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Reduced frontopolar activation during verbal fluency task in schizophrenia: A multi-channel near-infrared spectroscopy study

Ryu Takizawa [a,*], Kiyoto Kasai [a], Yuki Kawakubo [a], Kohei Marumo [a], Shingo Kawasaki [b], Hidenori Yamasue [a], Masato Fukuda [c]

[a] Department of Neuropsychiatry, Graduate school of Medicine, The University of Tokyo, Tokyo, Japan
[b] Hitachi Medical Corporation, Application Development Office, Optical Topography Group, Tokyo, Japan
[c] Department of Psychiatry and Human Behavior, Graduate School of Medicine, Gunma University, Maebashi, Japan

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Abstract

Functional neuroimaging studies to date have shown prefrontal dysfunction during executive tasks in schizophrenia. However, relationships between hemodynamic response in prefrontal sub-regions and clinical characteristics have been unclear. The objective of this study is to evaluate prefrontal hemodynamic response related to an executive task in schizophrenia and to assess the relationship between activation in the prefrontal sub-regions and clinical status. Fifty-five subjects with schizophrenia and age- and gender-matched 70 healthy subjects were recruited for this case-control study in a medical school affiliated hospital in the Tokyo metropolitan area, Japan. We measured hemoglobin concentration changes in the prefrontal (dorsolateral, ventrolateral, and frontopolar regions) and superior temporal cortical surface area during verbal fluency test using 52-channel near-infrared spectroscopy, which enables real-time monitoring of cerebral blood volumes in the cortical surface area under a more restraint-free environment than positron emission tomography or functional magnetic resonance imaging. The two groups showed distinct spatiotemporal pattern of oxy-hemoglobin concentration change during verbal fluency test. Schizophrenia patients were associated with slower and reduced increase in prefrontal activation than healthy controls. In particular, reduced activations of the frontopolar region, rather than lateral prefrontal or superior temporal regions, showed significant positive correlations with lower global assessment of functioning scores in the patient group, although task performance was not significantly associated with the scores. These results suggest that reduced frontopolar cortical activation is associated with functional impairment in patients with schizophrenia and that near-infrared spectroscopy may be an efficient clinical tool for monitoring these characteristics.

Keywords: Schizophrenia; Near-infrared spectroscopy (NIRS); Frontopolar prefrontal cortex; Verbal fluency test; Global assessment of functioning (GAF)

1. Introduction

Neuroimaging studies have identified schizophrenia as being associated with dysfunction of the prefrontal cortex (Callicot et al., 2000; Carter et al., 1998; Curtis et al., 1998), an area involved in almost all high-level cognitive functions such as working memory, memory

* Corresponding author. Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, 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).

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retrieval, executive function, and language (Cabeza and Nyberg, 2000). Moreover, recent advances in neuroscience have sought to clarify functional segregation in the prefrontal cortical surface areas such as dorsolateral, ventrolateral, and frontopolar (anterior frontal) regions (Daw et al., 2006; Fletcher and Henson, 2001; Fox et al., 2006). The ventrolateral and dorsolateral sub-regions are involved in the updating/maintenance of information and to the selection/manipulation/monitoring of that information, respectively (Fletcher and Henson, 2001). In contrast, frontopolar cortex (BA 10), which has been suggested to have enlarged and become specialized during hominid evolution (Semendeferi et al., 2001), provides higher level of control to coordinate ventrolateral and dorsolateral functions in order to maximize task performance (Koechlin et al., 1999; Fletcher and Henson, 2001; Braver and Bongiolatti, 2002), which has led to the idea that frontopolar region is likely to have a vital role in achieving high-order executive control in everyday life (Burgess et al., 2000). However, it remains unclear which specific sub-regions of the prefrontal cortex is most directly associated with clinical characteristics in schizophrenia.

An independent line of work has suggested that cognitive deficits as indexed by neuropsychological assessments are more tightly coupled with social functioning in patients with schizophrenia than positive or negative symptoms (Green, 1996; Green et al., 2000; Green et al., 2004; Flashman and Green, 2004). Whereas progress has been made for an association between psychosocial impairment and electrophysiological measures such as P300, N200b, and mismatch negativity event-related potentials (Ikebuchi et al., 1996; Iwanami et al., 1999; Kawakubo and Kasai, 2006; Light and Braff, 2005; Ohno et al., 2000) and brain morphological measures (Ho et al., 2003; Milev et al., 2003; Prasad et al., 2005; Staal et al., 2001; Wassink et al., 1999), the relationships between functional hemodynamic response in the sub-regions of the prefrontal cortex and clinical characteristics in schizophrenia has been unclear. These research questions may be an important step towards developing an objective monitoring tool and ultimately an effective intervention strategy for cognitive and social dysfunction in schizophrenia.

Multi-channel near-infrared spectroscopy (NIRS), a recently developed functional neuroimaging technology, enables the non-invasive detection of spatiotemporal characteristics of brain function (Strangman et al., 2002a, 2003; Boas et al., 2004; Huppert et al., 2006). NIRS has enabled non-invasive and bedside measurement of the concentrations of oxy-hemoglobin ([oxy-Hb]) and deoxy-hemoglobin ([deoxy-Hb]), which are assumed to reflect the regional cerebral blood volume (rCBV). While functional brain imaging methodologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have an excellent spatial resolution, they are limited in that they require large apparatuses which prevents their use in a bedside setting for diagnostic and treatment purposes. In contrast, NIRS is a neuroimaging modality that, for the following reasons is especially suitable for psychiatric patients (Matsuo et al., 2003a). First, because NIRS is relatively insensitive to motion artifact, it can be applied to experiments that might cause some motion of the subjects such as vocalization. Second, the subject can be examined in a natural sitting position, without any surrounding distraction. Third, the cost is much lower than other neuroimaging modalities and the set-up is very easy. Fourth, the high temporal resolution of NIRS is useful in characterizing the time course of prefrontal activity of psychiatric disorders (Kameyama et al., 2006; Suto et al., 2004). Accordingly, NIRS has been used to assess brain functions in many psychiatric disorders, including schizophrenia, bipolar disorder, depression, dementia, post traumatic stress disorder, and pervasive developmental disorders (Fallgatter et al., 1997; Hock et al., 1997; Kameyama et al., 2006; Kubota et al., 2005; Kuwabara et al., 2006; Matsuo et al., 2003a, b, 2004; Shinba et al., 2004; Suto et al., 2004).

A previous study (Suto et al., 2004) showed reduced [oxy-Hb] changes in the prefrontal cortex during verbal fluency task in patients with schizophrenia using a NIRS machine with insufficient coverage of important sub-regions of the prefrontal cortex such as ventrolateral portions. The purpose of the present study was to use an NIRS machine with a wide coverage of the prefrontal cortex in order to investigate more precisely the relationship between activity in the prefrontal sub-regions and the clinical characteristics in a larger group of patients with schizophrenia.

2. Materials and methods

2.1. Subjects

Fifty-five patients with schizophrenia and 70 age- and gender-matched healthy subjects participated in the study (Table 1). All the participants were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native Japanese speakers.

