diazepam (mg)[b]	N.A.	N.A.	3.6	5.3	12.7	10.3	13.5	19.0	=0.027[e]	3.77
Biperiden (mg)[b]	N.A.	N.A.	0.1	0.4	2.4	3.9	3.1	2.2	<0.001[e]	9.43

Significant group differences are shown to the right. [a] Chi-square test, and [b] one-way ANOVA and post hoc Tukey–Welsch tests were used for testing group differences. Otherwise, *t*-tests were used. $p<0.05$ was considered significant. [c] HC, UHR, FEP<ChSZ, [d] FEP<ChSZ, [e] UHR<FEP, ChSZ.
Abbreviations: IQ, intelligence quotient; PANSS, positive and negative symptom scale; GAF, global assessment of functioning; DUP, duration of untreated psychosis; DOM, duration of medication for psychosis; CP, chlorpromazine; pt., participant.

participants who were clearly diagnosed with autistic disorder according to the DSM-IV criteria. Well-practiced psychiatrists (S.K. and Y.T.) took detailed clinical histories from the subjects themselves and their family members, and diagnosed UHR individuals according to the SIPS criteria as well as first-episode psychosis and schizophrenia according to the DSM-IV criteria during measurement (Table 2).

The participants in the HC group were matched by age to the UHR and FEP groups, and by sex to the other 3 groups in this study. The participants in the ChSZ group were matched by premorbid IQ (Matsuoka et al., 2006; Matsuoka and Kim, 2006), age at onset, and DUP to the FEP group to estimate the long-term outcomes of the effectiveness of early detection and intervention (average duration of medication for psychosis [DOM]: 7.9 years).

The participants, except for the ChSZ group, had never been analyzed before. However, 22 out of the 38 patients with ChSZ also participated in our previous studies (Takizawa et al., 2008, 2009).

The participants in the UHR, FEP, and ChSZ groups were assessed for their functioning and symptoms, using the Global Assessment of Functioning (GAF) (American Psychiatric Association, 1994) and the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) on the same day as the NIRS measurements. If they took any antipsychotics, anxiolytics, and/or antiparkinsonian agents, we calculated the chlorpromazine, diazepam, and biperiden equivalent doses, respectively.

2.2. Letter fluency task

We used the 160-s block-designed LFT, which is well adapted to NIRS measurement as an activation task (Takizawa et al., 2008, 2009). Briefly, in the 60-s task period, a participant was instructed to say aloud as many words that started with a phonological syllable given from a computer as possible when he/she heard it. The task period was split into 3 subperiods, and the instructed syllables consisted of 9 syllables (first, /to/, /a/, or /na/; second, /i/, /ki/, or /se/; third, /ta/, /o/, or /ha/) and changed every 20 s so that the participant avoided being silent. In the 30-s pretask and 70-s posttask periods, the participant was instructed to say Japanese vowels (/a/, /i/, /u/, /e/, and /o/) aloud repeatedly to control and remove task-related motion artifacts when he/she heard a start command from the computer. We recorded the total number of correct words the participant generated during the task period as the task performance.

Table 2
Number of diagnoses in UHR individuals according to the SIPS as well as patients with FEP and ChSZ according to the DSM-IV at their measurement points.

Diagnosis	Number
UHR	
BIPS	1
APS	15
GRDS	1
BIPS + APS	1
APS + GRDS	4
FEP	
295.1 Schizophrenia, disorganized type	2
295.2 Schizophrenia, catatonic type	0
295.3 Schizophrenia, paranoid type	15
295.4 Schizophreniform disorder	6
295.7 Schizoaffective disorder	0
295.9 Schizophrenia, undifferentiated type	2
297.1 Delusional disorder	1
298.8 Brief psychotic disorder	1
298.9 Psychotic disorder not otherwise specified	0
ChSZ	
295.1 Schizophrenia, disorganized type	7
295.2 Schizophrenia, catatonic type	2
295.3 Schizophrenia, paranoid type	15
295.6 Schizophrenia, Residual type	4
295.7 Schizoaffective disorder	1
295.9 Schizophrenia, undifferentiated type	9

Abbreviations: BIPS, brief intermittent psychotic symptoms; APS, attenuated psychotic symptoms; GRDS genetic risk and deterioration.

