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ORIGINAL PAPER

Masahiro Suzuki · Sakae Takahashi · Eisuke Matsushima · Masahiko Tsunoda · Masayoshi Kurachi · Takashi Okada · Takuji Hayashi · Yohei Ishii · Kiichiro Morita · Hisao Maeda · Seiji Katayama · Ryuzou Kawahara · Tatsui Otsuka · Yoshio Hirayasu · Mizuho Sekine · Yoshiro Okubo · Mai Motoshita · Katsuya Ohta · Makoto Uchiyama · Takuya Kojima

Exploratory eye movement dysfunction as a discriminator for schizophrenia

A large sample study using a newly developed digital computerized system

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Abstract In our previous studies, we identified that exploratory eye movement (EEM) dysfunction appears to be specific to schizophrenia. The availability of a biological marker specific to schizophrenia would be useful for clinical diagnosis of schizophrenia. Consequently, we performed the discriminant analysis between schizophrenics and non-schizophrenics on a large sample using the EEM test data and examined an application of the EEM for clinical diagnosis of schizophrenia. EEM performances were recorded in 251 schizophrenics and 389 non-schizophrenics (111 patients with mood disorders, 28 patients with neurotic disorders and 250 normal controls). The patients were recruited from eight university hospitals and three affiliated hospitals. For this study with a large sample, we developed a new digital computerized version of the EEM test, which automatically handled large amounts of data. We measured four parameters: number of eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL) and responsive search score (RSS). These parameters of schizophrenics differed significantly from those of the other three groups.

M. Suzuki · S. Takahashi (✉) · M. Uchiyama · T. Kojima
Dept. of Neuropsychiatry
Nihon University School of Medicine
30-1 Oyaguchi-Kamicho
Itabashi-ku, Tokyo 173-8610, Japan
Tel.: +81-3/3972-8111
Fax: +81-3/3974-2920
E-Mail: sakae@med.nihon-u.ac.jp

E. Matsushima · M. Motoshita · K. Ohta
Section of Liaison Psychiatry and Palliative Medicine
Graduate School of Tokyo Medical and Dental University
1-5-45 Yushima
Bunkyo-ku, Tokyo 113-8519, Japan

M. Tsunoda · M. Kurachi
Dept. of Neuropsychiatry
Graduate School of Medicine and Pharmaceutical Sciences
University of Toyama
2630 Sugitani
Toyama 930-0194, Japan

T. Okada · T. Hayashi
Dept. of Neuropsychiatry
Graduate School of Medicine, Kyoto University
54 Kawahara-cho, Shogoin, Sakyo-ku
Kyoto 606-8507, Japan

Y. Ishii · K. Morita
Cognitive and Molecular Research Institute of Brain Diseases
Kurume University
67 Asahi-machi
Kurume 830-0011, Japan

H. Maeda
Wakahisa Hospital
Wakahisa 5-3-1
Minami-ku, Fukuoka 815-0042, Japan

S. Katayama
Faculty of Medicine, Dept. of Neuropsychiatry
Tottori University
36-1 Nishi-machi
Yonago, Tottori 683-8504, Japan

R. Kawahara
Midorigaoka Mental Clinic
2793-1 Okazaki, Kushira-cho
Kanoya, Kagoshima 893-1603, Japan

T. Otsuka · Y. Hirayasu
Dept. of Psychiatry
Yokohama City University School of Medicine
3-9 Fukuura, Kanazawa-ku
Yokohama 236-0004, Japan

M. Sekine · Y. Okubo
Dept. of Neuropsychiatry
Nippon Medical School
1-1-5 Sendagi
Bunkyo-ku, Tokyo 113-8603, Japan

T. Kojima
Ohmiya-Kosei Hospital
1 Katayanagi, Minuma-ku
Saitama, Saitama 337-0024, Japan

EAPCN 850

The stepwise regression analysis selected the TESL and the RSS as the valid parameters for discriminating between schizophrenics and non-schizophrenics. In the discriminant analysis using the RSS and TESL as prediction parameters, 184 of the 251 clinically diagnosed schizophrenics were discriminated as having schizophrenia (sensitivity 73.3%); and 308 of the 389 clinically diagnosed non-schizophrenic subjects were discriminated as non-schizophrenics (specificity 79.2%). Based on our findings we believe that the EEM measures may be useful for the clinical diagnosis of schizophrenia.