The patients were recruited among outpatients and inpatients at the University of Tokyo Hospital. Diagnosis of schizophrenia was made through the Structured Clinical Interview for DSM-IV Axis I Disorders (First

Table 1
Clinical characteristics of the study groups

	Patients with schizophrenia (N=55)		Healthy subjects (N=70)		Group difference P value
	Mean	SD	Mean	SD	
Age, year	40.1	11.1	37.4	13.6	.22
Gender, women/men	26/29		34/36		.89[a]
Handedness	92.4	17.3	92.9	16.3	.85
Education, year	14.7	2.5	15.6	2.0	.022
Self socio-economic status (SES)	3.4	1.1	2.0	.6	<.001
Parental SES	2.5	.7	2.3	.7	.18
Estimated premorbid IQ	102.3	12.2	108.3	9.8	.006
Number of words generated	14.3	4.6	17.3	4.4	<.001
Age at onset, years	26.4	8.7	NA		
Duration of illness, years	13.8	10	NA		
PANSS					
Positive	16.7	5.6	NA		
Negative	21.6	6.4	NA		
General psychopathology	38.2	7.9	NA		
Global Assessment of Functioning (GAF)	47.2	12.9	NA		
Medication					
Chlorpromazine equivalent dose, mg/day	778	655	NA		
Diazepam equivalent dose, mg/day	13.4	18.5	NA		
Biperiden equivalent dose, mg/day	3.2	2.3	NA		

Abbreviations: IQ, Intelligence Quotient; PANSS, Positive and Negative Symptom Scale; NA, not applicable.
[a] Chi-square test was used for testing group difference. Otherwise, t-test was used.

et al., 1997) by an experienced psychiatrist (K.K.). For screening of healthy subjects, SCID non-patient edition (SCID-NP) was used. On the same day as the near-infrared spectroscopy (NIRS) experiment, psychiatric symptoms and the level of social functioning were evaluated by one psychiatrist (K.K.) using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Global Assessment of Functioning scores (GAF) (American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data. At the time of the study, the patients with schizophrenia were on medication with antipsychotics and/or anxiolytics and/or antiparkinsonian agents. Socioeconomic status (SES) and parental SES were assessed using the Hollingshead scale (Hollingshead, 1965). Premorbid IQs were estimated using Japanese version of the National Adult Reading Test (Matsuoka et al., 2006) (Table 1). The reliability of the GAF as an assessment of social functioning was confirmed based on the high correlation between GAF scores and total scores on the Japanese version of Life Skills Profile (N=55, r=.61, P<.001) (Parker et al., 1991; Japanese version, Hasegawa et al., 1997).

The exclusion criteria for both 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, and alcohol/substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease in themselves or a family history of axis I disorder in their first-degree relatives. The ethical committee of the Hospital of Tokyo University approved this study. All subjects gave written informed consent according to the Declaration of Helsinki after a complete explanation of the study.

2.2. Activation task

[Hb] changes were measured during a cognitive activation task. Each participant sat on a comfortable chair with their eyes open throughout the measurements. The subjects were instructed to minimize movement such as head movements, strong biting and eye blinking during the NIRS measurements, for they can produce artifacts or changes in cerebral perfusion unrelated to the task.

The cognitive activation task included a 30-s pre-task baseline, a 60-s verbal fluency task (letter version), and a 70-s post-task baseline. The verbal fluency test was chosen, because it has been often used for cognitive activation in NIRS studies, and previous reports showed measurable prefrontal activation during the letter fluency task in healthy subjects (Herrmann et al., 2003, 2006; Kameyama et al., 2004). This procedure was similar to that of Suto et al. (2004), Ito et al. (2005) and Kameyama

et al. (2006) except for the use of a 70-s post-task baseline instead of their 60 s, to enable a more complete return of [Hb] change to the baseline in the post-task period.

For the pre- and post-task baseline periods, the subjects were instructed to repeat Japanese vowels (/a/, /i/, /u/, /e/ and /o/) aloud. This was intended to correct the data during the fluency task for activation due to vocalization.

During the verbal fluency task period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible, which is commonly used in Japanese letter version of the verbal fluency task since Japanese words inevitably begin with a vowel or consonant-vowel syllable. The three initial syllables (first; /to/, /a/, or /na/, second; /i/, /ki/, or /se/, third; /ta/, /o/, or /ha/) were presented in the order which was counterbalanced among the subjects and changed every 20 s during the 60-second task to reduce the time during which the subjects remained silent. The subjects were instructed by an auditory cue at the start and end of the task and when the syllable was changed. Because the number of words generated was not significantly different among the three initial syllables (one-way repeated measures ANOVA; $F[2, 123]=1.28$, $P=.28$, n.s.), the total of correct words generated during verbal fluency tasks was defined as a measure of task performance (Table 1).

2.3. NIRS measurement

The 52-multi-channel NIRS machine (ETG-4000, Hitachi Medical Co.) measures relative changes of [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). The [total-Hb] was calculated as the sum of [oxy-Hb] and [deoxy-Hb]. In this system, these [Hb] values include differential pathlength factor (DPF). The distance between pairs of source-detector probes was set at 3.0 cm and we defined each measuring area between pairs of source-

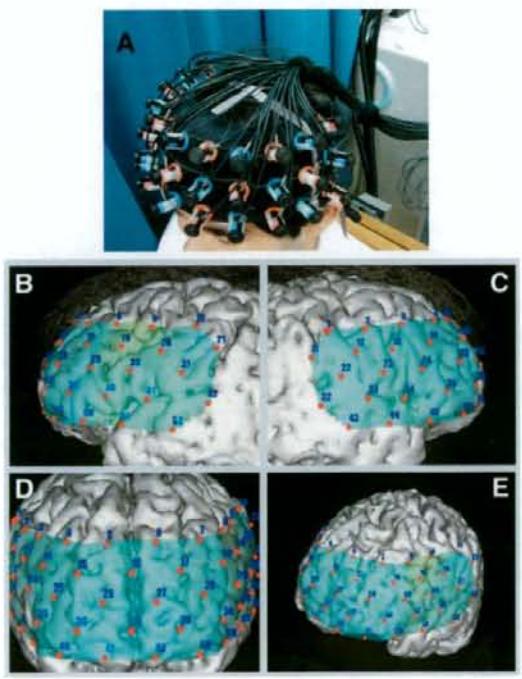

Fig. 1. The probe setting and measurement points of 52-channel near-infrared spectroscopy (NIRS). Panel A: the probes with thermoplastic 3×11 shells were placed over a subject's bilateral frontal regions. Panels B–E: the 52 measuring positions of the NIRS machine are superimposed on 3D-reconstructed cerebral cortical surface from magnetic resonance imaging of a representative subject. The channel numbers are indicated above the measuring points.

detector probes as 'channel'. It is supposed that the machine, in which the source-detector spacing is 3.0 cm, measures points at 2–3 cm depth from the scalp, that is, the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003a,b; Toronov et al., 2001). The probes of the NIRS machine were fixed with thermoplastic 3×11 shells, with the lowest probes positioned along the Fp1-Fp2 line according to the international 10–20 system used in electroencephalography. The time needed for this fixation is usually less than 5 min, which is less-demanding for the subjects. The 52 measuring areas are labeled ch1-ch52 from the right-posterior to the left-anterior. This arrangement of the probes can measure [Hb] from bilateral prefrontal (approximately dorsolateral [Brodmann's area (BA) 9, 46], ventrolateral [BA 44, 45], and frontopolar [BA 10]) and superior temporal cortical surface regions (Fig. 1, panel A). The correspondence of the probe positions and the measuring areas on the cerebral cortex was confirmed by superimposing the measuring positions on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex of a representative subject (Fig. 1, panels B–E).