2.3. NIRS instrument

We used a 52-channel NIRS instrument (ETG-4000; Hitachi Medical Co., Tokyo, Japan) for measuring hemoglobin changes. The same instrument was used in our previous studies (Suto et al., 2004; Takizawa et al., 2008, 2009) where the NIRS probe attachments were thermoplastic 3 × 11 shells set with 52 fixed channels (Fig. 1); the lowest probe line was set along the Fp1–Fp2 line defined by the international 10–20 system used in electroencephalography. This probe arrangement can measure hemoglobin changes in the approximate surface regions bilaterally in the dorsolateral prefrontal cortex (DLPFC; Brodmann's area [BA] 9 and 46), ventrolateral prefrontal cortex (VLPFC; BA 44, 45, and 47), fronto-polar (BA 10), and anterior part of the temporal cortex (aTC; BA 21 and 22) (Fig. 1). The 52 measuring areas are labeled from the right-superior (ch1) to the left-inferior (ch52).

Participants only needed to sit on a chair in a relaxed state with her/his eyes open and the cap with thermoplastic attachments of the NIRS probes on her/his head. To minimize motion artifacts, we instructed them to refrain from physical movement such as head motions and strong biting during the measurement.

The theoretical methodology regarding hemoglobin concentration measurement by NIRS instruments is described in detail elsewhere (Takizawa et al., 2008). In brief, the NIRS instrument measures relative changes in [oxy-Hb] and [deoxy-Hb] using 2 wavelengths (695 and 830 nm) of infrared light (indicated as mM) on the basis of the Beer–Lambert law. We could not measure the path length because each participant had a different path length from the scalp to the cerebral cortex; therefore, we recorded the relative values of hemoglobin concentrations indicated by mM·mm.

The distance between pairs of source-detector probes was set at 3.0 cm. We defined each measurement area between pairs of source-detector probes as one "channel," which was enough to measure the points at a depth of 20–30 mm from the scalp, which corresponded to the surface of the cerebral cortex. Because the NIRS signal was occasionally unstable at the start of measurements due to technical issues and/or a participant's tense state, the acquired mean values across the last 10 s of the pretask period and the last 5 s of the posttask period were determined as the pre- and posttask baselines, respectively; a linear fitting was performed on the basis of the data between the 2 baselines. Next, although the time resolution of the NIRS signal was 0.1 s, we set the moving average window at 5 s to remove short-term artifacts.

Regardless of these artifact rejection methods, visible artifact waveforms sometimes remained. Thus, we used a newer version of the same computer program used in our previous studies that rejects a channel when it has a visible artifact waveform. Because we excluded the rejected channels from further analysis, the number of available channels varied among individuals (HC: number of channels, 37–52 [mean, 49.8; SD, 3.0]; UHR: number of channels, 43–52 [mean, 49.7; SD, 2.3]; FEP: number of channels, 43–52 [mean, 50.7; SD, 2.5]; ChSZ: number of channels, 40–52 [mean, 50.2; SD, 3.3]; n.s.).

Finally, we localized the estimated cortical regions at each channel by using a virtual registration method shown in Fig. 1 and at http://brain.job.affrc.go.jp/wordpress/ (Tsuzuki et al., 2007; Shattuck et al., 2008).

2.4. Statistical analysis

First, we tested the difference from the pretask baseline to the task period in the controls using *t*-tests for every channel. Since we performed 52 *t*-tests for each channel, we adopted the false discovery rate (FDR) method to correct multiple comparisons. We set the value specifying the maximum FDR to 0.05 so that there were no more than 5% false positives on average (Singh and Dan, 2006). We then tested the