Key words schizophrenia · exploratory eye movement (EEM) · biological marker · digital computerized system of the EEM test · discriminant analysis

Introduction

Clinical diagnosis of schizophrenia is based on patient interviews and observation of the patient's behavioral patterns. According to the interview and observation, schizophrenia is symptomatically characterized by hallucinations, delusions, disorganized thinking or negative symptoms, etc. These symptoms may be based on a neurobiological brain dysfunction associated specifically with schizophrenia. Therefore, in addition to the interview and observation of the patient, a biological marker related to the brain dysfunction of schizophrenia may also be useful in determining the clinical diagnosis of schizophrenia.

In order to find a biological marker of schizophrenia, many researchers have performed psychophysiological or cognitive neuroscience tests related to the potential brain dysfunction of schizophrenia [5, 40]. Disturbances of event related potentials (ERPs), P300 [4], P50 [35] and mismatch negativity (MMN) [6, 27], prepulse inhibition (PPI) [33, 44], saccadic and smooth pursuit eye movements [8, 11, 21, 37], and working memory [3] have been reported in schizophrenia. Moreover, abnormalities of P50, saccadic and pursuit eye movements, and working memory were utilized for endophenotypes of schizophrenia in genetic studies [1, 2, 7, 28]. Therefore, the above physiological or neuroscience defects may show promise as biological markers of schizophrenia.

We have studied eye movements while subjects freely viewed horizontal S-shaped figures. This method is called the exploratory eye movement (EEM) test. In most previous studies, only schizophrenics have revealed consistent disturbances of the EEM [16–20, 24, 25, 30, 43]. In addition, the parents of schizophrenics showed EEM dysfunctions [41]. Moreover, the EEM showed a significant linkage to chromosome 22q11 [42]. The chromosome 22q11 is one of the most interesting regions in the genetic etiology of schizophrenia [15]. Thus, in addition to the above physiological or neuroscience defects, EEM disturbance may also be a biological marker of schizophrenia.

Based on these findings, we have proposed that the EEM test may be useful as a biological marker for the clinical diagnosis of schizophrenia [19, 26]. Matsushima et al. [26] performed discriminant analysis between 30 schizophrenics and 70 non-schizophrenics using EEM data. They discriminated schizophrenics from non-schizophrenics with a sensitivity of approximately 75% and a specificity of approximately 80%. Kojima et al. [19] also tried to discriminate 145 schizophrenics from 116 depressed patients and 124 healthy controls using EEM data, and obtained a high rate of discrimination with both the sensitivity and specificity being over 80%. These results suggest that EEM may be useful for clinical diagnosis of schizophrenia; however, the sample size of these studies was not very large. Thus, replicated studies with larger samples were needed to confirm these findings. Nevertheless, since our prior method employed an offline analog system, we were not able to handle a large amount of data in our previous studies. For the present study, we developed a new digital computerized version of the EEM test. Using this system, we were able to automatically handle a large amount of data. Consequently, to confirm our previous findings [19, 26], we used a larger sample in the discriminant analysis between schizophrenics and non-schizophrenics using the EEM test data. According to results of the discriminant analysis, we examined an application of the EEM for the clinical diagnosis of schizophrenia in this study.