The time resolution of the NIRS machine was set at .1 s. [Hb] changes were analyzed using the first-order correction to exclude task-unrelated changes during the verbal fluency task. The pre-task baseline was determined as the mean across the last 10 s of the pre-task period and the post-task baseline was determined as the mean across the last 5 s of the post-task period, and a linear fitting was performed based on the data between the two baselines. Moving average methods were applied to remove short-term motion artifacts in the analyzed data (moving average window: 5 s). Grand mean waveforms averaged across subjects were created separately for type of [Hb] and for each group. The moving average methods cannot correct all the artifacts and the most researchers qualitatively judge and remove the data with significant

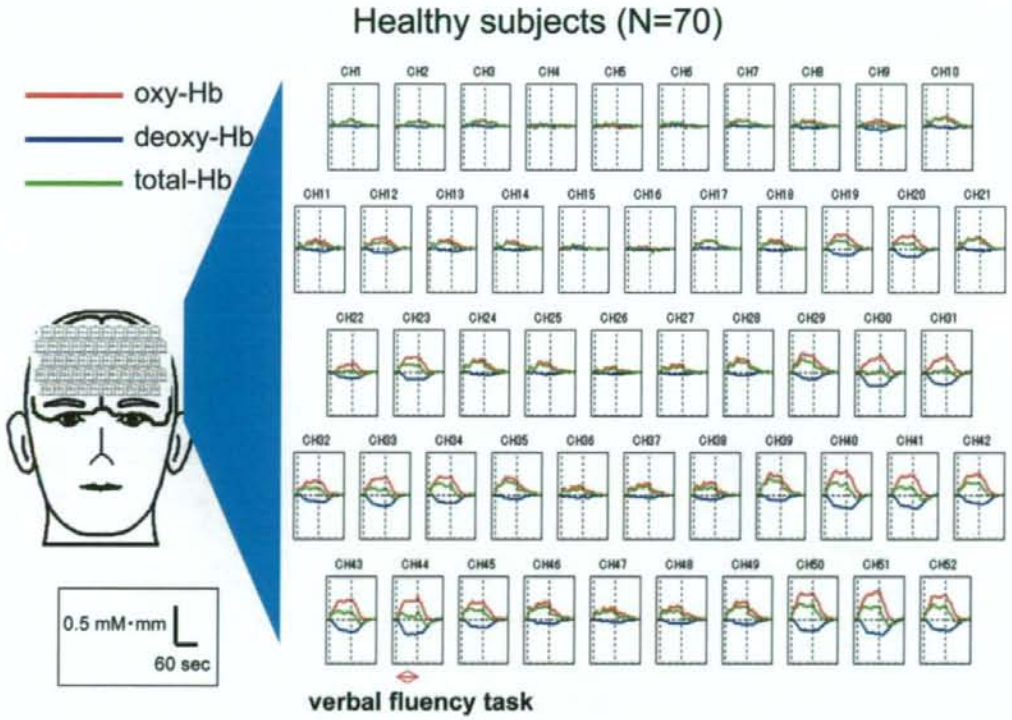

Fig. 2. Grand average waveforms in healthy subjects (N=70). Oxy-, deoxy-, and total-hemoglobin concentration changes during cognitive activation are presented as grand average waveforms in 52 channels in red, blue, and green lines, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

artifacts; however, it remains subjective (Sato et al., 2006). Thus, we developed an algorithm to quantitatively evaluate the artifacts which enables a fully automatic rejection of data with artifacts (see Supplementary material I for details) separately for each channel; i.e., the number of averaged subjects varied across channels (schizophrenia: $N=30$–53 [mean, 43.8; SD, 5.4]; healthy subjects: $N=34$–67 [mean, 58.1; SD, 6.7]; percentage: schizophrenia, 80.7%; healthy subjects, 84.4%, n.s.).

2.4. Statistical analysis

For data analysis using parametric statistical tests, obtained [Hb] data of each channel were averaged across the two time segments (pre-task baseline and task period). We focused on [oxy-Hb] here, since [oxy-Hb] change 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), although the analysis of [deoxy-Hb] was also shown (see Supplementary material II for details). First, at each channel, the mean [Hb] for the pre-task baseline period and that for the task period were compared using Student's paired t-test in order to confirm the statistically significant increase associated with the verbal fluency task. Since we performed 52 paired t-tests, the correction for multiple comparisons was made using false discovery rate (FDR) (two-tailed; we set the value of q specifying the maximum FDR to .05, so that there are no more than 5% false positives on average (Singh and Dan, 2006)). Next, the mean [Hb] changes during the 60-s task period were compared between the two groups for each channel by Student's t-test (two-tailed was used since task-load-dependent hypo- or hyperperfusion of prefrontal cortex in schizophrenia was found in previous literature; FDR correction for multiple comparisons [52 channels] was applied). As a confirmatory analysis, we performed the same group comparison of the performance-matched (50 healthy controls: mean, 15.8 [SD=3.5]; 50 schizophrenia patients: mean, 15.0 [SD=4.1]; $t[2,98]=1.02$, $P=.31$, n.s.) and premorbid

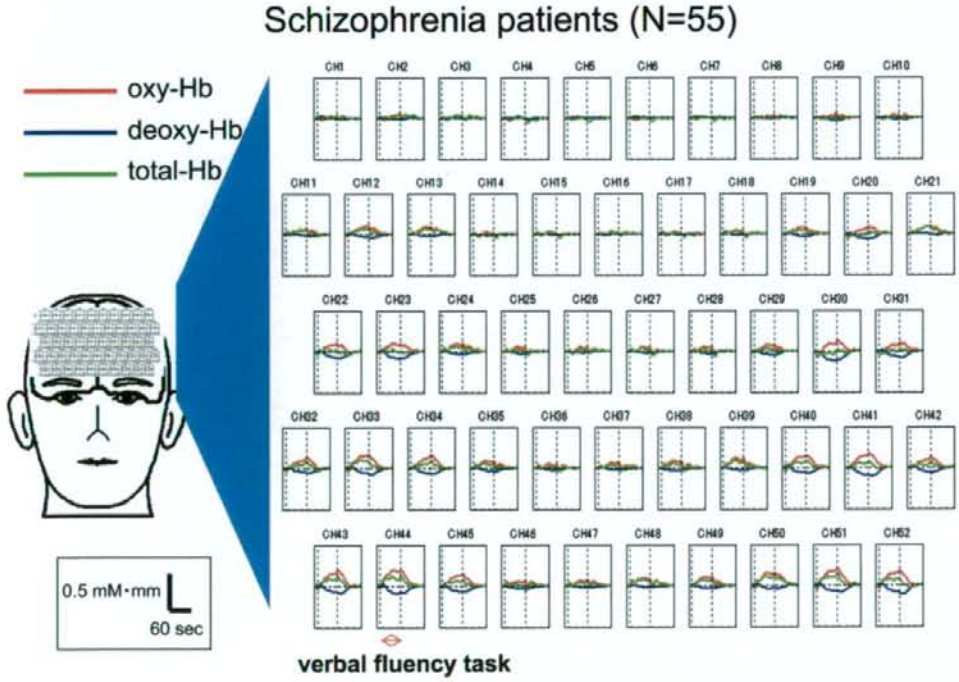

Fig. 3. Grand average waveforms in schizophrenia patients ($N=55$). Oxy-, deoxy-, and total-hemoglobin concentration changes during cognitive activation are presented as grand average waveforms in 52 channels in red, blue, and green lines, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

IQ-matched (48 healthy controls: mean, 106.8 [SD = 9.0]; 48 schizophrenia patients: mean, 104.9 [SD = 10.1]; $t[2,94] = .96$, $P = .34$, n.s.) samples. Third, for analysis in time course of [Hb] change, the slope of the first 5-s during the task period were compared between the two groups for each channel by Student's paired t-test (two-tailed; FDR correction for multiple comparisons [52 channels] was applied).

For the schizophrenia group, Pearson's correlation coefficients were calculated for a relationship between the mean [Hb] changes during the task period and the GAF and PANSS scores for each channel. Degrees of freedom varied across the channels due to the artifact rejection procedure explained above. Since we sought to explore which regions of the brain showed more association with clinical assessment, we did not use the multiple correction; rather, we performed multiple correlational analyses for each channel and evaluated the graduation of the r values that reached a significance level of $P < .05$ over the frontotemporal regions (Fig. 5).

Additionally, we performed correlational analysis of [Hb] and age, duration of illness, dose of medication in the schizophrenia group. Statistical analysis was performed using SPSS 10.1.3J software (Tokyo, Japan).

3. Results

3.1. Test for significance in [Hb] change during activation period relative to baseline

The grand averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] during cognitive activations in healthy controls and schizophrenia patients were shown in Figs. 2 and 3.