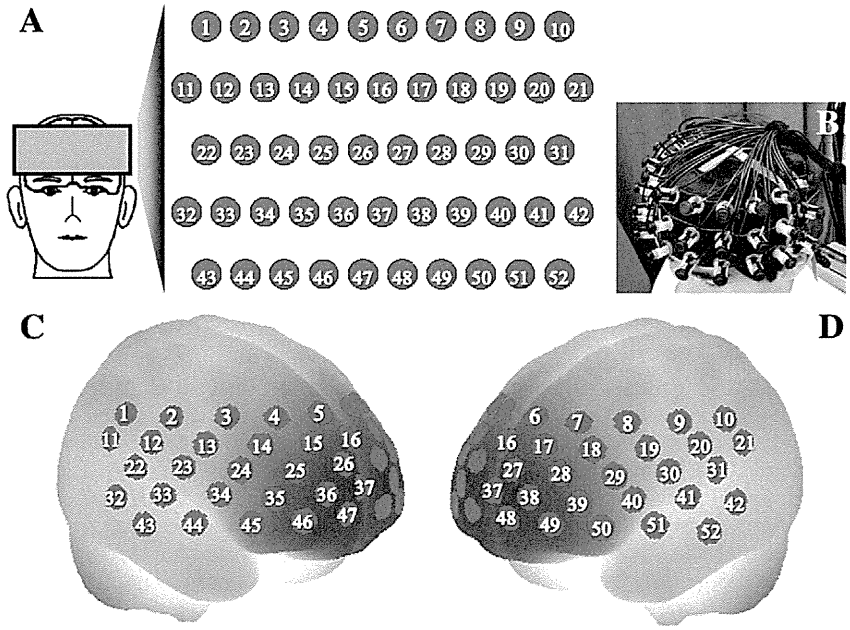

Fig. 1. Probe settings and estimated cortical regions of the 52-channel near-infrared spectroscopy (NIRS). A: 2-D topography with all channel numbers. B: probe settings with 3 × 11 thermoplastic shells in a left-anterior view. C, D: estimated cortical regions using the virtual registration method in right-anterior (C) and left-anterior (D) views. The channel numbers are indicated above the estimated cortical regions.

difference in task performance among the 4 groups by one-way analysis of variance (ANOVA); if the task performances were significantly different among the groups, we analyzed [oxy-Hb] changes using task performances as a covariate. We tested the average [oxy-Hb] changes in the task period among the 4 groups by one-way ANOVA for each channel, adopting the FDR method. Post hoc Tukey–Welsch tests were performed on these significant channels. We also investigated correlations between [oxy-Hb] changes, premorbid IQ, GAF, and PANSS scores, and task performance for each group by Pearson's correlation coefficient on whole channels, adopting the FDR method. All analyses in this study were conducted using SPSS 17.0 J (SPSS Inc., Chicago, IL, USA).

3. Results

Among the UHR, FEP, and ChSZ groups, there were no differences in premorbid IQ, GAF, and PANSS total scores or in PANSS positive, negative, and general subscores (Table 1). Sixteen UHR individuals and 2 patients with FEP were antipsychotics naïve, and 8 UHR individuals and 1 FEP patient were FEP drug naïve at their measurement points. The chlorpromazine, diazepam, and biperiden equivalent doses of the FEP group did not differ from those of the ChSZ group. Letter numbers as task performances were not significantly different among the 4 groups ($F = 2.28$, $p = 0.083$).

3.1. Mean [oxy-Hb] changes during the task period

Time courses of [oxy-Hb] changes are shown in Fig. 2. From the pretask baseline to the task period, the controls showed significantly increased activation in all 52 channels (FDR-corrected $p = 0.001$ to 0.0044). Among all groups, we found significant main effects for [oxy-Hb] changes in 50 channels (except ch2 and 42; $F = 2.76$ to 11.55, FDR-corrected $p = 0.001$ to 0.046). Post hoc Tukey–Welsch tests revealed that the UHR, FEP, and ChSZ groups had significantly smaller activations than the HC group at 18 channels (ch11, 14, 17, 21, 22, 24, 31–33, 37, 40, 41, 43, 45, 48, 49, 51, and 52; Fig. 3, top) that formed a cluster of channels approximately located at the bilateral VLPFC, bilateral fronto-polar, and bilateral aTC regions. On the other hand, the activations in the bilateral DLPFC and right VLPFC regions became smaller with advancing clinical stage (Fig. 3, middle and bottom). Although we adopted the artifact rejection method for each channel, the demographic characteristics were still matched in all channels.

3.2. Correlation between [oxy-Hb] changes and demographic characteristics

In the FEP group, we found significant positive correlations between mean [oxy-Hb] changes during the task period and PANSS positive scores at ch43 (FDR-corrected $p = 0.001$, Pearson's $r = 0.615$), and marginally significant correlations at ch32 ($p = 0.0058$, $r = 0.546$). We also found positive correlations between [oxy-Hb] changes and PANSS negative scores at ch33 and 43 (FDR-corrected $p = 0.001$ to 0.002; $r = 0.606$ and 0.759, respectively), and marginally significant correlations at ch8 ($p = 0.0033$, $r = 0.575$) and ch32 ($p = 0.0037$, $r = 0.570$). Ch32, 33, and 43 formed a cluster of channels that was located approximately at the right temporal cortex region. We also found marginally significant positive correlations between [oxy-Hb] changes and PANSS general scores at ch32 ($p = 0.0012$, $r = 0.621$) and ch43 ($p = 0.0012$, $r = 0.602$).

