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Relationship between prepulse inhibition of acoustic startle response and schizotypy in healthy Japanese subjects

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Abstract

Prepulse inhibition (PPI) of the acoustic startle reflex (ASR) is the most common psychophysiological index of sensorimotor gating. Several studies have investigated the relationship of PPI of ASR to schizotypy in Caucasians. However, little has been reported on this relationship in Asians. We investigated a possible relationship between PPI of ASR and schizotypy in 79 healthy Japanese subjects. Schizotypy was assessed by the Schizotypal personality Questionnaire (SPQ). PPI was evaluated at signal-to-noise ratios (SnRs: difference between background noise intensity and prepulse intensity) of +12, +16, and +20 dB. The total SPQ score, cognitive/perceptual score, and interpersonal score correlated negatively with PPI at SnR of +16 and +20 dB. We conclude that PPI is associated with the trait of schizotypy in healthy Asian subjects.

Descriptors: Prepulse inhibition, Sensorimotor gating, Schizotypy, Acoustic startle response, Asians

Sensorimotor gating is thought to be a process which regulates sensory input by filtering out irrelevant or distracting stimuli, prevents sensory information overflow, and allows for selective and efficient processing of relevant information. Prepulse inhibition (PPI), which is usually defined as a reduction of the startle reflex due to weak sensory prestimulation (Braff, Stone, Callaway, Geyer, Glick, et al., 1978) of the acoustic startle reflex (ASR), is the most common psychophysiological index of sensorimotor gating.

Recently, PPI has been considered a candidate intermediate phenotype (endophenotype) of schizophrenia (Braff & Light, 2005; Turetsky, Calkins, Light, Olincy, Radant, & Swerdlow, 2007) and schizotypy (Cadenhead & Braff, 2002). Previous studies have consistently demonstrated PPI reductions in patients with schizophrenia (reviewed by Braff, Geyer, Light, Sprock, Perry, et al., 2001). Reports of PPI reductions not only in schizophrenia patients but also in unaffected relatives (Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000; Kumari, Das, Zachariah, Ettinger, & Sharma, 2005) suggest a substantial heritability of PPI impairment (Anokhin, Heath, Myers, Ralano, & Wood, 2003). Deficient PPI is also seen in patients with schizotypal personality disorder (SPD) (Cadenhead, Geyer, & Braff, 1993; Cadenhead et al., 2000), and to a lesser extent in normal participants scoring high on psychometric measures of psychosis-proneness (Kumari, Toone, & Gray, 1997; Simons & Giardina, 1992; Swerdlow, Filion, Geyer, & Braff, 1995).

Since the profile of startle measures is thought to differ across race (Hasenkamp, Norrholm, Green, Lewison, Boshoven, et al., 2008; Swerdlow, Sprock, Light, Cadenhead, Calkins, et al., 2007; Swerdlow, Talledo, & Braff, 2005), PPI should be comprehensively explored in Asian subjects. Recent reports indicate that, as well as in Caucasians, PPI is impaired in Asian patients with schizophrenia (Kunugi, Tanaka, Hori, Hashimoto, Saitoh et al., 2007; Takahashi, Iwase, Ishii, Ohi, Fukumoto, et al., 2008). However, to our knowledge, the relationship between PPI and schizotypy has not yet been investigated in non-Caucasian subjects.

In this study, we aimed at determining a possible association between PPI and schizotypy in a sample of 79 healthy Japanese subjects. We evaluated PPI at signal-to-noise ratios (SnRs:

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difference between background noise intensity and prepulse intensity) of +12, +16, and +20 dB. To measure schizotypy, we used the three factor model (Raine, Reynolds, Lencz, Scerbo, Triphon, & Kim, 1994) of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991).

Method

Participants

One hundred and nine Japanese volunteers were recruited by local advertisements in Osaka, as psychiatrically, medically, and neurologically healthy volunteers who were not receiving psychiatric medication, and had no first- or second-degree relatives with psychosis. Volunteers were screened for psychiatric disorder with the non-patient edition of the modified structured clinical interview for the Diagnostic and Statistical Manual—4th Edition, Axis I Disorders (SCID-I/NP) (First, Spitzer, Gibbon, & Williams, 1997), which was conducted by a well-trained psychologist. Two volunteers were excluded because they had psychiatric disorder (both anxiety disorder), and seven volunteers were excluded because they had first- or second-degree relatives with psychosis. As a result, 100 healthy Japanese subjects participated in this study. A portion of the subjects in the present study was from our previous sample (Takahashi et al., 2008). According to the screening interview, these subjects did not have clinically significant distress or impairment in social, occupational, or other important areas of functioning, which is necessary to be diagnosed as a personality disorder. None of the participants had any hearing impairments. Pregnant or lactating women were not included. The study procedure was conducted according to the Helsinki Declaration and approved by the Research Ethical Committee of Osaka University. All participants gave written informed consent after the study procedures were fully explained to them.

Schizotypy Questionnaire

Schizotypy was assessed using the SPQ. This is a 74-item questionnaire with a dichotomous response format (yes/no). The SPQ was developed to measure all of the nine diagnostic criteria stipulated by the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (American Psychiatric Association, 1987) for SPD. The factor analytical study of schizotypal personality by Raine et al. (1994) showed that the nine diagnostic subscales for SPD can be reduced to three latent factors: cognitive-perceptual, interpersonal, and disorganization. The cognitive-perceptual factor reflects the positive symptoms of schizotypy, characterized by ideas of reference, odd beliefs/magical thinking, unusual perceptual experiences, and suspiciousness/paranoid ideation. The interpersonal factor reflects the negative symptoms of schizotypy, characterized by suspiciousness/paranoid ideation, constricted affect, lack of close friends, and excessive social anxiety. The disorganization factor, which represents the disorganized schizotypy, consists of symptoms such as odd speech and odd or eccentric behavior. Scores for all 74 items are summed to produce the total SPQ score and the three SPQ latent factor scores. In this study, a Japanese version of the SPQ was used, and all participants filled out the questionnaire. The questionnaire had been administered to 258 Japanese college students in a validation study (Someya, Sasaki, & Takahashi, 1994), and the validity and reliability properties of this Japanese version of the SPQ were found to be similar to those of the original version of Raine (1991).

Startle Response Measurement

The methods for the startle paradigm, eyeblink acquisition, scoring parameters, and the procedure are described in detail in one of our earlier publications (Takahashi et al., 2008). A commercial computerized human startle response monitoring system (Startle Eyeblink Reflex Analysis System Map1155SYS, Nihonsanteku Co., Osaka, Japan) was used to deliver acoustic startle stimuli, and record and score the corresponding electromyographic activity. Stimulus presentation and data acquisition were controlled through a laptop computer with Windows XP operating system installed on it. All the auditory stimuli and the background noise were produced by a custom-built tone and noise generator and delivered binaurally to the subjects through stereophonic headphones (type DR-531, Elega Acous. Co. Ltd., Tokyo, Japan) with hard plastic bells.

Startle eyeblink electromyographic responses were recorded from the left orbicularis oculi muscle with a pair of Ag/AgCl disposable electrodes (sensor area 15 mm^2) filled with wet gel. The first electrode (Blue Sensor N-00-S, Ambu, Ballerup, Denmark) was positioned approximately 1 cm directly below the pupil of the left eye and low enough to not touch the lower eyelid, while the second electrode (Blue Sensor M-00-S, Ambu) was placed laterally and slightly superior to the first one, with the centers of the electrodes separated by approximately 2 cm. The impedance between the two electrodes was measured and deemed acceptable if below 10 kΩ. The impedance was measured with an electrode impedance meter (MaP811, Nihonsanteku Co.) at a measurement frequency of 30 Hz. The ground electrode (Blue Sensor M-00-S) was placed on the left angle of the mandible.

The skin area at the electrode site was cleaned with a cotton swab saturated with rubbing alcohol, then prepared by gently rubbing a small amount of Nuprep EEG & ECG Skin Prepping Gel (Bio-Medical Instruments Inc., Warren, MI), and cleaned with a cotton swab saturated with rubbing alcohol again. Electromyography (EMG) data were measured with an EMG Telemeter (PolyTele EMG, Nihonsanteku Co.). The measurement condition was adjusted as follows: the time constant was 0.03 s, which was equivalent to the low frequency filter of 5 Hz; the high frequency filter was 300 Hz. The sensitivity of the amplifier was 1000 times. The amplification gain control for the EMG signal was kept constant for all subjects. EMG data were digitized with a 12-bit A/D converter (MaP222, Nihonsanteku Co.) and collected on the PC. The sampling frequency was 1 kHz. Sampling on each trial began 1000 ms prior to the onset of the startle eliciting stimulus and continued for 1000 ms after the onset of the startle eliciting stimulus. The resulting data were baseline corrected with a moving average. The eyeblink magnitude of every startle response was defined as the voltage of the peak activity of the EMG within a latency window of 20–85 ms following startle eliciting stimulus onset. The data were stored and exported for analyses in microvolt values.

Participants were tested in a startle paradigm, which consisted of 3 blocks with a continuously presented 70 dB sound pressure levels (SPL) background white noise. Pulse stimuli consisted of broadband white noises with an instantaneous rise/fall time lasting for 40 ms presented at 115 dB SPL. Prepulse stimuli were also broadband white noises with an instantaneous rise/fall time lasting for 20 ms presented at three different intensities (82, 86, and 90 dB SPL, equivalent to SnR of +12 dB, +16 dB, and +20 dB, respectively). The lead interval (from prepulse onset to pulse onset) was 120 ms. In block 1, the startle response for pulse alone trial (PA trial) was recorded 6 times. Block 2 consisted of PA

trials or trials of pulse with prepulse at the three different intensities (PP trials) performed eight times for each condition. Block 3 was the same as block 1 to explore the habituation phenomenon in one of our previous publications (Takahashi et al., 2008). However, because habituation was not assessed in this study, Block 3 was not used for analysis of these data. All trials were presented in a fixed pseudorandom order, separated by inter-trial intervals of 15–25 s (20 s on average). The startle paradigm consisted of a total of 44 trials. The session lasted approximately 20 min, including 5 min acclimation to the background noise.