A significant increase in [oxy-Hb] changes occurred during the task period relative to the pre-task baseline at 43 channels (ch7-14, ch17-25, ch27-52; FDR-corrected P: .001 to .041) in healthy controls and at 23 channels (ch12-13, ch19, ch24, ch29, ch32-35, ch37-45, ch48-52;

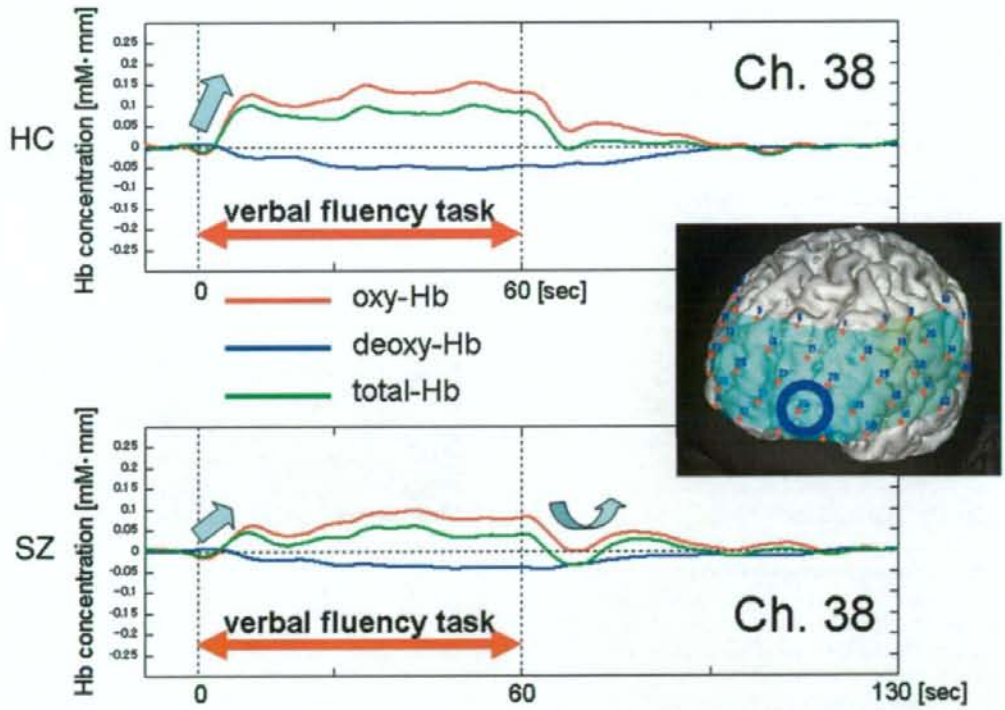

Fig. 4. The differential time course of [Hb] changes in healthy subjects and schizophrenia patients. The differential time course of [Hb] changes between healthy controls (HC; $N = 70$) and schizophrenia patients (SZ; $N = 55$) were indicated in a representative channel (channel 38; left frontopolar region).

FDR-corrected P: .001 to .022) in schizophrenia patients.

3.2. Group comparison

Schizophrenia patients were associated with significantly lower [oxy-Hb] increase than healthy subjects at 20 channels (ch 17-18, ch24-25, ch28-29, ch 35-40, ch42, ch46-52; FDR-corrected P: .001 to .019). The statistical conclusion did not significantly change when the task-performance-matched sample (significance found at 37 channels [ch1, ch3, ch7-8, ch10, ch14, ch17-21, ch24-25, ch27-32, ch34-43, ch45-52; FDR-corrected P: .001 to .036) or the premorbid IQ-matched sample [significant found at 33 channels (ch7-10, ch14, ch17-21, ch24-25, ch28-29, ch31-32, ch34-43, ch45-47, ch49-52; FDR-corrected P: .001 to .031) were compared.

3.3. Time course of [oxy-Hb] change

The [oxy-Hb] slope of the first 5-s in the task period was significantly steeper in healthy subjects than those in schizophrenia patients at 33 channels (ch1, ch3, ch5, ch10, ch12-13, ch17-18, ch20-21, ch23-25, ch28-32, ch34-35, ch38-47, ch49-52; FDR-corrected P: .001 to .031). Fig. 4 indicates the differential time course between healthy subjects and schizophrenia patients in a representative channel (ch38; left frontopolar region). In healthy subjects, the [oxy-Hb] rapidly increased at the beginning of the verbal fluency task, remained at the activated level during the task and gradually decreased after the end of the task. In contrast, the [oxy-Hb] in schizophrenia patients showed more gradual and lower increase during the task period, and began to decrease immediately after the end of the task, then followed by an inefficient re-increase during the post-task period. These differential patterns were similar to the findings reported by Suto et al. (2004) using a similar protocol.

3.4. Correlational analysis

In schizophrenia patients, the mean [oxy-Hb] changes showed a significantly positive correlation with GAF scores in 10 channels (ch13: r=.34, P=.04; ch16: r=.29, P=.05; ch24: r=.29, P=.04; ch25: r=.40, P=.004; ch26: r=.32, P=.02; ch27: r=.30, P=.04; ch36: r=.38, P=.007; ch37: r=.29, P=.05; ch38: r=.38, P=.007; ch47: r=.32, P=.04), with the highest correlations located approximately in the frontopolar (BA 10) and right dorsolateral (BA 9, 46) regions (Fig. 5), although task performance during verbal fluency test was not significantly correlated with GAF scores.

The mean [oxy-Hb] changes during the task period were not significantly correlated with premorbid IQ or task performance for any channels in either group. The mean [oxy-Hb] changes also showed no significant correlation with clinical variables including duration of illness or dose of medication in the schizophrenia group, except for a significant correlation with age at channel 21 (r=−.35, P=.02). Correlations with PANSS scores were found in a few channels: positive (ch23: r=.37, P=.03; ch33: r=.38, P=.01; ch38: r=.33, P=.02; ch49: r=.31, P=.03); negative (none); general psychopathology (ch12: r=−.32, P=.04; ch25; r=−.36, P=.01; ch27: r=−.32, P=.03; ch36: r=−.35, P=.01; ch47: r=−.32, P=.03), which did not converge on specific sub-regions or in consistent directions.

3.5. Comparison between high- and low-social functioning group in schizophrenia

To confirm the relationship between prefrontal cortical activation and social functioning, we divided patients with schizophrenia into high- and low-social functioning groups by the GAF median value of 52. Student's t-test was used to compare [Oxy-Hb] change between 28 high social functioning group (14 male and 14 female) and 27 low-social functioning group (15 males and 12 females). Potential confounding factors such as age, gender, task performance and premorbid IQ were matched between the two condition groups (not

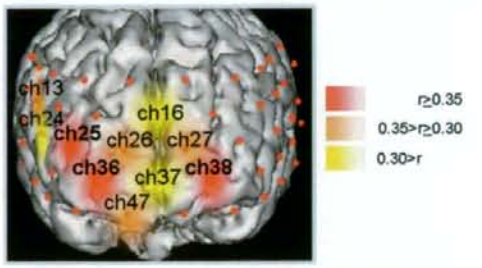

Fig. 5. The cortical distribution of a significant correlation between oxy-hemoglobin changes and global assessment of functioning (GAF) scores. The channels with a significant correlation (Pearson's correlation; P<.05) between the mean [oxy-Hb] changes and GAF scores were indicated with colored area. To illustrate the graduation of the correlation coefficients over the prefrontal cortical surface area, channels with $r \geq .35$ were colored in red, $.35 > r \geq .30$ in orange, and r<.30 in yellow. These areas approximately correspond to frontopolar region (BA 10) and right dorsolateral region (BA 9 and 46). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

described). We found a significant difference in the [oxy-Hb] change between the two groups in the channels located in frontopolar and right dorsolateral prefrontal regions (A significant difference at 5 channels; ch13 (right DLPFC), $P=.018$; ch25 (right DLPFC), $P=.037$; ch26 (right FPPFC), $P=.048$; ch38 (left FPPFC), $P=.029$; ch39 (left FPPFC), $P=.050$).