In our previous study, we found significant positive correlations between [oxy-Hb] changes and GAF scores (Takizawa et al., 2008). In this study, we replicated a similar trend at ch26 ($p = 0.047$, $r = 0.325$) and ch37 ($p = 0.035$, $r = 0.344$) in the ChSZ group.

In the UHR group, we found no significant channel between antipsychotics-naïve and medicated individuals, and no channel between drug-naïve and medicated individuals.

4. Discussion

Our results show that the task-related hemoglobin changes over the prefrontal cortical surface areas and the anterior part of the temporal cortex regions gradually decrease with advancing clinical stages of psychosis (i.e., UHR, FEP, and ChSZ). The activation in the UHR group was lower than that of the controls but not significantly different when compared to the reduced activations in the bilateral VLPFC, bilateral fronto-polar, and bilateral aTC regions in the FEP and ChSZ groups. On the contrary, the activations in the bilateral DLPFC regions decreased with advancing clinical stages of psychosis. Correlational analyses show that the activations in the right temporal cortex region are greater with severe

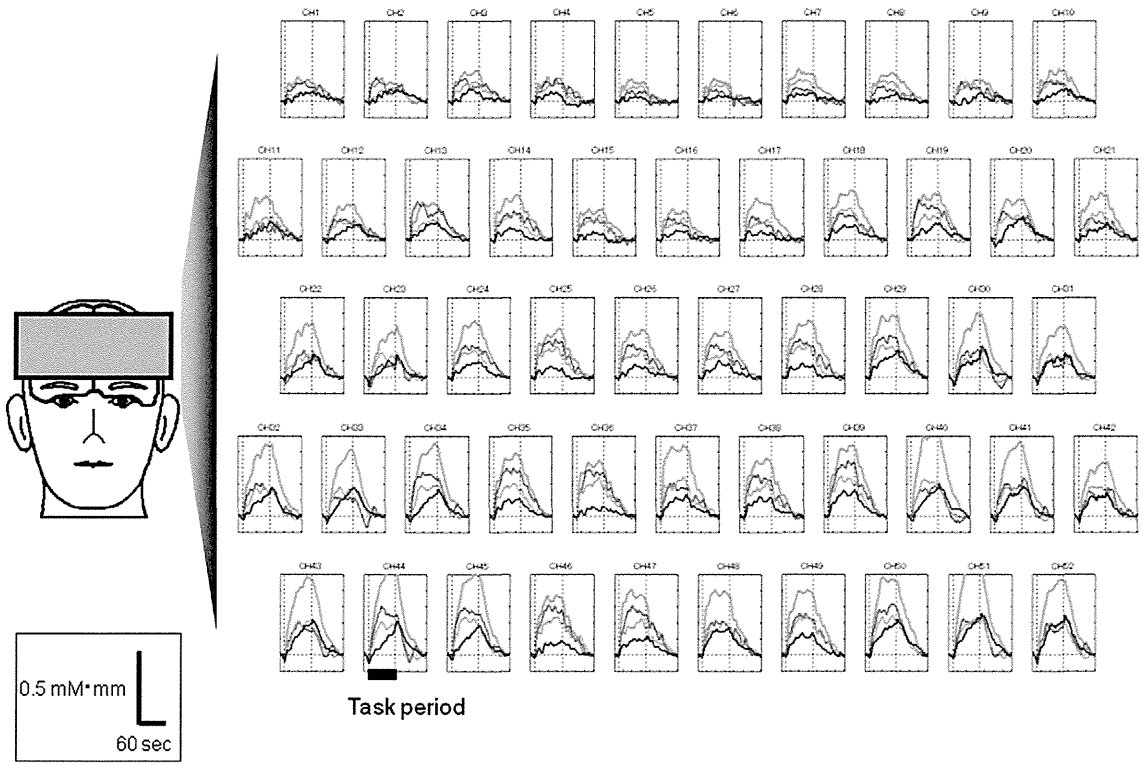

Fig. 2. Time-course [oxy-Hb] changes in the control, UHR, FEP, and ChSZ groups (light green, red, orange, and blue, respectively). The 52 measurement areas are labeled ch1–52 from the right-superior to the left-inferior. The task period is shown between the vertical dash lines (also indicated by a black bar).

negative symptoms in the FEP group. To the best of our knowledge, this is the first study that directly compares differences in hemodynamic activation changes with respect to the 3 clinical stages of psychosis and healthy controls and demonstrates different patterns of impairment according to the progression of clinical stages using multichannel NIRS instruments.