Methods

Subjects

We studied 251 schizophrenic patients, 111 patients with mood disorders, 28 patients with neurotic and stress related disorders and 250 normal controls. The patients were in/outpatients recruited from eight university hospitals and three affiliated hospitals. Diagnoses were made by experienced psychiatrists according to the ICD-10 criteria for research [45]. The control subjects were also recruited from the eight university hospitals and three affiliated hospitals. Most controls were employees of these hospitals. Table 1 shows the demographic characteristics of the subjects. There were significant differences between the groups in age, gender and duration of illness. Psychiatric patients who had a history of alcohol abuse or illicit substance abuse, or head injury were excluded from the study; also excluded were those with convulsive, neurologic or ophthalmologic disorders. Detailed subtypes of the patients are described in Table 2.

The clinical symptoms of the schizophrenic patients were assessed by the brief psychiatric rating scale (BPRS) [32], which yielded an average score of 41.5 ± 13.3. The clinical symptoms of the patients with mood disorders were assessed using the Hamilton depression rating scale (HAM-D) [10], for an average score of 12.1 ± 8.59. Of the 251 patients with schizophrenia, 249 received neuroleptic medication. The average daily dosage was expressed as a haloperidol equivalent [13] of 13.9 ± 10.7 mg. Of the 111 patients with mood disorders, 100 were taking antidepressant medication and an average daily dosage was expressed as an imipramine equivalent [13] of 107.7 ± 81.3 mg.

Table 1 Clinical and demographic characteristics of the subjects

Diagnosis	Schizophrenia	Mood disorder	Neurotic disorder	Controls
Subjects (*n*)	251	111	28	250
Age (years, mean ± SD)[a]	37.9 ± 11.3	44.3 ± 12.8	32.7 ± 10.3	37.1 ± 11.3
Gender (M/F)[b]	157/94	49/62	9/19	112/138
Duration of illness (years, mean ± SD)[c]	14.5 ± 13.1	5.9 ± 6.78	6.1 ± 6.6	

[a]ANOVA; F (3, 636) = 12.0, $P < 0.01$
[b]Chi-square test; Chi-square = 23.3, $df = 3$, $P < 0.01$
[c]ANOVA; $F(2, 387) = 25.6$, $P < 0.01$

Table 2 Subtypes of each patient group

ICD-10 diagnosis	*n* (%)
Schizophrenia	
Paranoid type	164 (65.3)
Hebephrenic type	40 (15.9)
Catatonic type	3 (1.2)
Undifferentiated types	13 (5.2)
Residual type	24 (9.6)
Simple type	4 (1.6)
Unspecified type	3 (1.2)
Mood disorder	
Bipolar disorder	13 (11.7)
Depressive disorder	97 (87.4)
Dysthymia	1 (0.9)
Neurotic and stress related disorder	
Panic disorder	13 (46.4)
Adjustment disorder	8 (28.6)
Others	7 (25.0)

The normal controls were healthy volunteers without physical, ophthalmologic, neurological or psychiatric disorders, and there was no family history of psychiatric disorders as distant as third degree relatives. This study was approved by the Ethics Committees of the eight universities. Written informed consent was obtained from all participants, after the procedures and possible risks of the study were fully explained.

Procedure

For this study, we developed a new digital eye-mark recording system (nac Image Technology, EMR-NS, Tokyo, Japan) (Fig. 1). In the white box, there was an eye camera that detected corneal reflection of infrared light to identify eye movements, and a 15-in. LCD monitor (1,024 × 768 pixels) to display target figures for the EEM tasks. This system automatically recorded the subjects' eye movements while he/she was viewing the figures on the LCD monitor.

The subject sat on a chair and a pair of goggles with a flexible band was fixed on his/her face. The face was positioned 425 mm from the LCD panel on which the target figures appeared. Three horizontal S-shaped figures (an original target figure and two figures slightly different from the original target figure) were individually displayed on the LCD monitor (Fig. 2). The figures were 845 pixels wide and 724 pixels high at a sight angle of 33°.

A standard test of EEM was performed. The method is briefly shown as follows:

1. Retention task

The subject was instructed to carefully view the figure for the purpose of drawing it later. The subject was then shown the original target figure (Fig. 2a) for 15 s. (the subject drew the original figure from memory at the end of the test).