4. Discussion

Using a 52-channel NIRS with a wide coverage over the prefrontal cortical surface area, it was shown that [oxy-Hb] change during verbal fluency test was significantly slower and smaller in schizophrenia patients as compared with age- and gender-matched healthy subjects, which was not explained by difference in task performance or premorbid IQ. Furthermore, this smaller [oxy-Hb] change following cognitive activation was significantly associated with severer functional impairment in the schizophrenia patients, although the relationship between GAF score and verbal fluency task performance was not significant. And, the regions that showed significant association with the global assessment of functioning were relatively localized in frontopolar regions (BA 10). These results suggest that reduced frontopolar cortical activation associated with executive tasks may be associated with functional impairment in schizophrenia and that NIRS may offer promise as a non-invasive clinical method for evaluating these differential patterns in schizophrenia patients.

4.1. Prefrontal sub-regions

The present study has segregated specific regions in the prefrontal cortex associated with functional impairment in patients with schizophrenia. Petrides' model proposed that ventrolateral prefrontal regions (BA 44/45) are involved in simple short-term operation, whereas middorsal regions perform high-level executive or working memory operations, such as monitoring, reasoning and planning (Petrides, 1994; 1995; Owen, 1997). Fletcher and Henson (2001) attributed ventrolateral and dorsolateral activations to the updating/maintenance of information and to the selection/manipulation/monitoring of that information, respectively. In contrast, recent studies have shed light upon an important role of frontopolar regions (also known as anterior prefrontal cortex) (BA 10), which has been relatively less recognized in functional neuroimaging studies, in higher-order integrative prefrontal function (Ramnani and Owen, 2004). Interestingly, area 10 has been suggested to have enlarged and become specialized during hominid evolution by comparative studies of humans and apes (Semendeferi et al., 2001). Frontopolar regions might provide higher level of control to coordinate ventrolateral and dorsolateral functions in order to maximize task performance, or to achieve these goals (Koechlin et al., 1999; Fletcher and Henson, 2001; Braver and Bongiolatti, 2002). Christoff and Gabrieli (2000) proposed that frontopolar activations become recruited when internally generated information needs to be evaluated. Areas 9/10 are also involved in selecting among competing candidate responses (Desmond et al., 1996; Thompson-Schill et al., 1997).

4.2. Verbal fluency task and prefrontal cortex

In the present NIRS study, the verbal fluency test recruited widespread regions of the prefrontal cortical surface area and superior temporal regions, which is in accordance with previous studies using fMRI and PET (Elfgren and Risberg, 1998; Cabeza and Nyberg, 2000). The verbal fluency test not only requires retrieval of items from long-term memory storage but also concurrently requires working memory capacity to hold the already-generated words, maintenance of cognitive effort, and inhibition of inappropriate response (Henry and Crawford, 2004). This characteristic of the task demands may recruit frontopolar regions as well as lateral prefrontal cortex. Social daily activities require complex operations of working memory, executive function and memory retrieval that including monitoring, reasoning, organizing, selecting and planning, rather than simple short-term operations. Burgess et al. (2000) noted that the high-level of executive control associated with the frontopolar region is likely to be a vital component of everyday life. Considering these observations together, it may be reasonable to postulate that the smaller activations observed in the frontopolar regions during verbal fluency test in the present study were associated with severer functional impairment in schizophrenia.

Our study replicated the findings of reduced prefrontal activation during the letter version of the verbal fluency test in schizophrenia patients (Curtis et al., 1998; Suto et al., 2004). However, neuropsychological studies on Western populations have suggested that the category version of the verbal fluency test is more severely impaired than the letter version of the verbal fluency test in schizophrenia (Bokat and Goldberg, 2003). However, Japanese patients with schizophrenia have been shown to have a similar degree of impairments in both tasks (Sumiyoshi et al., 2004). Future studies should conduct an NIRS measurement during letter and category fluency test and investigate the relationship with functional outcome in Japanese patients with schizophrenia.

4.3. Limitations

Some comment upon methodological considerations is necessary. First, the continuous-wave NIRS enables measurement of Hb concentration changes not as absolute values but as measures relative to pre-task baseline. Therefore we cannot empirically rule out the possibility that the present findings may be due to a difference in prefrontal blood volume during the pre-task period (i.e., *hyper*perfusion in the pre-task period in schizophrenia). However, PET studies have found significant *hypo*perfusion during the resting state in the frontal areas of schizophrenia as compared to healthy controls (Hill et al., 2004). More recently, a near-infrared time-resolved spectroscopy study replicated a hypoperfusion in the resting state in patients with schizophrenia (Hoshi et al., 2006). Thus, decreased activation during the cognitive task was not likely to be due to a saturated hemodynamic state in the pre-task baseline in schizophrenia. Second, although we did not find a significant correlation between [oxy-Hb] change and dose of medication, we cannot fully rule out the possible effect of antipsychotics in the observed prefrontal activation in schizophrenia patients. Third, our study design was cross-sectional and used chronic patients. Investigations into longitudinal relationship between NIRS and functional outcome should be an important next step. Fourth, spatial resolution for detecting hemodynamic response from the scalp surface using NIRS is lower than that of fMRI and PET. Future investigations should conduct a simultaneous measurement of NIRS and fMRI, which is technically possible (Strangman et al., 2002b), using a cognitive task directly segregating frontopolar, dorsolateral, and ventrolateral prefrontal cortex (Koechlin et al., 1999).

Further, the difficulty in making a real-time measurement of the accurate differential pathlength factor (DPF) in vivo is one of the major considerations regarding data accuracy of NIRS method. In this continuous-wave NIRS system, "hemoglobin concentration change*DPF" (ΔC*L) is calculated as a solution to the simultaneous equations based on the modified Beer–Lambert law.

It should be also noted that controversies exist regarding DPF in NIRS measurement. Some researchers have estimated the DPF value by one-channel time-resolved NIRS system and have incorporated it into the calculation of the modified Beer–Lambert law. However, if one uses a one-channel time-resolved NIRS system, one could detect the sum of 'partial optical pathlengths within the cerebral and extracerebral tissues' in another session, but could not make a real-time measurement of the precise 'optical pathlength within the cerebral tissue' (Hoshi, 2003). Since commonly used NIRS systems employ the multiple wavelengths, the incorporation of one constant DPF value of a certain wavelength estimated from one-channel time-resolved NIRS system into the calculation of the modified Beer–Lambert law in all the multi-channels would not necessarily mean the improvement of accuracy. It is for this reason that we examined the NIRS signals including DPF (ΔC*L) with clinical evaluation in schizophrenia, according to the previous researches that have reported the results of ΔC*L closely agreed with various clinical data (Fallgatter et al., 1997; Kameyama et al., 2006; Matsuo et al., 2002; Suto et al., 2004).

Meanwhile, Zhao et al. (2002) used a Monte Carlo simulation to report the estimated DPF in various brain regions and suggested that the estimated DPF variation in the forehead region of adult humans was regarded as roughly homogeneous (in accordance with Ferrari et al., 1993). Also, from a practical point of view, the characteristics of time course pattern in the NIRS signals (ΔC*L) of the prefrontal cortex was found to be significantly different between mental disorder groups and healthy control group during verbal fluency task, but not during motor activation task (finger tapping that is cognitively less-demanding task) (Kameyama et al., 2006; Suto et al., 2004). These results suggest that only the difference of DPF could not account for the between-group difference in the NIRS signals (ΔC*L) of the prefrontal cortex during verbal fluency task.

However, to improve the accuracy of NIRS data, when feasible, the technology for the real-time measurement of the estimated DPF at each channel and the incorporation into the calculation of the modified Beer–Lambert law would be an issue for the future NIRS study.

4.4. Conclusions

In conclusion, our study suggested reduced hemodynamic response in frontopolar sub-region of prefrontal cortex during executive task and its relationship with functional impairment in patients with schizophrenia. NIRS may be a candidate biological marker for objectively monitoring the functional level in schizophrenia which may be potentially useful not only for clinicians, but also for consumers and families with severe mental illness such as schizophrenia.