4.1. Different hemodynamic response patterns in the prefrontal cortical subregion

Our results replicate previous results in which controls exhibit a task-related hemoglobin increase over the prefrontal cortical surface areas and in the bilateral aTC regions (Suto et al., 2004; Takizawa et al.,

	Channels
Controls > UHR, FEP, ChSZ	11,14,17,21,22,24, 31-33,37,40,41,43,45, 48,49,51,52
Controls > UHR, ChSZ	7,23
Controls >FEP, ChSZ	26,27,30,44,50
Controls > UHR, FEP, ChSZ FEP > ChSZ	18
Controls > UHR, FEP, ChSZ UHR, FEP > ChSZ	28
Controls > FEP, ChSZ UHR > ChSZ	13,19,29,34,35,38,39
Controls, FEP > ChSZ	8,9
HC, UHR, FEP > ChSZ	25,36,46

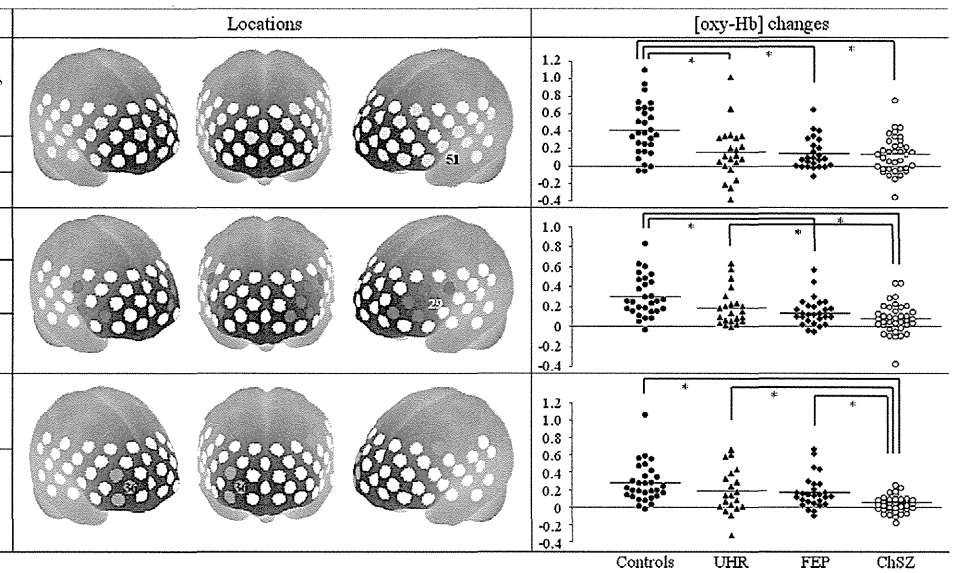

Fig. 3. 3D topographic maps of different hemodynamic response patterns in the prefrontal cortical sub-regions according to the clinical stages of psychosis. Impairment even in the UHR group, gradual impairment, and impairment only in the ChSZ group were illustrated with yellow, red, and green, respectively. Left: The channels showing significant mean [oxy-Hb] changes during the task period by post hoc Tukey–Welsch tests. Center: 3D topographic maps in which clusters of significant channels are divided into 3 different patterns: impairment in the UHR group but unchanged in the ChSZ group (top, yellow), gradual impairment according to progression of clinical stages (middle, red), impairment in the ChSZ stage but statistically unchanged until the FEP stage (bottom, green). Right: Dot plots of the mean [oxy-Hb] changes at typical channels (top, ch51; middle, ch29; bottom, ch36) during the task period. Bars show the averages of the [oxy-Hb] changes and asterisks show significant results between groups by post hoc Tukey–Welsch tests ($p<0.05$).

2008, 2009). A LFT requires retrieval from long-term memory, verbal working memory, executive function, and inhibition of repetitive and inappropriate responses, which are assumed to be major functions of the prefrontal cortex.