The following startle measures were examined: PPI82, PPI86, PPI90: prepulse inhibition at prepulse intensities of 82 dB, 86 dB, and 90 dB SPL, respectively. PPI for each prepulse intensity was computed as the percentage of magnitude reduction between PA and PP trials in block 2 by the formula: (1 – average eyeblink magnitude of startle response to PP trials in block 2/average eyeblink magnitude of startle response to PA trials in block 2) × 100.

Prior to data analyses, exclusion criteria were established for both trials and subject data. Trials were discarded if the voltage of their peak activity of the EMG within a latency window of 0–20 ms following startle eliciting stimulus onset was more than 30 microvolt. Subjects were excluded from further analyses as nonresponders if the voltages of their peak activity of the EMG within a latency window of 20–85 ms following startle eliciting stimulus onset were less than 30 microvolt in more than half of the trials in block 1. Analyses of PPI were not conducted if more than half of the PP trials at any prepulse intensity or PA trials in block 2 were discarded.

Upon arriving at the laboratory, each subject read and signed an informed consent form and completed a brief medical history questionnaire including demographic data. The subjects were informed about the general purpose of the study, about the stimuli and procedure, and that they could withdraw from the study at any time. Subjects were told that the experiment aimed to measure their reactivity to a number of noise bursts. There was no restriction on smoking intake, but we took care to avoid testing smokers within 30 min of smoking a cigarette, as this could potentially increase PPI (Kumari, Soni, & Sharma, 2001). Subjects were then seated in the testing room. During the task, the subjects were instructed to keep their eyes open and to maintain their gaze on a fixed point 100 cm away. Thereafter, the skin area at the electrode site was cleaned and the electrodes were attached. The door to the experimental chamber was closed.

Nineteen subjects were excluded from the analyses. One female subject could not stand the startle stimuli and did not complete the session. There were a total of 8 nonresponders. Ten subjects were excluded from analyses because their PPI were not evaluated according to the above exclusion criteria. There was one outlier, who was more than 3 standard deviations above or below the mean of all subjects, in cognitive/perceptual scores, and there was also another outlier in disorganization scores. We excluded these two outliers from further analyses. Thus, the final sample size was 79 (males $N = 33$, females $N = 46$; age [years]: $M = 38.5$, $SD = 10.7$, range 21–60). The percentage of smokers was higher in males than females (nonsmoker/smoker: males 22/11; females 39/7), although the difference did not reach statistical significance ($\chi^2(1) = 3.58$, $p = .101$, Fisher's exact test). Age did not differ significantly across sex (males: $M = 36.5$, $SD = 9.4$; females: $M = 39.8$, $SD = 11.4$; $t[77] = -1.36$, $p = .179$) and smoking status (nonsmokers: $M = 38.5$, $SD = 11.4$; smokers: $M = 38.3$, $SD = 7.7$; $t[41.2] = -.10$, $p = .922$). Those subjects excluded from the analyses did not differ significantly from the included subjects in demographic characteristics, such as age, sex distribution, smoking status, and also in the SPQ scores.

Statistical Analysis

None of the SPQ scores and startle measures was normally distributed based on the Shapiro–Wilkes W statistic ($p < .001$ for all SPQ scores; PPI82, $W = .963$, $p = .021$; PPI86, $W = .957$, $p = .009$; PPI90, $W = .969$, $p = .049$). Therefore, we performed nonparametric analyses. The Mann-Whitney U test was used for comparison of mean SPQ scores and startle measures. Within group differences in PPI across the three prepulse intensities were analyzed using the non-parametric Friedman χ^2 test. Spearman's rank order correlations examined the relationship of PPI to psychiatric symptoms. All p-values reported here were two-tailed. Statistical significance was considered when p-value was $< .05$. Statistical analyses were performed using SPSS Ver. 12 (SPSS Japan, Tokyo, Japan).

Results

Difference in Schizotypal Personality Questionnaire Scores and Startle Measures Across Sex and Smoking Status

The SPQ scores and startle measures of the subjects in the present study are shown in Table 1. Since sex and smoking status may affect startle measures (Abel, Waikar, Pedro, Hemsley, & Geyer, 1998; George, Termine, Sacco, Allen, Reutenauer, et al., 2006; Kumari, Aasen, & Sharma, 2004; Kumari, Checkley, & Gray, 1996; Kumari et al., 2001; Rissling, Dawson, Shell & Nuechterlein, 2007; Swerdlow, Auerbach, Monroe, Hartston, Geyer, & Braff, 1993; Swerdlow, Hartman, & Auerbach, 1997), and are also related to schizotypy (Badcock & Dragovic, 2006; Esterberg, Jones, Compton, & Walker, 2007; Kremen, Faraone, Toomey, Seidman, & Tsuang, 1998; Wan, Crawford, & Boutros, 2007), we assessed the difference in SPQ scores and startle measures across sex groups and smoking status. PPI differed significantly across the three prepulse intensities ($\chi^2(2) = 36.9$, $p < .01$), with PPI82 showing the lowest PPI, and PPI90 showing the highest PPI. This difference was also observed after separate analyses for sex (male: $\chi^2(2) = 25.9$, $p < .01$, female: $\chi^2(2) = 14.39$, $p < .01$), and smoking status (smoker: $\chi^2(2) = 9.33$, $p < .01$, nonsmoker: $\chi^2(2) = 30.33$, $p < .01$). As shown in Table 1, females had significantly decreased PPI for all three prepulse intensities compared to males, and SPQ scores did not differ significantly across sex. We did not find significant difference in SPQ scores or startle measures between smokers and nonsmokers (PPI82, $U = 442$, $p = .211$; PPI86, $U = 463$, $p = .315$; PPI90, $U = 514$, $p = .682$; the total SPQ score, $U = 469$, $p = .349$; cognitive/perceptual score, $U = 525$, $p = .776$; interpersonal score, $U = 463$, $p = .312$; disorganization score, $U = 484.5$, $p = .445$).

Relationship of Startle Measures to Schizotypy[1]

Figure 1 shows scatterplots of prepulse inhibition by scores on SPQ. PPI86 correlated negatively with the total SPQ score, $p = .002$, as well as with cognitive/perceptual scores, $p = .026$, and with interpersonal scores, $p = .003$. PPI90 also correlated negatively with the total SPQ score, $p = .020$, as well as with

[1]Since smoking status might have affected our results, we additionally investigated the relationship of startle measures and SPQ scores in nonsmokers. We found significant correlation between PPI86 and interpersonal scores in nonsmokers, rho = −.268, $p = .037$.

Table 1. *Scores on Schizotypal Personality Questionnaire and Startle Measures*

		All ($N = 79$)				Male ($N = 33$)		Female ($N = 46$)				
		M	*SD*	Skewness	Kurtosis	*M*	*SD*	*M*	*SD*	*U*	*p*	Effect size
Scores on SPQ	Total SPQ score	9.4	6.5	0.76	−0.21	9.2	7.1	9.5	6.1	703.5	0.580	0.057
	Cognitive/perceptual score	2.7	2.6	1.04	1.08	2.7	3.0	2.8	2.2	682.5	0.440	0.053
	Interpersonal score	4.6	3.8	1.00	0.46	4.5	3.7	4.7	3.9	725.0	0.734	0.075
	Disorganization score	2.6	2.3	0.60	−0.61	2.6	2.5	2.6	2.1	732.0	0.786	0.018
Startle measures	PPI82 (%)	27.2	27.2	−0.65	0.28	37.6	27.0	19.7	25.2	448.0	0.002	0.656
	PPI86 (%)	31.9	27.5	−0.38	−0.82	41.4	25.4	25.2	27.1	506.5	0.012	0.590
	PPI90 (%)	40.7	26.0	−0.39	−0.36	50.7	23.6	33.5	25.5	462.0	0.003	0.662

Note: SPQ: Schizotypal personality questionnaire; PPI82, PPI86, PPI90: prepulse inhibition of acoustic startle reflex in prepulse of 82 dB, 86 dB, and 90 dB, respectively. *U*: Mann-Whitney *U* test.

cognitive/perceptual scores, $p = .037$, and with interpersonal scores, $p = .048$. There was no other significant correlation between SPQ scores and PPI.

Since there was gender difference in PPI, we investigated the relationship of startle measures to SPQ scores separately for sex groups. In female subjects, PPI86 correlated negatively with the total SPQ score, rho = −.41, $p = .005$, with cognitive-perceptual scores, rho = −.30, $p = .042$, and with interpersonal scores, rho = −.41, $p = .005$, whereas PPI90 correlated negatively with the total SPQ score, rho = −.31, $p = .037$. However, we found no significant correlation between PPI and SPQ scores in male subjects.

Discussion

In this study, we investigated a possible association between PPI and SPQ scores in a sample of 79 healthy Japanese subjects. We found that the total SPQ score, cognitive/perceptual score, and interpersonal score correlated negatively with PPI86 and PPI90.