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Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Ryu Takizawa, Kiyoto Kasai, Masato Fukuda designed the study and wrote the protocol. Ryu Takizawa and Kiyoto Kasai undertook the statistical analysis. Ryu Takizawa, Kiyoto Kasai, Yuki Kawakubo, and Kohei Marumo conducted data acquisition. Ryu Takizawa, Kiyoto Kasai, Shingo Kawasaki, and Hidenori Yamasue analyzed the data. Ryu Takizawa and Kiyoto Kasai 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

Drs. Kasai, Kawasaki, and Fukuda have potential conflict of interest (please see below for details). Other authors have no relevant conflict of interest.

Dr. Kiyoto Kasai: Since July 31, 2003 through present, the University of Tokyo and The Research and Developmental Center, Hitachi Medical Corporation has had an official contract for a collaborative study on clinical application of near-infrared spectroscopy 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, Hitachi Medical Corporation provided a project grant (JPY 300,000/year) and material support (temporary rental of a near-infrared spectroscopy (Optical Topography) machine, ETG-4000).

Dr. Shingo Kawasaki: His contribution to this study was in part thorough his role as an employee of Hitachi Medical Corporation. Since May 17, 2002 through present, Gunma University and Hitachi Group (Advanced Research Laboratory, Hitachi Ltd. and the Research and Developmental Center, Hitachi Medical Corporation) have had the official contract for a collaborative study on clinical application of near-infrared spectroscopy in psychiatric disorders. The principal investigator of this study is Masato Fukuda. For this study, Hitachi Group provides a project grant (JPY 1,000,000–1,500,000/year) and material support (temporary rental of a near-infrared spectroscopy (Optical Topography) machine, ETG-4000). Since July 31, 2003 through present, Tokyo University and Hitachi Medical Corporation (Application Development Office, Optical Topography Group) have had an official contract for a collaborative study on clinical application of near-infrared spectroscopy in psychiatric disorders. The principal investigator of this study is Kiyoto Kasai. For this study, Hitachi Medical Corporation provided a project grant (JPY 300,000/year) and material support (temporary rental of a near-infrared spectroscopy (Optical Topography) machine, ETG-4000).

Dr. Masato Fukuda: Since May 17, 2002 through present, Gunma University and Hitachi Group (Advanced Research Laboratory, Hitachi Ltd. and The Research and Developmental Center, Hitachi Medical Corporation) has had an official contract for a collaborative study on clinical application of near-infrared spectroscopy in psychiatric disorders. The principal investigator of this study is Masato Fukuda. For this study, Hitachi Group provided a project grant (JPY 1,000,000–1,500,000/year) and material support (temporary rental of a near-infrared spectroscopy (Optical Topography) machine, ETG-4000).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2007.10.025.

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Disrupted integrity of the fornix is associated with impaired memory organization in schizophrenia

Kunio Takei [a,*], Hidenori Yamasue [a], Osamu Abe [b], Haruyasu Yamada [b], Hideyuki Inoue [a], Motomu Suga [a], Kayoko Sekita [b], Hiroki Sasaki [b], Mark Rogers [a,c], Shigeki Aoki [b], Kiyoto Kasai [a]

[a] *Department of Neuropsychiatry, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
[b] *Department of Radiology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
[c] *Department of Psychology, Monash University, Clayton 3800, Victoria, Australia*

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Abstract

Background: The fornix is a major projection of the hippocampus to and from other brain regions. A previous diffusion tensor imaging (DTI) study has reported disrupted integrity of the fornix in patients with schizophrenia. However, functional significance of the DTI abnormalities of the fornix in schizophrenia has not been fully studied yet. We investigated an association between DTI abnormalities of the fornix and impairment of memory organization in schizophrenia.

Methods: Thirty-one patients with schizophrenia and 65 age- and gender-matched healthy controls underwent DTI, and fractional anisotropy (FA) and mean diffusivity (MD) were measured in cross-sections of fornix tractography. In addition, all of the patients and 32 controls performed a verbal learning task specialized for evaluating memory organization, the verbal memory subscale of the Wechsler Memory Scale-Revised, the category- and letter fluency tests, and the Japanese version of National Adult Reading Test.

Results: Statistically significant reduction of FA and increase of MD were found in the fornix of patients with schizophrenia compared with controls with no significant lateralization. A significant patients-specific correlation was found between increased MD in the left fornix and lower scores on utilization of semantic organization in the verbal learning task. In addition, increased MD in the right fornix showed a patients-specific association with poorer performance on the category fluency test, which indexes organization of long-term semantic memory. These patients-specific correlations, however, were not statistically lateralized to either hemisphere.

Conclusions: These results indicate that disrupted integrity of the fornix contributes to impaired memory organization in schizophrenia.

Keywords: Schizophrenia; Fornix; Memory organization; Diffusion tensor imaging; Verbal learning task; Category fluency test

1. Introduction

The fornix is a major projection of the hippocampus to and from other brain regions such as the mamillary

* Corresponding author. Tel.: +81 3 3815 5411; fax: +81 3 5800 6894.
E-mail address: takeik-tky@umin.ac.jp (K. Takei).

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bodies, septal region, prefrontal cortex, and nucleus accumbens. Since all of these fornix-connected regions are deeply involved in the pathophysiology of schizophrenia (Gothelf et al., 2000; Kajimoto et al., 2003; Lauer et al., 2001; Weinberger et al., 2001), the fornix should have a key role in schizophrenia.

A previous diffusion tensor imaging (DTI) study (Kuroki et al., 2006) reported disrupted integrity of the fornix such as reduced fractional anisotropy (FA) and increased mean diffusivity (MD) in male patients with schizophrenia compared with male controls. However, the functional significance of the DTI abnormalities of the fornix in patients with schizophrenia has not been fully studied yet. Only one recent study (Nestor et al., 2007) reported a correlation between reduced FA of the fornix and general memory dysfunction in patients with schizophrenia.

Among memory functions, patients with schizophrenia have a particular deficit in 'memory organization', that is, an ability to utilize latent semantic organizational structure in their verbal recall (Koh et al., 1973; Matsui et al., 2006). Prefrontal cortex is indicated as an anatomical basis of memory organization deficits in schizophrenia (Nohara et al., 2000). Together with a central role of the hippocampus in memory functions, memory organization should require connectivity between the hippocampus and other regions such as prefrontal cortex via the fornix. Consequently we chose to assess an association between structural integrity of the fornix and memory organization in schizophrenia.

To assess memory organization, the current study employed two neuropsychological tests; stimulus category repetition (SCR) of the verbal learning task (Nohara et al., 2000) and the category fluency test (CFT). SCR reflects the degree to which the subject has utilized the implicitly provided conceptual categories to assist in organization (Koh et al., 1973), and has been used to evaluate memory organization (Araki et al., 2006). On the other hand, the CFT reflects the ability to recall categorized semantic words. While patients with schizophrenia have been shown to be impaired on both category and letter fluency measures when compared to healthy controls, patients are particularly impaired on the CFT (Bokat and Goldberg, 2003). Patients' disproportionate impairment of category fluency is presumably caused by impaired clustering, and disorganization of semantic memory storage (Bozikas et al., 2005). Thus the CFT assesses the organization of the long-term semantic memory system. Importantly, both prefrontal cortex (Audenaert et al., 2000) and hippocampus (Gleissner and Elger, 2001) are implicated in the retrieval of categorized words such as indexed by the CFT.

The present study hypothesized that disrupted integrity of the fornix correlates with impairment of memory organization, not with other cognitive function than memory organization, in patients with schizophrenia. Based on the hypothesis, it was predicted that DTI measures of the fornix would correlate with SCR scores of the verbal learning task and with performance of the CFT, not with verbal memory subscale of the Wechsler Memory Scale-Revised (WMS-R), the letter fluency test (LFT) or premorbid IQs estimated from Japanese version of National Adult Reading Test (JART) in patients with schizophrenia.