Fig. 1 Digital eye-mark recording system (nac Image Technology, EMR-NS)

2. Comparison task

(a) The subject was instructed to compare a new figure with the original figure (Fig. 2a) and was then shown a figure slightly different from the original one, which had one bump in a different position (Fig. 2b), for 15 s.
(b) After 15 s had elapsed and with the figure still in view, the subject was asked whether it differed from the original figure and, if it did, how it differed.
(c) After the subject had replied and while the figure was still displayed, he/she was asked "Are there any other differences?".

#. The above 2a–2c were repeated with a figure without bumps (Fig. 2c).

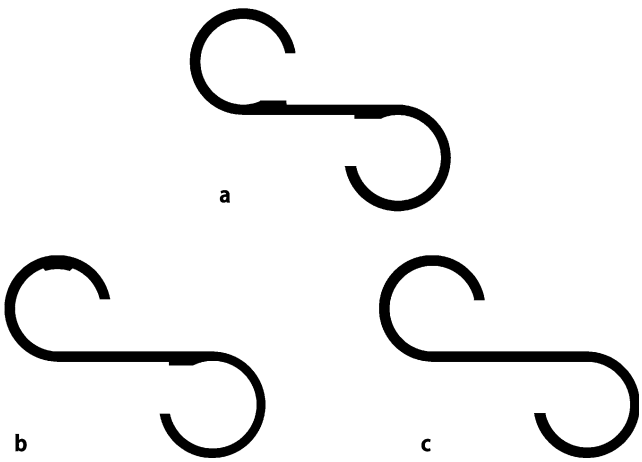

Fig. 2 The original target figure (**a**) and two figures slightly different from the target (**b**, **c**)

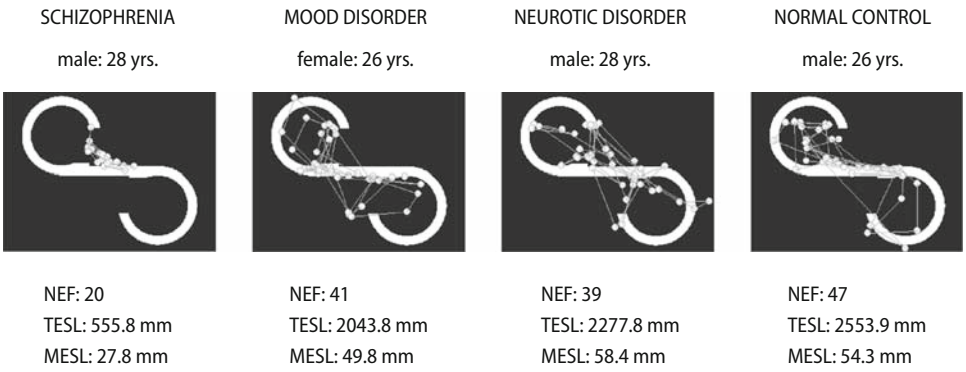

Fig. 3 The retention task, NEF, TESL and MESL in a schizophrenic patient, a mood disorder patient, a neurotic patient and a normal control

Table 3 Results of the ANCOVA [*F* (*df*) and *P*]

	Diagnosis	Gender	Diagnosis × gender	Age
Parameters of retention task				
NEF	34.61 (3, 631), $P < 0.0001$	1.56 (1, 631), $P = 0.21$	0.25 (3, 631), $P = 0.85$	0.45 (1, 631), $P = 0.49$
TESL	42.27 (3, 631), $P < 0.0001$	0.44 (1, 631), $P = 0.50$	0.19 (3, 631), $P = 0.89$	0.00 (1, 631), $P = 0.97$
MESL	22.64 (3, 631), $P < 0.0001$	0.19 (1, 631), $P = 0.65$	0.35 (3, 631), $P = 0.78$	1.52 (1, 631), $P = 0.21$
Parameter of comparison task				
RSS	60.77 (3, 631), $P < 0.0001$	0.33 (1, 631), $P = 0.56$	1.33 (3, 631), $P = 0.26$	0.30 (1, 631), $P = 0.58$