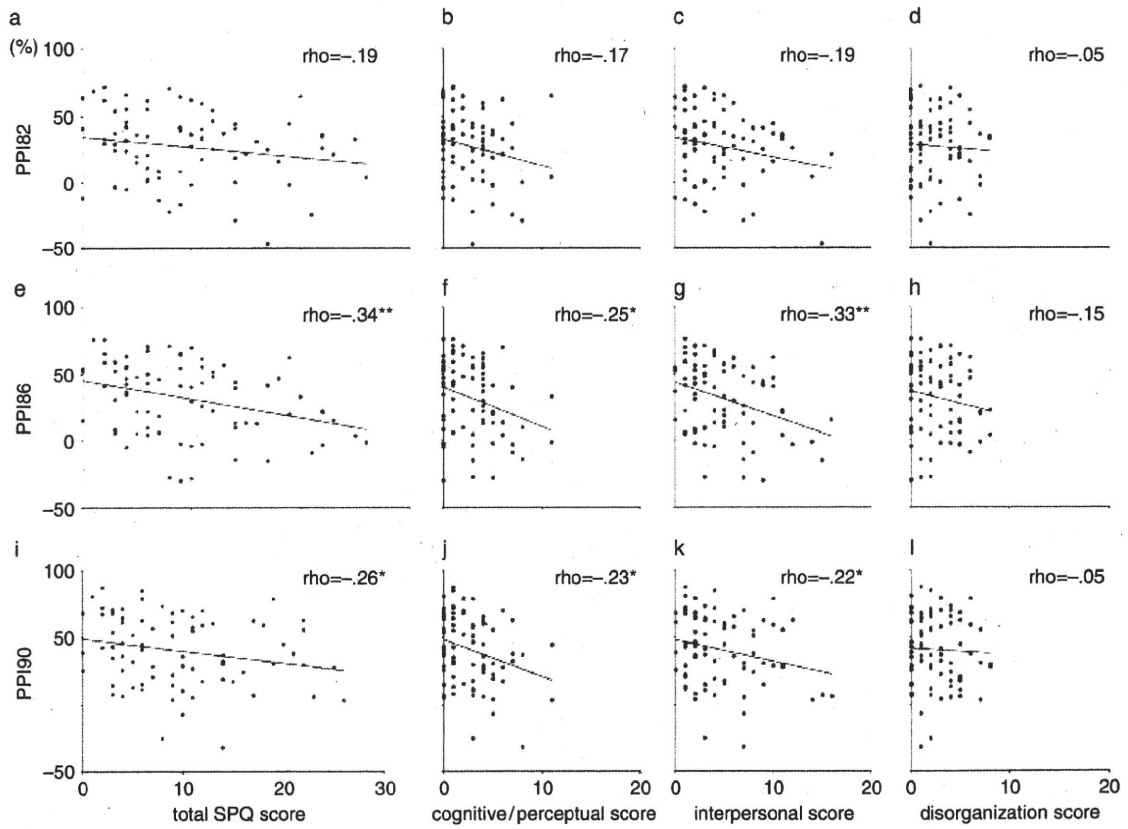

Figure 1. Scatterplot of prepulse inhibition by scores on schizotypal personality questionnaire ($N = 79$) Scatterplots of (a) PPI82 for the total SPQ score, (b) PPI82 for cognitive/perceptual score, (c) PPI82 for SPQ interpersonal score, (d) PPI82 for SPQ disorganization score, (e) PPI86 for the total SPQ score, (f) PPI86 for cognitive/perceptual score, (g) PPI86 for SPQ interpersonal score, (h) PPI86 for SPQ disorganization score, (i) PPI90 for the total SPQ score, (j) PPI90 for cognitive/perceptual score, (k) PPI90 for SPQ interpersonal score, and (l) PPI90 for SPQ disorganization score. Variables are rho. SPQ: Schizotypal personality questionnaire; PPI82, PPI86, PPI90: prepulse inhibition of acoustic startle reflex in prepulse of 82 dB, 86 dB, and 90 dB, respectively. Spearman's rank order correlations; $*p < .05$; $**p < .01$.

To our knowledge, this is the first study to investigate the relationship between PPI and schizotypy in non-Caucasian subjects. Since the profile of startle measures, which includes PPI, appears to be different in Caucasians compared with non-Caucasian populations (Hasenkamp et al., 2008; Swerdlow et al., 2005, 2007), the relationship between PPI and schizotypy might be different across race. However, we found that PPI86 and PPI90 negatively correlated with the total SPQ scores in healthy Japanese subjects. Our results indicate that the association of PPI to schizotypy might be detected across race. Further replication studies in non-Caucasian participants will be necessary to confirm this argument.

We used SPQ to assess schizotypy in relation to PPI. Although SPQ is a rather novel questionnaire to assess schizotypy, a recent study (Wuthrich & Bates, 2006) reported that SPQ scores showed good correlation with an established questionnaire of schizotypy, the Chapman schizotypy scales, which include the Chapman Magical Ideation (Eckblad & Chapman, 1983), Perceptual Aberration (Chapman, Chapman, & Raulin, 1978), and Revised Social Anhedonia (Eckblad, Chapman, Chapman, & Mishlove, 1982) scales. The SPQ assesses the nine diagnostic subscales of DSM-defined SPD, and the factor analytical study (Raine et al., 1994) showed that these nine diagnostic subscales for SPD can be reduced to three dimensions of schizotypy. Similarities between the three symptom factors of schizophrenia (Arndt, Alliger, & Andreasen, 1991; Bilder, Mukherjee, Rieder, & Pandurangi, 1985; Gruzelier, 1996; Liddle & Barnes, 1990) and the three SPQ dimensions of schizotypy suggested that analysis of the SPQ dimensions of schizotypy could be useful for evaluating the different components of schizotypy. In fact, the three-factor model (Raine et al., 1994) of SPQ has been suggested to underlie individual differences across samples of normal and schizophrenic patients (Rossi & Daneluzzo, 2002). Thus, the SPQ has been widely used to investigate the relationship of schizotypy to cognitive functions (Chen, Hsiao, Hsiao, & Hwu, 1998; Noguchi, Hori, & Kunugi, 2008) or to a psychophysiological index, such as P50 (Wan, Crawford, & Boutros, 2006, 2007; Wang, Miyazato, Hokama, Hiramatsu, & Kondo, 2004), P300 (Mannan, Hiramatsu, Hokama, & Ohta, 2001) or prefrontal activation patterns measured with near-infrared spectroscopy (Hori, Nagamine, Soshi, Okabe, Kim, & Kunugi, 2008; Hori, Ozeki, Terada, & Kunugi, 2008). By using SPQ, we could find a negative correlation between PPI and the trait of schizotypy.

Our result that females exhibited smaller PPI than males is consistent with findings of most previous PPI studies (Aasen, Kolli, & Kumari, 2005; Abel et al., 1998; Della Casa, Höfer, Weiner, & Feldon, 1998; Kumari et al., 2004; Swerdlow et al., 1993, 1995, 1997, 1999, 2006). In addition, the analysis of the data by sex difference indicated that association between SPQ scores and PPI remained significant among female subjects but not among male subjects. However, it is important to point out that, with the analytic approach used herein, we cannot ensure that reliable associations exist between sex and PPI in schizotypy in our data. Our results also showed a significant relationship between PPI and schizotypy exclusively for PPI86 and PPI90. This supports recent reports of a significant impact of stimulus SnR on PPI of ASR (Blumenthal, Noto, Fox, & Franklin, 2006; Franklin, Bowker, & Blumenthal, 2009; Franklin, Moretti, & Blumenthal, 2007). Of note, the correlation of PPI with schizotypy for PPI82 nearly reached statistical significance (the total SPQ score, $p = .103$; cognitive/perceptual scores, $p = .128$; interpersonal scores, $p = .097$). Thus, it is conceivable that an increase in sample size could also result in significant difference for this PPI intensity. Overall, although effects of sex and SnR on PPI may be interesting, the present study was not specifically designed to examine this issue but to assess the cross-cultural variability of the PPI–schizotypy relationship. Further studies will be necessary to clarify the effects of these factors on the relationship between PPI and schizotypy.

There are several limitations to the current study. First, we enrolled only healthy volunteers who have no family history of psychosis and were relatively mature-aged subjects. This might have restricted the range on the SPQ and influenced the relationship between PPI and SPQ scores. SPQ scores are reported high in relatives of patients with schizophrenia (Bora & Veznedaroglu, 2007) and are thought to become lower with increasing age (Badcock & Dragovic, 2006). Although SPQ scores in our sample were similar to those of mature, healthy populations (Chen et al., 1998), including those with participants without family history of psychiatric illness (Hori, Nagamine, et al., 2008; Hori, Ozeki, et al., 2008; Noguchi et al., 2008; Wang et al., 2004) (these studies have reported mean total SPQ scores ranging from 8.1 to 12.9), SPQ scores in our study were relatively smaller than those of previous studies on schizotypy, for instance, a study by Raine (1991) found a mean total SPQ score of 26.9. In addition, although symptom dimensions of schizotypy in relatives of patients with schizophrenia are reported in association with patient symptoms (Schürhoff, Laguerre, Szöke, Méary, & Leboyer, 2005), little is known about the relationships of symptom dimensions of schizotypy and schizophrenia. Further studies investigating the relationship between SPQ and PPI in relatives and non-relatives of patients with psychiatric disorders are needed.

Second, some SPQ scores, such as the interpersonal, cognitive-perceptual, and total SPQ scores, are associated with trait-anxiety (Braunstein-Bercovitz, 2000). Some previous studies (Duley, Hillman, Coombes, & Janelle, 2007; Franklin et al., 2009; Ludewig, Ludewig, Geyer, Hell, & Vollenweider, 2002) have reported a relationship between PPI and anxiety. Because we did not assess trait-anxiety of our subjects, the possibility that anxiety is more responsible for PPI than symptom dimension of schizotypy is not testable in this study. Future studies are needed to evaluate the association of PPI to psychiatric symptoms, including symptom dimension of schizotypy and anxiety.

Conclusion

In the present study, PPI correlated negatively with the trait of schizotypy in healthy Asian subjects.

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Discriminant analysis in schizophrenia and healthy subjects using prefrontal activation during frontal lobe tasks: A near-infrared spectroscopy

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ABSTRACT

While psychiatric disorders such as schizophrenia are largely diagnosed on symptomatology, several studies have attempted to determine which biomarkers can discriminate schizophrenia patients from non-patients with schizophrenia. The objective of this study is to assess whether near-infrared spectroscopy (NIRS) measurement can distinguish schizophrenia patients from healthy subjects. Sixty patients with schizophrenia and sixty age- and gender-matched healthy controls were divided into two sequential groups. The concentration change in oxygenated hemoglobin (Δ[oxy-Hb]) was measured in the bilateral prefrontal areas (Fp1-F7 and Fp2-F8) during the Verbal Fluency Test (VFT) letter version and category version, Tower of Hanoi (TOH), Sternberg's (SBT) and Stroop Tasks.