2. Methods

2.1. Instruments

The full list of instruments used in the current study was as follows:

2.1.1. Demographical and clinical assessments

Edinburgh handedness Inventory (Oldfield, 1971)
Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I) (First et al., 1997)
Positive and Negative Syndrome Scale (PANSS) and its five factor version (Kay et al., 1987; Bell et al., 1994)
Hollingshead socioeconomic status (SES) (Hollingshead, 1965)

2.1.2. Neuropsychological tests

Japanese version of National Adult Reading Test (JART) (Nelson, 1982; Matsuoka et al., 2006)
Stimulus category repetition (SCR) of the verbal learning task (Nohara et al., 2000)
Verbal fluency tests (category fluency test (CFT), and letter fluency test (LFT)) (Sumiyoshi et al., 2004)
The Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987)

2.1.3. Magnetic resonance images

Diffusion tensor imaging (DTI)

2.2. Subjects

Thirty-one right-handed (determined using the Edinburgh Inventory) in- and outpatients with schizophrenia were recruited from the Department of Neuropsychiatry, Hospital of Tokyo University, Japan. Of these, twelve were male. Those patients who had already been clinically diagnosed as schizophrenia were reviewed according to DSM-IV criteria through the Structured

Clinical Interview for DSM-IV Axis I Disorder (SCID-I) by a trained psychiatrist (K.K. or H.Y.), and patients with diagnostic correspondence were recruited. The subtypes of schizophrenia were disorganized ($n=1$), catatonic ($n=1$), paranoid ($n=22$), residual ($n=1$), and undifferentiated ($n=6$). Psychiatric symptoms were assessed by a trained psychiatrist (H.Y.) according to PANSS (Kay et al., 1987) within three days before the MRI scanning. A five component model based on factor analysis of the PANSS (Bell et al., 1994) was used as an alternative to the rationally derived categories, since the five components, including Positive, Negative, Cognitive, Hostility, and Emotional Discomfort, have the advantage of separating cognitive from negative symptoms (Table 1). Sixty-five right-handed age- and gender-matched healthy subjects were recruited for comparison. Socioeconomic status (SES) and parental SES were assessed using the Hollingshead scale.

The exclusion criteria for both 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, and substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease in themselves or a family history of axis I disorder in their first-degree relatives. The ethical committee of the University of Tokyo Hospital approved this study. All subjects gave written informed consent after a complete explanation of the study.

2.3. Neuropsychological assessment

All of the patients and 32 of 61 healthy controls performed the neuropsychological tests: the Japanese version of the verbal learning task and the CFT as neuropsychological indices of fornix integrity; the verbal memory subscale of the WMS-R, the LFT, and the JART as control indices.

The procedures followed for administration of the CFT and LFT were similar to those adopted by Sumiyoshi et al. (2004). Briefly, subjects were asked to utter as many words as possible in 60 seconds. For the CFT, subjects uttered words belonging to each category as follows: ANIMALS, VEGETABLES or ELECTRIC

Table 1
Demographic data, clinical information, and neuropsychological scores

		Control subjects ($n=65$)		Patients with schizophrenia ($n=31$)		*t*-tests		
		Mean	SD	Mean	SD	*df*	*t* value	*P*
Age (range)		34.7 (21–54)	9.7	33.8 (22–55)	9.0	94	0.46	0.64
Male/female		24/41		12/19				
Education, years				14.3	1.8			
SES[a]		1.9	0.7	3.5	1.2	92	−8.66	<0.001
Parental SES[a]		2.2	0.6	2.7	0.9	91	−2.70	0.008
Neuroleptic dose[b], mg/day				830	382			
Onset of illness, years				24.9	5.6			
Duration of illness, years (range)				9.7 (1–30)	8.1			
PANSS[c]	Positive			15.8	4.3			
	Negative			23.5	7.1			
	Cognitive			20.4	4.4			
	Hostility			7.3	2.7			
	Emotional discomfort			10.3	2.8			
JART		115.2	13.1	84.8	20.1	60	7.06	<0.001
WMS-R	Verbal memory	120.0	18.3	75.5	20.5	61	7.46	<0.001
Verbal learning task	Random	31.8	6.3	20.2	7.3	60	6.71	<0.001
	Blocked	43.1	4.0	29.1	10.5	60	6.91	<0.001
	Unblocked	38.0	5.9	24.2	9.5	60	6.90	<0.001
	SCR	22.6	8.2	9.0	7.9	60	6.66	<0.001
Verbal fluency test	Category fluency	50.7	12.0	37.0	13.0	59	4.28	<0.001
	Letter fluency	40.2	10.4	24.5	11.4	59	5.63	<0.001

PANSS, Positive and Negative Symptom Scale; JART, Japanese version of National Adult Reading Test; WMS-R, Wechsler Memory Scale-Revised; SCR, Stimulus Category Repetition.

[a] Socioeconomic status, assessed using the Hollingshead scale. Higher scores indicate lower status.

[b] Based on chlorpromazine equivalents.

[c] Derived by a five component model based on factor analysis of the PANSS (Bell et al., 1994).

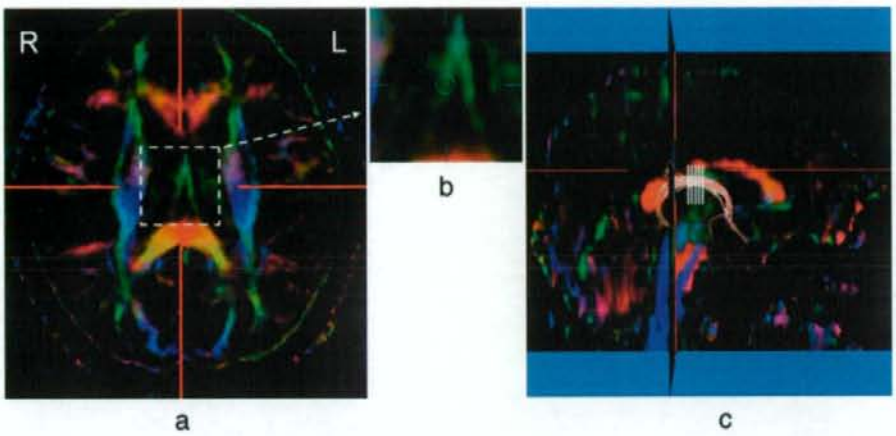

Fig. 1. Diffusion tensor tractography of the fornix on fractional anisotropy (FA) color maps. Red, green, and blue colors represent fibers running along the right–left, anterior–posterior, and superior–inferior orientations respectively. a) The axial slice showing the maximum size of the fornix (square dashed line). b) A magnified view of the square dashed line of (a). The circle on the right fornix shows the maximum cross-section of the seed-sphere from which tractography began. c) The bundle of the right fornix (pink) drawn by tractography method. Five equally spaced coronal cross-sections of the horizontal part of fornix tractography were measured. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

APPLIANCES. For the LFT, subjects uttered words beginning with each syllable as follows: /i/, /re/, or /si/. The number of words generated was defined as the measure of task performance.

The procedures of the verbal learning task are described in detail in a previous study (Nohara et al., 2000). Briefly, the verbal learning task was composed of three 20-word lists: a random list, a blocked list, and a semi blocked list. These three lists differed in degree of semantic organization. The random list consisted of 20 unrelated nouns. The blocked list contained subgroups of four taxonomic categories (stationery, vehicles, colors, and sports), each of which included five exemplars in a row. In the semi blocked list, five exemplars from each of four categories (animals, countries, musical instruments, and vegetables) were mixed so that related items never appeared consecutively. Thus, the words of the semi blocked list are categorized implicitly. The subjects were instructed to memorize the items they heard. For each list, three trials were repeated consecutively. Categorical clustering was evaluated as SCR (Bousfield and Bousfield, 1966) in recall of the semi blocked list. SCR is defined as the total number of occasions on which an item in a category is immediately

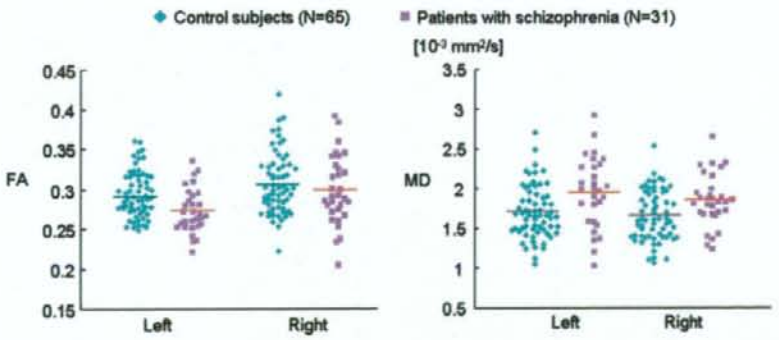

Fig. 2. Group difference in the diffusion tensor measures. Scatter plots of FA (left) and MD (right) of the fornix. Horizontal bars indicate mean values. FA, fractional anisotropy; MD, mean diffusivity.