Our study shows the different impairment patterns among the clinical stages of psychosis according to the cortical region (Fig. 3). These results were still significant when age was considered a covariate. The hemodynamic changes in the bilateral VLPFC, bilateral fronto-polar, and bilateral aTC regions were significantly smaller in the UHR group than in the controls but not than the FEP and ChSZ groups (Fig. 3, top). Although there are few functional neuroimaging studies that directly compare psychotic groups at 3 or more clinical stages, a functional MRI study during an odd-ball task shows that the UHR group has intermediate BOLD signal changes and lower activation in the inferior frontal gyrus than controls, but higher than those of the FEP and ChSZ groups (Morey et al., 2005). Another functional MRI study using an event-related LFT task also shows intermediate BOLD patterns in the left-inferior frontal gyrus (Broome et al., 2009). However, the results of hypo-/hyperactivation are inconsistent, owing to variable characteristics of the study participants and/or task settings (Keshavan et al., 2008; Minzenberg et al., 2009). A functional MRI and PET combination study using the same event-related LFT task shows that UHR individuals have greater activation in the left-inferior frontal gyrus than controls; furthermore, these activations are positively correlated with striatal F-Dopa uptake (Fusar-Poli et al., 2009). Our results replicate decreased hemodynamic activation patterns in the bilateral VLPFC regions and particularly, a larger cluster of significant channels in the left VLPFC region. The reason why our results show lower activation in the UHR group but similar activations in the FEP and ChSZ groups may be due to differences in modalities and tasks. However, there are few studies that directly compare various clinical stages. More studies are needed to clarify these mechanisms of hypo-/hyperactivation with respect to the characteristics of participants and tasks.

In contrast, the activations in the bilateral DLPFC as well as part of the right VLPFC region decreased with the advancing clinical stages (Fig. 3, middle and bottom). Neuroimaging studies suggest that the DLPFC plays a central role in the working memory system (D'Esposito et al., 1995, 1999) and shows reduced working memory capacity in schizophrenics (Callicott et al., 2003; Manoach, 2003; Jansma et al., 2004). However, the hypo-/hyperactivations in the DLPFC also depend on tasks (Schneider et al., 2007; Keshavan et al., 2008). A functional MRI study using an n-back task shows that UHR individuals have smaller BOLD signal changes in the middle frontal gyrus than controls (Fusar-Poli et al., 2010). Another study that compared 3 clinical stages and controls shows that the BOLD signals in the middle frontal gyrus decrease with advancing clinical stage (Morey et al., 2005). This indicates that our results are in line with those of previous UHR studies.

Our results of the activation pattern in the fronto-polar region are similar to those in the VLPFC regions. There are few functional neuroimaging studies regarding the relationship between this region and psychosis; however, it is critical to consider the relationship between the functions in this region and the progression and prognosis of psychosis. Previous studies suggest that the fronto-polar region plays a crucial role in high-level coordination with other brain functions and that these functions are required in social interactions such as self-perception, person perception, and mentalizing in humans (Frith and Frith, 1999; Kampe et al., 2001; Northoff et al., 2006; Badre and D'Esposito, 2009; Suda et al., 2010). Impairment in this region may directly reflect social dysfunction in daily life. Our previous study found a positive correlation between activation in the fronto-polar region and GAF scores in schizophrenics (Takizawa et al., 2008). Our results also show a trend-level correlation between activation in this region and GAF scores in the ChSZ group, even in those matched for age-at-onset and DUP. The reason why these correlations are absent in the UHR and FEP groups may be because those participants became ill recently and have discrepancies between the one-time assessment of GAF scores and potential capacities regarding social interaction. This effect regarding the timing of clinical assessment is assumed to reflect similar PANSS scores among the groups, because the patients in the FEP and ChSZ groups were measured in their relatively stable conditions after onset although the UHR individuals were measured when they suffered from sub-threshold psychotic symptoms and functional declines. Activation in the fronto-polar region may not reflect their present states and may rather predict their social outcomes in future prognoses.

4.2. Correlation between [oxy-Hb] changes and symptoms in the FEP group

Our results show unexpected findings in that the patients with FEP exhibited significant positive correlations between [oxy-Hb] change in the right aTC region, and PANSS positive and negative scores as well as marginally significant PANSS general scores; this indicates that the activation is greater when the symptoms are worse.