In the first group, schizophrenia patients showed poorer task performance on all tasks and less prefrontal cortex activation during all but the Stroop Task compared to healthy subjects. In the second group, schizophrenia patients showed poorer task performance and less prefrontal cortex activation during VFTs and TOH tasks than healthy subjects. We then performed discriminant analysis by a stepwise method using Δ[oxy-Hb] and task performance measures as independent variables. The discriminant analysis in the first group included task performance of TOH, VFT letter and VFT category and Δ[oxy-Hb] of VFT letter. As a result, 88.3% of the participants were correctly classified as being schizophrenic or healthy subjects in the first analysis. The discriminant function derived from the first group correctly assigned 75% of the subjects in the second group. Our findings suggest that NIRS measurement could be applied to differentiate patients with schizophrenia from healthy subjects.

1. Introduction

Major psychiatric disorders such as schizophrenia are largely diagnosed on symptomatology (World Health Organization, 1992; American Psychiatric Association, 1994). While the validity of diagnostic criteria continues to be debated, major advances have been made in understanding the biology of these disorders. However, identified biological markers of psychiatric diseases, including schizophrenia, are not currently used in their diagnosis.

Candidate biological markers of schizophrenia include pathogenetic factors, physical findings, neurophysiological and neuropsychological functioning, and structural and functional brain imaging. In particular, neuroimaging techniques hold significant advantages and have provided evidence for localized anatomical and functional abnormalities, complemented by the use of cognitive neuroscience (Abou-Saleh, 2006). Abnormalities in the prefrontal cortex as well as other brain regions (Arnold and Trojanowski, 1996; Bogerts et al.,

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1990; Carter et al., 1998; Harrison, 2005; Heckers et al., 1998; Laurens et al., 2005; Torrey, 2007) and connections between these regions (Fletcher, 1998; Volkow et al., 1988; Weinberger et al., 1992) have been identified as substrates of the clinical features of schizophrenia. For example, positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies identified prefrontal cortex dysfunction as one of the characteristic features of the disease (Callicot et al., 2000; Carter et al., 1998; Curtis et al., 1998). These studies highlight the prefrontal cortex as a promising brain region in the potential use of functional imaging as a biological marker of psychiatric disorders.

Near-infrared spectroscopy (NIRS), a brain functional measuring technique, can measure changes in the concentration of oxygenated Hemoglobin ([oxy-Hb]), deoxygenated Hemoglobin ([deoxy-Hb]) and total Hemoglobin ([total-Hb]), which are presumed to reflect regional cerebral blood flow (Jobsis, 1977). These hemodynamic parameters are assumed to be a stable marker of cerebral oxygenation changes induced by cognitive tasks (Nakahachi et al., 2008; Suto et al., 2004; Takizawa et al., 2008;). NIRS is advantageous for clinical application over other neuroimaging techniques such as PET, SPECT and functional magnetic resonance imaging (fMRI), due to its non-invasive nature, high time resolution, portable and simple mounting, low cost, robustness against motion artifacts, short time of measurement and little training required for operation and data analysis. Therefore, the prefrontal dysfunction in schizophrenia has been frequently investigated with NIRS in a clinical setting. Studies in the frontal cortex have demonstrated a significant smaller increase in the prefrontal activation during the Verbal Fluency test (Ikezawa et al., 2009; Kubota et al., 2005; Suto et al., 2004; Takizawa et al., 2008; Watanabe and Kato, 2004), the Random Number Generation task (Hoshi et al., 2006) and the Tower of Hanoi task (Ikezawa et al., 2009) in patients with schizophrenia compared to healthy control subjects. However, patients with schizophrenia showed no differences during divergent thinking task (Folley and Park, 2005), and possibly a larger increase during the unilateral finger tapping task (Suto et al., 2004) or letter number span test (Watanabe and Kato, 2004). These studies suggest that NIRS measurement of frontal lobe activity may represent a biological marker of schizophrenia on which frontal lobe tasks are employed.

Despite the potential benefit of NIRS measurement of frontal lobe activity as a biological marker of schizophrenia, to our knowledge, discriminant analysis with NIRS has not previously been applied to distinguish schizophrenia patients from healthy subjects. The present study aimed to evaluate whether the NIRS measurement in the frontal cortex could reliably distinguish patients with schizophrenia from control subjects and to identify the task which would provide the highest correct classification rate.

2. Methods

2.1. Subjects

Subjects were assigned to two independent groups according to the order of study inclusion. The first group consisted of a total of 60 subjects, including 30 patients with schizophrenia and 30 age- and gender-matched healthy control subjects. The period of study for this group was from November 2006 to May 2007.

The second group for the prospective validation also consisted of 60 subjects: 30 with schizophrenia and 30 age- and gender-matched healthy control subjects. The period of study for this group was from June 2007 to April 2008.

The patients were inpatients and outpatients of the Department of Psychiatry, Osaka University Hospital. Each patient underwent a Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002), and two or more experienced psychiatrists reached a consensus diagnosis of schizophrenia according to the DSM-IV (American Psychiatric Association, 1994) and ICD-10 for research (World Health Organization, 1992) on the basis of SCID and all other sources of clinical data. At the time of study, in the first group, 2 patients were medication naïve and 28 patients were medicated (2 patients were receiving typical antipsychotics, 11 patients were receiving atypical and 15 patients were receiving both types of antipsychotics). In addition, 11 patients were taking anxiolytics and 2 patients were taking antidepressants. In the second group, all patients (except one from which medication data was missing) were on medication (4 patients were receiving typical antipsychotics, 14 patients were receiving atypical antipsychotics and 11 patients were receiving both types of antipsychotics). In addition, 23 patients in the second group were taking anxiolytics and 3 were taking antidepressants (Table 1).

Advertisements were posted at local hospitals to recruit healthy subjects. Healthy subjects were diagnostically interviewed and assessed to verify that they had neither personal nor family history of psychiatric disease, and had taken no antipsychotics. All of the healthy subjects had at least no fourth-degree relative with a psychiatric disorder and had an estimated IQ of 70 or greater. All patients were physically healthy at the time of recruitment, and none had a history of head trauma, serious medical or surgical illness, or alcohol/substance abuse disorder. All procedures were approved by the ethical committee of the Osaka University hospital.

All participants provided written informed consent according to the Declaration of Helsinki after they were given a complete explanation of the study procedures.

2.2. Tasks and procedure

The cognitive paradigm employed in the present study consisted of the letter and category versions of the Verbal Fluency Test (VFT), Tower of Hanoi (TOH), Sternberg's Task (SBT), and the Chinese character version of the Stroop Task part III (SRT). These frontal activation tasks comprised a 30-s pre-task baseline period, a 60-s or 120-s task period, and a 60-s post-task baseline periods (Fig. 1). These procedures were similar to that of Suto et al. (2004), Ito et al. (2005) and Kameyama et al. (2006) except for the use of a 120-s task period for SBT or STR instead of the 60-s used in their studies. We used a longer interval for these two tasks to enable a more satisfactory [oxy-Hb] activation compared to the baseline in the pre-task period. This is described in detail elsewhere (Ikezawa et al., 2009).

2.2.1. Verbal Fluency Test letter and category versions

For the pre- and post-task baseline periods of the VFT letter and category versions, the subjects were instructed to repeat the voice vowels (/a/, /i/, /u/, /e/ and /o/ (Phonetic Alphabet)) constantly. During the VFT periods, they were instructed to alternately produce as many Japanese nouns as possible

Table 1
Clinical characteristics of the study groups.

Variable	Schizophrenia, $n=30$	Control, $n=30$	Group difference	*df*	*t*
	Mean(SD)	Mean(SD)	*P value*		
a. First group					
Age (year)	38.7 (11.7)	37.3 (8.7)	.601	58	−0.53
Gender Male/Female	12/18	13/17	.793*	1	
Handedness (Right/Left)	30/0	30/0	—*	1	
Education (year)	13.3(2.4)	15.5(2.1)	.001	48.23	3.51
JART premorbid IQ	100.8(10.6)	105.9(8.4)	.049	49.43	2.02
Outpatient/Inpatient	13/17	NA			
Age of onset (year)	24.3(10.2)	NA			
Medication					
Typical/Atypical/Combined (*n*)	2/11/15, 2 medication naïve	NA			
CPZeq dose (mg/day)	842.6 (704.2)	NA			
BZDeq dose (mg/day)	17.1 (11.1)a	NA			
Illness duration (year)	14.7 (13.0)	NA			
PANSS positive	18.8 (5.5)	NA			
PANSS negative	18.2 (6.4)	NA			
PANSS general psychopathology	36.8 (9.1)	NA			
b. Second group					
Age (year)	39.6 (13.1)	39.5 (13.1)	.977	58	−0.03
Gender Male/Female	16/14	18/12	.602*	1	
Handedness (Right/Left)	29/1	30/0	.313*	1	
Education (year)	14.4 (1.8)	15.5 (3.0)	.108	57	1.64
JART premorbid IQ	104.1 (10.4)	106.2 (6.8)	.356	57	0.93
Outpatient/Inpatient	21/9	NA			
Age of onset (year)	25.8 (10.8)	NA			
Medication					
Typical/ Atypical/ Combined (n)	4/14/11, 1 NA	NA			
CPZeq dose (mg/day)	881.4 (761.6)	NA			
BZDeq dose (mg/day)	18.9 (19.7)b	NA			
Illness duration (year)	13.1 (11.7)	NA			
PANSS positive	18.9 (7.5)	NA			
PANSS negative	21.1 (8.6)	NA			
PANSS general psychopathology	41.0 (11.9)	NA			

Abbreviations: JART, the Japanese version of the National Adult Reading Test; IQ, Intelligence Quotient; CPZeq, chlorpromazine equivalent; BZDeq, benzodiazepine equivalent; PANSS, the Positive and Negative Syndrome Scale; NA, not applicable.
*Chi-square test was used.
a,Eleven patients or b,23 patients received anxiolytics.

beginning with a designated syllable (/a/, /ka/, /sa/) or belonging to a certain category of words (animals, vegetables, conveyance), which is commonly used in Japanese VFT letter/category version. The three initial/categorical syllables/words were presented in an order which was counterbalanced among the subjects. These were changed every 20 s during the 60-s task period to prevent the subjects from being at a loss for words for the entire 60-s task. An auditory cue was used to change from one task period to another during the measurements. The total number of correct words generated during VFT was used as a measure of task performance.