NEF number of eye fixations, *TESL* total eye scanning length, *MESL* mean scanning length, *RSS* responsive search scores

In the digital eye-mark recording system, the detected eye movements were automatically analyzed by a digital computerized EEM analyzer. As a result, four parameters emerged: number of eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL) and responsive search score (RSS). The NEF, TESL and MESL were based on data of eye movements that occurred during 15 s of the retention task. In the comparison task, the RSS was based on data of eye movements that occurred for 5 s immediately after the question: "Are there any other differences?". More detailed descriptions of the EEM test methods have been presented in our previous studies [16, 19].

Statistical analysis

As mentioned above, there were significant differences between the groups in the demographic data (age, gender and duration of illness; see Table 1). Thus, differences for each parameter (NEF, TESL, MESL or RSS) were tested by a two-way (diagnosis × gender) analysis covariance (ANCOVA) with age as a covariate. The duration of illness was not adopted as a covariate; this was based on the hypothesis that the duration of illness for different diseases was not essential for the group comparisons. For pairwise multiple comparisons, Bonferroni adjustment was used (SPSS manual). In order to discriminate between schizophrenics and non-schizophrenics, we performed the discriminant analysis between schizophrenics and non-schizophrenics with stepwise variable selection method using the above four parameters. Statistical significance was set at $P < 0.01$. All statistical analyses were performed using SPSS for Windows version 14.0.

Results

Group comparisons of the EEM test parameters

Parameters in the retention task

Figure 3 shows the representative examples of the eye scanning tracks of a schizophrenic patient, a mood disorder patient, a neurotic disorder patient and a healthy control for the retention task. The eye fixation points were less frequent, and the length of eye scanning was shorter in the schizophrenic patients than in other groups.

Table 3 shows the results of the ANCOVA. There was a significant main effect for diagnosis but not for gender or the interaction between diagnosis and gender (diagnosis × gender) on each retention task parameter (NEF, TESL or MESL). Age as the covariate was also not significant for any parameter. In the multiple comparisons, the NEF, TESL and MESL were significantly lower in the schizophrenic patients than in the other three groups. None of the parameters in the retention task showed statistically significant differences between the other three groups (Table 4, Fig. 4).

Responsive search score in the comparison task

The representative examples of the RSSs for a schizophrenic patient, a mood disorder patient, a neurotic disorder patient and a healthy control are shown in Fig. 5b. Figures that were slightly different from the original target figure were shown to the subjects. The top figures have a bump in the left upper part of the circles, but no bump on the left horizontal plane. The bottom figures have no bump. In the comparison task, the subjects explore the figure again and attempt to search for differences after the question, "Are there any other differences?" The normal control subject looked at six sections in the top figure and six sections in the bottom figure. Consequently,

Table 4 Comparison of eye movement parameters among groups

	Schizophrenia	Mood disorder	Neurotic disorder	Controls
Parameters of retention task				
NEF (mean ± SD)	26.49 ± 8.69	32.72 ± 7.85*	33.36 ± 7.70*	33.15 ± 6.99*
TESL (mm, mean ± SD)	1097.85 ± 533.54	1490.46 ± 492.86*	1599.90 ± 377.76*	1619.22 ± 546.64*
MESL (mm, mean ± SD)	40.39 ± 11.45	45.21 ± 10.55*	49.00 ± 9.17*	48.12 ± 9.72*
Parameter of comparison task				
RSS (mean ± SD)	6.36 ± 2.37	8.43 ± 2.23*	8.86 ± 2.32*	8.87 ± 1.95*

NEF number of eye fixations, *TESL* total eye scanning length, *MESL* mean scanning length, *RSS* responsive search scores
*$P < 0.01$ versus schizophrenia of Bonferroni