One of the major functions of the aTC, specifically the superior temporal gyrus, is assumed to be acoustic perception and comprehension (Szycik et al., 2009; Warren et al., 2009), especially for integrating meaningful verbal information in the dominant region and processing nonverbal acoustic information in the nondominant region (Kriegstein and Giraud, 2004; Warren et al., 2009). In a functional connectivity study, activities integrated bilaterally in these regions may be associated with speech perception and comprehension, and play a major role in social cognition (Warren et al., 2009). Patients with schizophrenia have difficulty in acoustic perception and communication related to social interactive functions such as the mirror neuron system, A functional MRI study shows that patients with schizophrenia have less activation in the right superior temporal gyrus, pars opercularis, and middle frontal sulcus during incongruent audiovisual speech stimuli (Szycik et al., 2009).

In this study, we found that the patients with FEP exhibited smaller activation in the right aTC region than controls; in group comparison, they showed larger activation when they had severe symptoms. The reason for this unexpected finding may be a compensatory response or overactivation of brain dysfunction related to the onset of psychosis. Although the patients in the FEP group were in their relatively stable conditions at measurement, they were still in the acute phase (DOM = 1.8 month), which might have possibly altered their PANSS scores for a short duration. Although we have to investigate the changes of this correlation coefficient longitudinally, it is possible that this finding can be applied to determine therapeutic efficiency in clinical settings. Further investigations are required to determine why these correlations are observed only in the FEP stage and are obscured in the chronic phase.

4.3. Limitations

Our results have some methodological limitations. First, as there were small subject numbers especially in the UHR group, we cannot fully detect differences among groups; studies with larger samples and more observation details are needed. Second, because this study had a cross-sectional design, we could not examine the participants' longitudinal prognoses, especially regarding the prediction for psychosis. We are currently conducting 3-month repetitive measurements for UHR and FEP individuals in a longitudinal fashion, exploiting the easy setting and noninvasive characteristics of the NIRS instruments. Furthermore, as we carry out long-term clinical follow-up and NIRS measurement on these individuals every 3 months, we will be able to demonstrate the predictive biomarkers related to the onset of psychosis as well as symptomatic and functional outcomes. Finally, as this study was naturalistic and therefore not controlled with respect to drug usage, we cannot rule out the effects of drugs. However, we found no differences in the [oxy-Hb] changes with respect to antipsychotics or

other drug usage. In clinical settings, although it is hard to control for drug usage, we aim to examine the responses and effects of medication.

5. Conclusion

In conclusion, we found that hemodynamic changes decrease with advancing clinical stages of psychosis (i.e., at-risk mental state, first-episode psychosis, and chronic stage of schizophrenia) over the prefrontal cortical surface areas and in the bilateral anterior part of the temporal cortex regions using multichannel NIRS instruments. Although this study was cross-sectional, future studies are needed to carry out longitudinal clinical follow-up and NIRS measurements for UHR and FEP individuals to develop candidate biomarkers that can detect the clinical stages of psychosis and predict the onset of psychosis.

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Contributions

SK contributed to project management and wrote the manuscript. RT and YN conducted NIRS measurements and data analysis. Y. Takano contributed to project management, and clinical assessment and management. YN, Y. Takayanagi, HH, and YO contributed to NIRS measurements and assessment of clinical information in the Tokyo Metropolitan Matsuzawa Hospital. MK contributed to NIRS measurements. TA, MF, and KK coordinated the entire research design and took responsibility for the management of this study. All authors contributed to the critical revision and final approval of the manuscript.

Conflict of interest

The principal investigators of each site (Masato Fukuda of Gunma University, Yuji Okazaki of Tokyo Metropolitan Matsuzawa Hospital, and Kiyoto Kasai of The University of Tokyo) have potential conflicts of interest. Each site and the Hitachi Group (Advanced Research Laboratory, Hitachi Ltd. and The Research and Developmental Center, Hitachi Medical Corporation) have had official contracts for a collaborative study on the clinical application of near-infrared spectroscopy in psychiatric disorders. For this study, the Hitachi Group provided project grants (MF: JPY 1,000,000 per year since April 1, 2002; YO: JPY 500,000 per year since April 1, 2003; KK: JPY 300,000 per year since July 31, 2003) and material support (temporary rental of a near-infrared spectroscopy [Optical Topography] system, ETG-4000) for each site. The material support for KK of The University of Tokyo ended in 2009. The other authors have no relevant conflicts of interest.

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