2.2.2. Tower of Hanoi

This test consists of three or four disks of different sizes slotted onto three pegs. The subjects are given a stack of some disks, initially stacked in decreasing size on one of the three

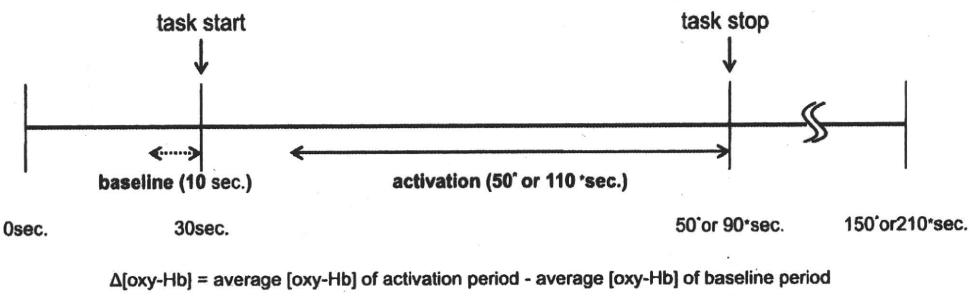

Fig. 1. Design for the sequence of five tasks with letter and category versions of the Verbal Fluency Test *, Tower of Hanoi *, Sternberg's Task ⋆ and Stroop Task ⋆. Subjects performed 150* s. or 210 ⋆ s. prefrontal tasks consisting of 30 s. pre-task period before the activation task, 60* s. or 120 ⋆ s. activation period, and 60 s. post-task period after each task. Data were sampled for the 10 s. as baseline data and for 50 * s. or 110 ⋆ s. just 10 s. after the activation task started as activation data. The difference of the average levels between activation condition and baseline was defined as the size of activation (Δ[oxy-Hb]). See text for details.

pegs. The objective is to transfer the entire tower to one of the other pegs, replicating the original stack by moving only one disk at a time and never a larger disk onto a smaller disk. The subjects are required to complete the task in as few moves as possible. The score is represented by the number of correct moves employed to transfer the entire stack (Gras-Vincendon et al., 1994). Before the recording, the subjects were sufficiently trained to perform this TOH task with three disks. The four-disk version of TOH was employed during NIRS measurement. For the pre- and post-task baseline periods, the participants were instructed to move one disk from one of the other pegs from side to side repeatedly. This was intended to correct the data during the TOH for activation due to manual movement. During the 60-s recording periods, subjects were instructed to complete the TOH task in as few moves as possible. The subjects were instructed by an auditory cue at the start and end of the task. The score of correct moves employed during TOH was used as a measure of task performance.

2.2.3. Sternberg's task

For the pre- and post-task baseline periods, of the SBT, subjects were asked to look at a point of fixation on a 15in. monitor connected to a desktop PC placed about 1 m away from the subject. During the 120-s recording periods, the subjects performed a modified Sternberg's memory task (Sternberg, 1966) which comprised 8 trials. Each trial is as follows: a set of five different numbers is presented for 2 s; then 3 s later a series of 3 single numbers are presented for 0.8 s. The subjects were requested to answer 'yes' or 'no' if the number was included or not in the previous set. The next trial commenced 2 s later. Trial types were fixed. The subjects were instructed visually by a cue at the start and end of the task. The number of correct answer was used as a measure of task performance.

2.2.4. Stroop task part III (Chinese character version)

The Chinese character version of the Stroop Task was used (Stroop, 1935; modified according to Zysset et al., 2001; Kato, 2001). In our test, each Chinese character has the semantic value of a color. For the pre- and post-task baseline periods of the SRT, the subjects were instructed to look at a point of fixation on a PC screen. During the 120-s recording periods, Chinese characters were displayed one by one on a screen set at subject eye-level and changed every 3 s with no interval. An experimental run consisted of 40 characters (20 incongruent and 20 congruent trials) in random order. The subjects were asked to answer the color of the character printed in a color, but not the semantic meaning. Each character was randomly printed in the same color as its meaning or in a different color from its meaning. The subjects were instructed by a visual cue at the start and the end of the task. The number of correct answers was used as a measure of task performance.

2.3. NIRS measurement

NIRS measurements were conducted with a two-channel NIRS system (NIRO 200, Hamamatsu Photonics, Japan). A pair of fiber ends (light emitter and detector) was attached to the surface of the scalp to record prefrontal activation while the subjects performed the tasks in a non-invasive and minimally restrictive way. The time needed for this attachment is usually less than 20 s with little demand on the subjects. The distance between emitter and detector ends was set at 4.0 cm to estimate penetration depth of approximately 2–3 cm (Villringer and Chance, 1997), that is, the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003a,b; Toronov et al., 2001). Then the light detector was symmetrically-placed at position Fp1 and Fp2 and the emitter was placed lateral to the corresponding detector on the Fp1-F7 and Fp2-F8 line according to the international 10–20 system used in electroencephalography. These positions correspond to the inferior frontal gyrus (Homan et al., 1987, Okamoto et al., 2004), which is part of the dorsolateral prefrontal cortex.

The NIRS machine measures changes in [oxy-Hb], [deoxy-Hb] and [total-Hb] using a reflectance mode with three different wavelengths (775, 810, 850 nm) of near-infrared light based on the modified Beer-Lambert law (Cope and Delpy, 1988). This technique primarily provides data on changes in chromophore concentrations from a discretionary base line. By assuming the differential path length factor to be 24 cm, the measure of changes in the chromophore concentration corresponds to A μmol/L. The time resolution of the NIRS measurements was every 1/6 s. The subjects sat on a chair with their eyes open throughout the measurements and were asked not to move their head, legs and any part of their body unrelated to the task to reduce artifacts. Changes in [oxy-Hb] were measured during the cognitive activation tasks.

2.4. Statistical analysis

2.4.1. Group comparison

In the majority of analyses, chi-squared or *t*-test were used for group comparison ($P<.05$). Symptom levels were measured with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Most of the patients were taking psychotropic medications at the time of the study. All the participants were native Japanese speakers. Premorbid intelligence quotient (IQ) was estimated using the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006).

2.4.2. Analysis of NIRS data

Since the change in [oxy-Hb] is the most sensitive indicator of rCBF changes (Hoshi et al., 2001), we evaluated the changes in [oxy-Hb] signals. In each subject, the average levels in [oxy-Hb] were calculated for both baseline and activation conditions for each task. The last 10-s of the pre-task period was defined as baseline and the 50- or 110-s of the active task period excluding the first 10-s intervals of the tasks, was defined as activation condition since stable elevation of [oxy-Hb] was usually observed several seconds after task initiation. The difference of the average levels between activation condition and baseline was defined as the size of activation (Δ[oxy-Hb]). Statistical analysis was conducted on the average of the bilateral Δ[oxy-Hb]s because Δ[oxy-Hb]s in both the right and left channels were highly correlated during the same task.

2.4.3. Linear discriminant analysis, a.k.a. LDA

The data were analyzed using SPSS for Windows version 12.0 (SPSS Japan Inc., Tokyo, Japan). In the first experiment, stepwise discriminant analyses using the Wilks' lambda method were performed to distinguish schizophrenia patients from healthy controls in the first group. The criterion for inclusion/exclusion of *P* value was 0.05.

Data in 10 variables was obtained as candidate independent variables; 5 measures for the performance of each task, and 5 averaged measures of Δ[oxy-Hb] during these tasks from the left and right sides of the prefrontal areas. To verify whether the NIRS measurements could contribute to discriminate between schizophrenia patients and healthy control, we decided to investigate three combinations: task performance only (5 variables), Δ[oxy-Hb] only (5 variables) and task performance plus Δ[oxy-Hb] (10 variables). In the second experiment, we used LDA to test the validity of the discriminant functions derived from the original study prospectively in the second group.

3. Results

3.1. Group comparison

Demographic and clinical characteristics of the study groups and group comparisons are displayed in Table 1. There was no significant difference between schizophrenia patients and healthy subjects in the first or second groups apart from educational year (*t*-test; $P=.001$) and JART (*t*-test; $P=.049$) in the first group. No significant correlation between educational year and the each task performance or each NIRS measurement was found in the first and second groups. There was a significant correlation between JART and the SBT performance of healthy subjects ($r=0.392$, $P=.032$) and patients ($r=0.597$, $P=.001$) in the first group, but no significant correlation in the second group.

Comparisons of frontal task performances and NIRS measurements between schizophrenia patients and healthy subjects are displayed in Table 2. Schizophrenia patients indicated significantly poor task performances compared to healthy subjects for all five tasks in the first group and for the VFT letter, VFT category and TOH in the second group. Likewise, schizophrenia patients showed lower [oxy-Hb] increases compared to controls during the VFT letter, VFT category, TOH and SBT in the first group and during the VFT letter, VFT category and TOH in the second group.