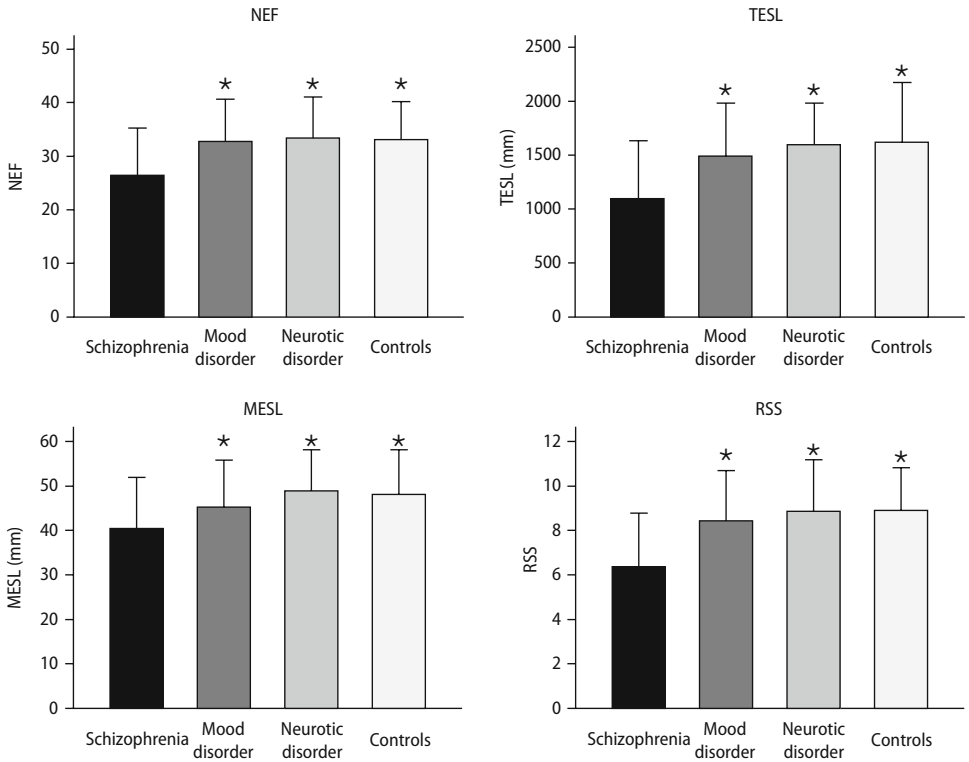

Fig. 4 The results of each parameter for schizophrenic patients, mood disorder patients, neurotic patients and normal controls
NEF number of eye fixations, *TESL* total eye scanning length, *MESL* mean scanning length, *RSS* responsive search scores
*$P < 0.01$ versus schizophrenia of Bonferroni

the RSS of the normal control was 12. Results for the mood disorder patient and the neurotic disorder patient were similar to the normal control. On the other hand, the schizophrenic patient looked at three sections of the top figure and three of the bottom. Thus, the RSS of the schizophrenic patient was six. The schizophrenic patient showed lower RSS than all other subjects.

There was a significant main effect for diagnosis but not for gender or the interaction between diagnosis and gender on the RSS by ANCOVA. Age as the covariate was also not significant (Table 3). In the multiple comparisons, the schizophrenic group had significantly lower RSS than all other groups. There were no significant differences between the patients with mood disorders, patients with neurotic disorders and healthy controls (Table 4, Fig. 4).

As shown in Table 1, there were significant differences between the groups for gender and age in the sample of this study. However, the two-way ANCOVA neither demonstrated significant main effects of gender as another factor of diagnosis nor gender by diagnosis interactions on all EEM test parameters. Moreover, group comparisons for all EEM parameters controlling for age as the covariate were significant. Therefore, this indicates that gender and age did not influence the group comparisons of the EEM parameters.