Table 2
Diffusion tensor measures in the fornix and statistical results

		Control subjects (n=65)		Patients with schizophrenia (n=31)		Repeated measures analysis of variance					
						Diagnosis		Side		Diagnosis × Side	
		Mean	SD	Mean	SD	F	P	F	P	F	P
FA	Left	0.291	0.029	0.273	0.027	3.95	0.049	24.4	<0.001	1.60	0.21
	Right	0.306	0.039	0.299	0.043						
MD [10^{-3} mm^2/s]	Left	1.71	0.33	1.94	0.45	8.96	0.004	5.60	0.02	0.46	0.50
	Right	1.66	0.32	1.85	0.33						

FA, fractional anisotropy; MD, mean diffusivity.

followed by an item in the same category during recall, and it reflects the degree to which the subject utilized the conceptual categories provided implicitly to assist in organization (Koh et al., 1973).

Premorbid IQs were estimated using JART (Matsuoka et al., 2006) (Table 1).

2.4. Diffusion tensor imaging acquisition and processing

All subjects underwent DTI. The methods of DTI acquisition and data analysis were similar to those in our previous studies (Yamasue et al., 2007). Briefly, MRI data were obtained using a 1.5-T Signa Echo Speed MRI system (General Electric Medical Systems, Milwaukee, WI). The pulse sequence was single-shot, diffusion-weighted, $1\sqrt{2}$, 0, $1\sqrt{2}$), ($-1\sqrt{2}$, 0, $1\sqrt{2}$), (0, $1\sqrt{2}$, $1\sqrt{2}$), (0, $1\sqrt{2}$, $-1\sqrt{2}$), ($1\sqrt{2}$, $1\sqrt{2}$, 0), ($-1\sqrt{2}$, $1\sqrt{2}$, 0). The structural distortion of diffusion-weighted MRI images was corrected based on each T2-weighted echo-planar image (b=0 s/mm^2) (Haselgrove and Moore, 1996). The six elements of diffusion tensor were estimated in each voxel, and the eigenvectors and eigenvalues ($\lambda_1 > \lambda_2 > \lambda_3$) of the diffusion tensor were determined. FA and MD were generated on a voxel-by-voxel basis. FA was defined as the standard deviation of the eigenvalues divided by the root mean square of the eigenvalues. MD was defined as the average of the eigenvalues (Basser et al., 1994).

2.5. Diffusion tensor tractography

DTI measurements were performed in native space of each subject, because spatial normalization of echo-planar DTI may cause error in highly-localized structure such as the fornix. A software package for medical image analysis (*dTV*; software available at http://www.ut-radiology.umin.jp/people/masutani/dTV/dTV_frame-e.htm) was used to visualize fiber tracking (tractography). The methodologies of tractography and DTI measurement were based on those in our previous studies (Aoki et al., 2005; Masutani et al., 2003). Briefly, "seed-sphere" was defined as the location for the initiation of the tracking algorithm. The maximum cross-section of seed-sphere was put on one side of the fornix in axial slice of FA maps (Fig. 1b). The axial slice in which the fornix is displayed for its maximum size was selected from FA maps for placement of a circle of the seed-sphere. The tracking algorithm then moved a distance of 0.66 mm along the principal axis. The diffusion tensor at the next location was determined from the adjacent voxels by trilinear filtering, and its principal axis was subsequently estimated. The tracking

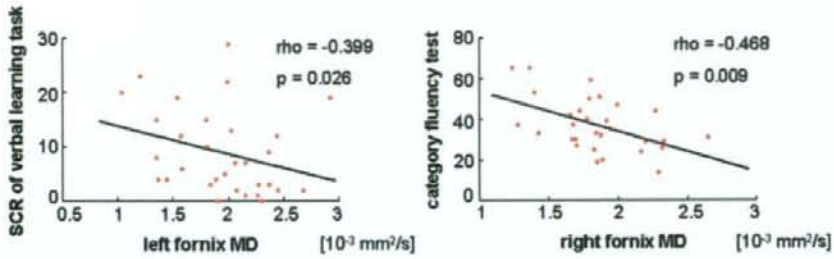

Fig. 3. Correlations between disrupted integrity of the fornix and impaired memory organization in the patients with schizophrenia. Scatter plots show correlations: left) between mean diffusivity in the left fornix and SCR of the verbal learning task, and right) between mean diffusivity in the right fornix and the category fluency test of the patients with schizophrenia. SCR, stimulus category repetition.

then traveled a further 0.66 mm along the same direction. Tracking lines were automatically traced in this way and were propagated in antegrade and retrograde directions until the FA fell below an assigned threshold (FA = 0.2).

Five coronal cross-sections, which were equally spaced with 1.875 mm interval along the horizontal part of fornix tractography, were measured (Fig. 1c). Then, the mean and standard deviation (SD) of FA and MD for the five cross-sections were calculated.

For interrater reliability, two raters (K.T. and S.S.) independently depicted tractographies and measured ten cases selected at random blind to diagnosis. The interclass correlation coefficient was 0.96/0.94 for left/right fornix FA and 0.99/0.98 for left/right fornix MD. Intrarater reliability, measured by one rater (K.T.) at two separate times (approximately 6 months apart), was 0.92/0.94 for left/right fornix FA and 0.98/0.97 for left/right fornix MD.

2.6. Statistical analyses

2.6.1. Group comparison

t-tests were employed in group comparisons of the demographic and neuropsychological data. For analysis of DTI measures, repeated measures ANOVAs were performed for between-group comparison of FA and MD in the fornix, adopting group (schizophrenia, control) as the between-subject factor, and side (left, right) as the within-subject factor. Then, in the case of a significant group-by-side interaction, post-hoc *t*-tests were conducted separately for each hemisphere. The significance level was set at $p<0.05$.

2.6.2. Correlational analysis

The association between DTI measures of the fornix in each hemisphere and neuropsychological scores was tested using Spearman's rank order correlation for each group separately. It was predicted that DTI measures in the fornix would show correlations with SCR of the verbal learning task and with CFT performance in the schizophrenia group. Thus, taking into account the hypothesis-driven nature of the correlational analysis, we set alpha at $p<0.05$.

Additionally, Spearman's rho was calculated for exploring the correlation between clinical measures (age, SES, parental SES, onset of illness, duration of illness, and neuroleptic dose) and DTI measures in each group separately. Alpha was set at $p<0.002$ (Bonferroni correction for 18 correlations [12 for schizophrenia group {2 DTI measures × 6 clinical measures}; 6 for control group {2 DTI measures × 3 clinical measures}]). Furthermore, Spearman's rho was calculated for exploring the correlation between factor analytic scores in the PANSS (Bell et al., 1994) and DTI measures in the schizophrenia group. Alpha was set at $p<0.0025$ (Bonferroni correction for 20 correlations (4 DTI measures × 5 symptom measures).

3. Results

The patients with schizophrenia showed significantly lower self- and parental SES than the control subjects ($p<0.01$), whereas the age and sex ratio did not differ significantly between groups (Table 1).

3.1. Neuropsychological scores

The patients with schizophrenia had significantly lower scores than the controls on all of the neuropsychological tests (JART score, verbal memory of WMS-R, verbal learning task, CFT, and LFT) (each $p<0.001$). The variances did not differ significantly between the patients and the controls on all of these tests except for the 'blocked' subscale of the verbal learning task (Table 1).