As for the association of drugs with task performances and NIRS measurements, there was a significant correlation between chlorpromazine equivalent (CPZeq) and performance of SRT ($r=-0.387$, $P=.035$), however, no significant correlation between CPZeq and the other task performances or each NIRS measurement was found in the first group. No significant

Table 2
Comparisons in frontal tasks and NIRS measurements between patients with schizophrenia and controls.

a. First group							
	Schizophrenia	Control	*df*	*t*	*P* value	C.C.	Effect size
	Mean (SD)	Mean (SD)				(%)	(d)
Task performance							
VFT letter	13 (3.9)	17.4 (3.8)	58	4.38	<.001	71.7	0.988
VFT category	23.7 (5.0)	28.9 (4.6)	57.5	4.22	<.001	73.3	0.962
TOH4	6.1 (3.1)	11 (3.6)	56.8	5.65	<.001	73.3	1.181
Sternberg	20.8 (2.8)	22.6 (1.7)	48.8	2.91	.005	66.7	0.707
Stroop	37.8 (4.0)	39.6 (0.67)	30.6	2.42	<.001	61.7	0.601
⊿[Oxy-Hb] (μmol/L)							
VFTletter	0.69 (0.86)	1.56 (1.01)	56.7	3.62	.001	70	0.851
VFTcategory	0.46 (0.68)	1.07 (0.85)	55.3	3.08	.003	70	0.744
TOH4	0.78 (0.78)	1.77 (1.18)	50.2	3.86	<.001	73.3	0.897
Sternberg	0.31 (0.72)	0.80 (0.87)	56	2.37	.021	66.7	0.589
Stroop	0.30 (0.87)	0.41 (0.95)	58	0.5	.621	50	0.129
b. Second group							
	Schizophrenia	Control	*df*	*t*	*P* value	C.C.	Effect size
	Mean (SD)	Mean (SD)				(%)	(d)
Task performance							
VFT letter	14.0 (4.7)	17.5 (4.8)	58	2.84	.006	65	0.692
VFT category	22.1 (5.9)	28.1 (4.4)	53.8	4.41	<.001	71.7	0.993
TOH4	9.7 (5.9)	13.9 (6.5)	57.4	2.63	.011	60	0.646
Sternberg	21.1 (3.5)	22.4 (2.0)	58	1.67	.102	60	0.425
Stroop	38.1 (3.5)	39.1 (2.9)	58	1.2	.237	60	0.307
⊿[Oxy-Hb] (μmol/L)							
VFTletter	0.15 (0.57)	0.73 (0.78)	52.9	3.28	.002	61.7	0.784
VFTcategory	0.34 (0.62)	0.82 (0.82)	54	2.56	.013	61.7	0.633
TOH4	0.56 (0.43)	1.17 (0.79)	45	3.73	<.001	63.3	0.873
Sternberg	−0.12(0.79)	0.36 (1.1)	58	1.98	.053	45	0.499
Stroop	−0.02(0.77)	0.27 (0.91)	58	1.33	.188	51.7	0.342

Abbreviation: C.C., correct classification.

correlation between CPZeq and the each task performance or each NIRS measurement was found in the second group. For anxiolytics, there was no significant difference in task performances and NIRS measurements between administered versus non-administered subjects in the first group, except for the VFT category task performance ($t=2.481$, $P=.019$) where the patients that received anxiolytics showed a significantly lower score than those who didn't.

3.2. Linear discriminant analysis, a.k.a. LDA

3.2.1. Analysis of the task performances

All five tasks performance of VFT letter, VFT category, TOH, SBT and SRT was analyzed using a stepwise discriminant analysis procedure, which included performance of TOH, VFT letter and SBT as independent variables successively. This order of inclusion meant a higher contribution to the discrimination analysis of the diagnostic groups. These three variables correctly classified 83.3% of the first group subjects with a sensitivity of 80% and a specificity of 86.7% (i.e., 24 of the 30 schizophrenia patients and 26 of the 30 control subjects, respectively) (Wilks' $\lambda=0.499$, $P<.001$). As a prospective validation, the linear discriminant function derived from the first group was then used to classify data from the second group of subjects. In these subjects, 63.3% (i.e., 14 of the 30 schizophrenia patients and 24 of the 30 control subjects, respectively) were correctly classified, with a sensitivity of 46.7% and a specificity of 80% (Fig. 2).

3.2.2. NIRS measurements

Five Δ[oxy-Hb] activation measurements during the VFT letter, VFT category, TOH, SBT and SRT tasks were analyzed using a stepwise discriminant analysis procedure, which included Δ[oxy-Hb] of TOH, VFT letter and VFT category as independent variables successively. This order of inclusion meant a higher contribution to the discrimination analysis of the diagnostic groups. These three variables correctly classified 78.3% in the first group subjects with a sensitivity of 80% and a specificity of 76.7% (i.e., 24 of the 30 schizophrenia patients and 23 of the 30 control subjects, respectively) (Wilks' $\lambda=0.711$, $P<.001$). As a prospective validation, the linear discriminant function derived from the first group was used to classify data from the second group of subjects. In these subjects, 65% (i.e., 29 of the 30 schizophrenia patients and 10 of the 30 control subjects, respectively) were correctly classified, with a sensitivity of 96.7% and a specificity of 33.3% (Fig. 2).

3.2.3. Task performances plus NIRS measurements

Performances on all five tasks and Δ[oxy-Hb] measurements during the VFT letter, VFT category, TOH, SBT and SRT tasks were analyzed using a stepwise discriminant analysis procedure, which successively included task performance of TOH and VFT letter, Δ[oxy-Hb] of VFT letter and task performance of VFT category. This order of inclusion meant a higher contribution to the discrimination analysis of the diagnostic groups. These four variables correctly classified 88.3% in the first group, with a sensitivity of 80% and a

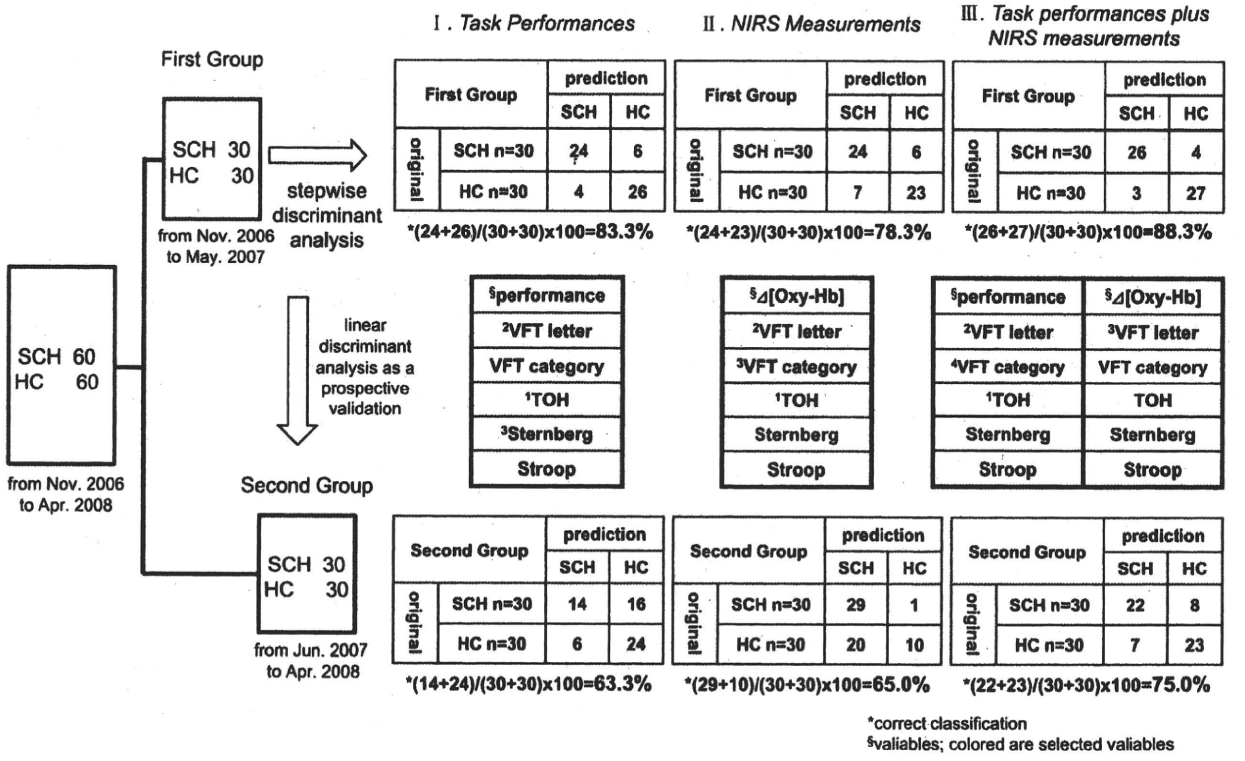

Fig. 2. Results.

Table 3
Recent studies for discriminant analysis in schizophrenia and non-patients with schizophrenia.

Article	Sample size	Variation study	Measure	Discrimination rate or sensitivity and specificity[a]
Physiological measures				
Kojima et al.	SCH = 145 HC = 124 Depression = 116	NA	Number of eye fixation Responsive search score	89.0% sensitivity 86.7% specificity
Matsushima et al.	SCH = 30 Non-SCH = 70[b]	SCH = 30 Non-SCH[a] = 70	Exploratory eye movement	76.7% sensitivity 81.4% specificity
Morihisa et al.	SCH = 25 HC = 11	NA	Brain electrical activity mapping	95.0%
Neuropsychological batteries				
Arango et al.	SCH = 85 HC = 36	*NA*	Neuropsychological test battery composed of Category Fluency, Trail Making Test, Neurological Evaluation Scale	81.8%
Leontieva et al.	SCH = 62 HC = 80	NA	Pictogram test composed of Attribute Index, Geometric Index and Concrete Index.	91.0%
Midorikawa et al.	SCH = 27 HC = 49	NA	Finger movement test, pegboard, general memory, Attention and concentration, delayed recall, Full scale IQ, Wisconsin Card Sorting Test	96.1%
Functional brain imaging				
Levy et al.	SCH = 12 HC = 11	NA	Positron emission tomography, visual task	82–92%
Structural brain imaging				
Davatzikos et al.	SCH = 69 HC = 79	NA	Magnetic resonance imaging (MRI), Gray matter, white matter, and ventricular cerebrospinal fluid volumes	81.1%
Kawasaki et al.	SCH = 30 HC = 30	SCH = 16 HC = 16	MRI, gray matter	90%
Yoon et al.	SCH = 53 HC = 52	NA	MRI, cortical thickness of each lobe	88.8–93.6%

Abbreviations: SCH, schizophrenia; HC, healthy control; NA, not applicable.
[a] Data reflect discrimination rate unless otherwise stated.
[b] Consisted of 10 each of patients with depression, methamphetamine psychosis, alcohol psychosis, anxiety disorder, temporal lobe epilepsy, frontal lobe lesions as well as healthy normal controls.

specificity of 90% (i.e., 26 of the 30 schizophrenia patients and 27 of the 30 control subjects, respectively) (Wilks' $\lambda = 0.432$, $P < .001$). As a prospective validation, the linear discriminant function derived from the first group was used to classify data from the second group of subjects. In these subjects, 75.0% (i.e., 22 of the 30 schizophrenia patients and 23 of the 30 control subjects, respectively) were correctly classified, with a sensitivity of 73.3% and a specificity of 76.7%. We found no significant characteristically or demographical difference between patients who were correctly classified and those who were not, in the first and second group (Fig. 2).

4. Discussion

4.1. Discriminant analysis in schizophrenia patients and healthy subjects

The present study investigated Δ[oxy-Hb] during performance of five kinds of cognitive tasks which involve activation of the prefrontal cortex, namely VFT letter, VFT category, TOH, SBT and SRT, in two groups of patients with schizophrenia and healthy controls. The discriminant analysis with applicable variables showed that task performance variables alone or NIRS Δ[oxy-Hb] variables alone differentiated schizophrenia patients from healthy subjects in the first group but not in the second group. To elucidate such discrepancy in discrimination power of task performance or NIRS alone, we compared clinical characteristics and demographic data between the first patient group and the second group, and examine the effects of these differences on the results of discriminant analysis. The comparison showed significantly more outpatients (chi-square test, $P = .039$) and more patients receiving anxiolytics (chi-square test, $P = .002$) were present in the second group. To assess whether these variables explained the difference in the discrimination of diagnostic groups between the first and second groups, we compared task performances and NIRS measurements between inpatients and outpatients and those medicated with anxiolytics and those not. In the first group, inpatients showed a significantly larger increase in the NIRS measurement using SBT than outpatients ($t = 2.267$, $P = .031$), and patients not taking anxiolytics showed a significantly higher VFT category performance than those taking anxiolytics ($t = 2.481$, $P = .019$). There was no significant difference in all other variables in the first or second groups. It is therefore unlikely that anxiolytic medication or outpatient/inpatient status account for the difference in discrimination of diagnostic groups between the first and second groups, since the stepwise method of linear discriminant analyses of task performance or NIRS alone included neither VFT category performance correlated with anxiolytic use nor NIRS measurement using SBT correlated with outpatient/inpatient status. The explanation for this difference is therefore unknown.

Higher accuracy of discrimination was demonstrated in both first and second groups by the use of both task performance and NIRS variables. In this analysis, the significant independent variables were VFT letter (NIRS [oxy-Hb]), TOH, VFT letter and VFT category (performance). These results suggest that the combination of NIRS measurements and task performances as biological markers is more desirable for clinical application than NIRS or task performances alone.

The use of biological markers as potential diagnostic criteria depends on their ability to discriminate between patients with schizophrenia and non-patients with schizophrenia in a sensitive and specific way. Previous studies have investigated discrimination of patients with schizophrenia from non-patients with schizophrenia using methods such as physiological measures, cognitive batteries, functional and structural brain imaging (Table 3). Most of these studies have demonstrated higher than 80% sensitivity and specificity. However, only two studies, Kawasaki et al. (2007) and Matsushima et al. (1998), have investigated prospective validation. In the present study we have demonstrated prospective validation and have shown that using a combination of NIRS measurements and certain cognitive tasks provides the best classification rate. This suggests that combining tools from multiple fields will allow the development of better biological marker, possibly reflecting the pleiotropic or multifaceted aspects of schizophrenia. Indeed, while we have demonstrated that the combination of Δ[oxy-Hb] and task performance yielded acceptable results in the prospective validation, further studies could utilize simultaneous evaluation of additional disease characteristics including structural and functional brain imaging, physiological measurements, biochemical examination, neuropsychological batteries as well as psychopathology. This should provide even clearer diagnostic discrimination by taking into account the varied bio-psycho-social background of each schizophrenia case. NIRS represents an excellent physiological tool in this aim due to its advantages in efficiency, inspection time and limited invasiveness.

4.2. Limitations

A few limitations of the present study must be taken into account. Firstly, we could not thoroughly rule out the effect of antipsychotic medication taken by patients on prefrontal activation measures, performances of employed tasks and the results of linear discriminant analyses. However, evidence suggests that antipsychotics do not significantly affect prefrontal activation (Goldberg and Weinberger, 1996) or even show slight cognitive benefits from newer antipsychotic drugs (Bilder et al., 2002). In the present study, there was significant correlation between CPZeq and performance of SRT in the first group. No significant correlation was found between CPZeq and other task performances or NIRS measurements in either group. Therefore, we guessed that antipsychotic medications did not affect the results of linear discriminant analyses since the performance of SRT was excluded by stepwise method and no correlation was found between anitpsychotics and each NIRS measurement.

Secondly, since this study included relatively chronic patients with schizophrenia, it is difficult to address the specificity of the present study. Further studies that include different sub-groups, for example first-episode schizophrenia patients, relatives of patients, populations at high-risk of developing schizophrenia, as well as bipolar disorder patients should be conducted to assess this specificity.

Thirdly, the two-channel NIRS system used in this study could not cover the entire brain surface but only the frontal region; hence we could not assess the contribution of other brain areas to executing the tasks employed in this study. Further studies using a multi-channel NIRS system may help elucidate this issue.

4.3. Conclusion

In summary, the findings of this study indicate that the combination of NIRS measurements and cognitive task performances were more effective than NIRS or task performances alone for differentiating patients with schizophrenia from healthy subjects in prospective validation. The independent variables contributing to the differentiation were Δ[oxy-Hb] of VFT letter and task performances of TOH, VFT letter and VFT category. Our findings suggest that further NIRS studies for clinical application to schizophrenia are warranted.

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Contributors

M.A. and M.I. designed the study and wrote the protocol and undertook the statistical analysis. M.A., K.I., R.K., T.N., M.F., K.O., Y.Y. and H.T. conducted data acquisition. M.A. and M.I. analyzed data. M.A. wrote the first draft of the manuscript. L.C. contributed to the editing of the final manuscript. All authors revised it critically for important intellectual content and have approved the final manuscript. M.I., R.I., R.H., H.K., and M.T. supervised the entire project.

Conflict of interest

None.

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研究と報告

著明な前頭葉症状と失語症状を呈した機能性精神病の1例*

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初老期に不安焦燥の強いうつ症状で発症し，緊張病症状に加え，模倣行動，利用行動，被影響性の亢進，考え不精などの前頭葉症状と失語症状を呈した機能性精神病の1例を経験した。脳血流SPECT検査で左優位の両側視床，基底核の血流低下を認めたが，頭部MRI検査，脳波，髄液，内分泌学的検査などでは異常を認めなかった。修正型電気けいれん療法により，前頭葉症状，失語症状は消失し，また抑うつ気分，意欲ともに改善した。本例では前頭側頭型認知症においてもみられる症候が特徴的であったが，自己の精神状態に対する心的葛藤を認めたことが異なっており，鑑別に有用と考えられた。

Key words

Functional psychosis, FTD, ECT

はじめに

認知症を来す疾患では，さまざまな認知機能障害に，精神症状や行動障害を伴うことが多いが，時に，精神症状や行動障害が認知機能障害よりも先行し，精神疾患との鑑別が困難な場合がある。たとえば，通常，記憶障害を初発症状とするアルツハイマー病が，妄想や抑うつなど精神症状で発症することがあり[3]，この場合，妄想性障害やうつ病などとの鑑別が難しい。レビー小体型認知症も初期に，幻視，抑うつ，不安，心気症状などの精神症状やレム睡眠行動異常が先行することが知られている[15]。しかし，全経過を通じて精神症状および行動障害が前景に立つ最も代表的な認知症疾患は，前頭側頭型認知症で，アルコール依存症，人格障害，うつ病などが前頭側頭型認知症と誤診されたり[2]，逆に前頭側頭型認知症が統合失調症と誤診されたりすることがある[15]。

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* A Case of Functional Psychosis with Marked Frontal Symptoms and Aphasia

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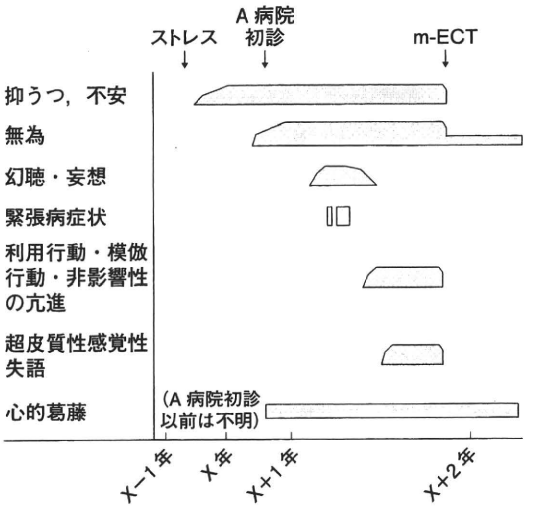

図1　症状経過

前頭側頭型認知症は，大脳の前頭葉，側頭葉前方部を中心に変性を来し，人格変化や行動障害を主徴とする変性性認知症を包括する疾患概念である[12]。The Lund and Manchester Groups により病理学的には前頭葉変性型，ピック型，運動ニューロン病型の3型に下位分類されている[16]。特に前頭葉変性型は，positron emission computed tomography (PET) や single photon emission computed tomography (SPECT) などの脳機能画像検査では，前頭葉を中心とした脳血流，あるいは脳代謝の低下が認められるものの，magnetic resonance imaging (MRI)，CT などの形態画像検査では明らかな脳萎縮を認めないため精神疾患との鑑別が問題になりやすい。

今回，我々は，模倣行動，利用行動，被影響性の亢進，考え不精などの著明な前頭葉症状と失語症状を呈したが，形態画像および機能画像で前頭葉の萎縮，血流低下を認めず，修正型電気けいれん療法 modified-electroconvulsive therapy (m-ECT) により前頭葉症状と失語症状が消失した機能性精神病の1例を経験したので報告する。

症例 (図1)

〈**症例**〉　57歳，右利き，男性。

家族歴　特記すべきことなし。

既往歴　高血圧症，胆嚢結石症。

嗜好歴　アルコール飲酒歴なし，喫煙歴なし。

生活歴　3人同胞の長男。出生，生育に特に問題はなかった。高校卒業後，運送関係の仕事に約40年間従事した。家庭では子煩悩な父親であり，ボランティアで野球の審判をするなど地域活動にも積極的に参加していた。

現病歴　X−1年，勤務していた会社が他社に吸収合併された。多くの同僚が解雇され，会社の方針が大きく変わったため，ストレスを感じるようになった。X年1月から食欲低下，不眠が出現した。同年4月に心窩部痛が出現し，総合病院内科を受診，胆嚢結石症と診断され，腹腔鏡下胆嚢摘出術を受けた。術後も不眠，食欲低下が悪化し，抑うつ気分，意欲低下も加わったため，近くの精神科クリニックを受診した。不安，焦燥もみられ，不安神経症と診断され，sulpiride，alprazolam，chlorpromazine などを処方されたが改善しなかった。X年8月頃には1日中家でテレビを眺めて過ごし，食事も家族のいる夕方に少し摂取するだけで，歯磨きや入浴もしなくなった。妻がA病院精神科への転医を希望し，X年9月4日，受診となった。

初診時現症　服装はだらしなく，表情は乏しく抑うつ的だった。質問に対してはうつむき加減でぼそぼそと短く答えた。困っていることは何かと問うと，「人間関係のストレスで仕事に復帰できないこと」と答えた。また「薬はどうせ効かないから，通院もしたくない」と悲観的で投げやりな発言がみられた。病歴から，抑うつ気分が持続しており，歯磨きや入浴もしないなど意欲低下が顕著であること，不眠，食欲低下を認めていること，診察場面でも制止が強いことから，診断はうつ病と考えられた。不安，焦燥はうつ病に伴って出現していると考えた。

初診後からA病院入院までの経過　うつ症状に加え，冷蔵庫を開けたまま，生の野菜をそのまま食べ散らかす，砂糖をばら撒くといった異常行動がみられた。落ち着かず立ったまま食事をするなど，徐々に焦燥が強くなった。情動不安定で希

死念慮を訴えることもあった。1日だけ体が動かなくなり，翌日には再び動けるようになるといったカタレプシーを疑わせる症状を一時的に認めた。「左側から人の声が聞こえます」と幻聴の訴え，「殺しにきます」などの被害妄想もみられた。混乱が強く，自らの症状を詳細に語ることはできなかったが，思いつめたような硬い表情が継続してみられており，自己の精神状態への心的葛藤が感じられた。

X+1年5月頃から，前頭葉症状を認めるようになった。甘いものを好むといった食行動変化，ダイニングテーブルに置いてある新聞をめくって自室に戻ることを繰り返すという常同行動，棚に置いてある漫画本のタイトルを読み上げずにおれないといった被影響性の亢進を認め，診察場面では質問に対し，早口で，「よくわかりません」と答えるか，「はい」「そうです」などと短く即答するなど考え不精を認めた。

薬物治療としては，初診時からparoxetine開始し，40 mg/日まで使用したが効果がみられず中止した。他の薬物も同様に効果がみられず，milnacipranは50 mg/日で激越，amoxapineは100 mg/日で尿閉，risperidoneは2 mg/日で安静時振戦がみられたため中止した。常に見守りが必要な状態となったため，5月8日，A病院に入院となった。

A病院入院中の経過　入院後，1日中ベッド上で無為に過ごし，他患者との交流はなかった。食事，排泄などは介助が必要であったが，拒絶することが多かった。X+1年6月10日，前傾姿勢で閉眼して立ったまま動かなくなり，呼びかけても応じないなど疎通が図れないといった緊張病性昏迷を呈した。6月11日には「お父さん，お父さん，おじいちゃん…」と早口で繰り返し，扉を激しくたたくなど興奮状態となり，男性看護師の股間に手を伸ばしたり，体をひねったりするなど過度の運動活動性を認めた。Diazepam筋注，haloperidol筋注などで鎮静を図ったが，身体拘束が必要な時期もあった。6月12日，問いかけても反応しない昏迷状態と「○○ちゃん，○○ちゃん」などと早口で繰り返し叫び続け，歩き回るなど過度の運動活動性が交互にみられた。6月14日にはこれらの症状は改善したが，再びベッド上で無為に過ごすようになった。入院中も，入院前と同様，一貫して表情は硬く，思い悩んでいるようであった。

被影響性の亢進は継続しており，机の上に置かれたホッチキスを見ると，手にとって何回もカチカチと空打し続けるなどの利用行動や，主治医が頭をかいたり，手を上げたりすると，やめるように指示しても真似てしまうなど模倣行動がみられた。考え不精も継続していた。また，この時期より喚語困難，了解障害がみられたため，前頭側頭型認知症を鑑別するために，X+1年8月27日B大学附属病院神経精神科に転院した。

B大学附属病院神経精神科での精査

①精神行動学的所見　診察場面では，硬い表情でうつむいており，あまり視線を合わせようとしなかった。考え不精に加え，「声が出ないんです」「自殺します」を繰り返して言うなど滞続言語を認めた。被害妄想は継続していたが，幻聴は明らかでなかった。不安，焦燥が著しく，抑うつ気分，意欲低下もみられた。病棟内での生活態度や生活自立度はA病院入院時と同様であった。

②神経学的所見　仮面様顔貌で声量は小さかったが，構音障害は認めなかった。頸部，両肘関節，両膝関節にparatonic rigidityを認めた。前傾姿勢，小歩で，歩行時の両上肢の振り幅が低下していた。以上のパーキンソン症状以外には，特記すべき異常所見を認めなかった。

③神経心理学的所見　注意障害，保続を認めた。患者の目の前に診察医の腕時計を置くと，勝手に自分の腕にはめてしまうといった利用行動が何度も観察され，A病院で認められた模倣行動も続いていた。

発話は流暢で，アナルトリーを認めなかった。自発話で喚語困難が目立ち，ボールペン，電灯，コンセントが呼称できないなど呼称障害を認めた。また，ボールペンを万年筆，体温計を体重計というなど語性錯語(意味性錯語が多かった)がみ

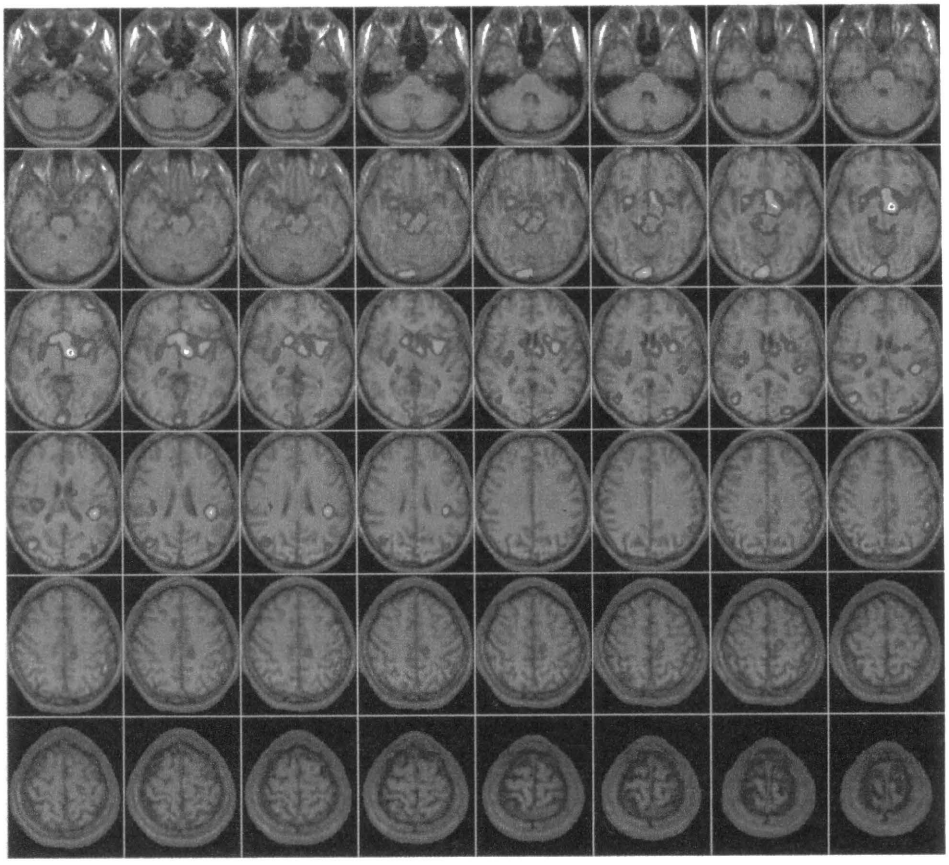

図2　ECD-SPECT eZIS解析による脳血流所見

られた。語頭音効果を認め，複数の物品から教示されたものを指示することは可能であった。Mini mental state examination (MMSE) の3段階命令，「時計と万年筆を入れかえる」「万年筆で時計にさわる」などの物品操作は不可であり，了解障害を認めた。復唱は保たれ，16音節の長文でも可能だった。失語型は，超皮質性感覚失語と考えられた。その他，double pentagon，立方体の模写ができないなど構成障害を認めた。主治医の顔，名前は覚えており記憶障害は目立たなかった。MMSEは8/30と著しく低下を認めたが，考え不精による得点低下も加味されていると考えられた。

④検査所見　血液，髄液一般検査では特記すべき異常所見を認めなかった。髄液中T-Tau蛋白および14-3-3蛋白の増加は認めなかった。プリオン蛋白遺伝子解析はcodon 129 Met/Met，codon 219 Glu/Lysと正常多型であった。脳波検査は，基礎波は10 Hz，20～50 μVで後頭葉優位に出現し，徐波の混入は目立たなかった。頭部MRIで明らかな虚血性病変，萎縮などは認めなかった。脳血流^{99}mTc-ethyl-cysteinate dimer SPECTを施行し，そのデータをeasy Z-score imaging system (eZIS) で解析した(図2)。eZISの解析の結果Z score 2以上の血流低下を認めた領域を抽出し，その脳部位をvoxel based stereotactic extraction estimationで同定した。その結果，おのおのの関心領域内のZ score 2以上の範囲の割合が50%以上であった領域は，左尾状核頭部(57.89%)，右尾状核頭部(69.17%)，左淡蒼球内節(100.00%)，左淡蒼球外節(83.59%)，左被殻(82.66%)，右被殻(66.12%)，左視床下部