The EEM test and duration of illness

In our previous studies, we have not investigated the relationship between the EEM test and duration of illness in detail. Hence, we examined it in this study. We divided schizophrenic patients into three groups based on illness history (duration of illness: 1–5, 5–10 and >10 years), and compared the EEM parameters

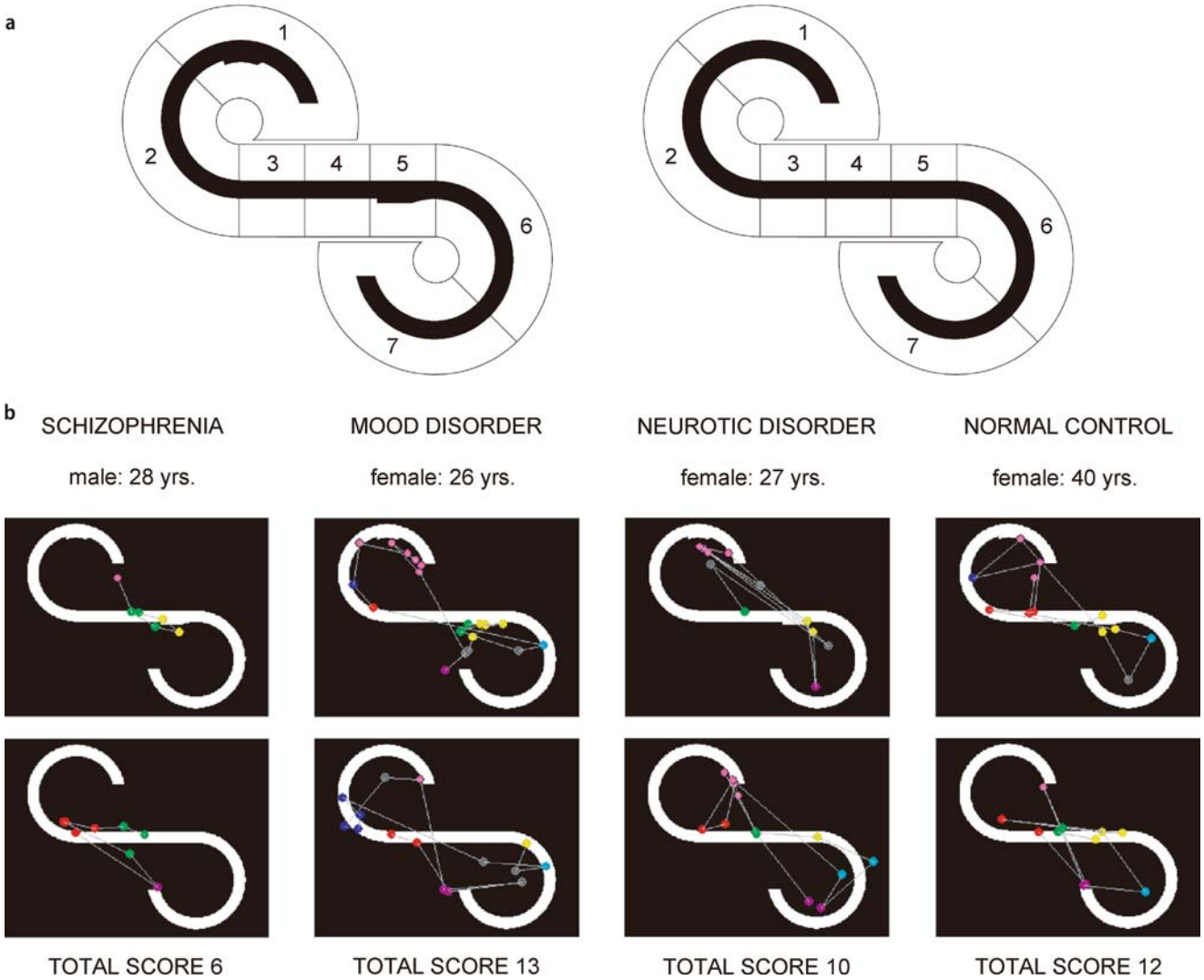

Fig. 5 **a** Seven sections for scoring the RSS. **b** The comparison task, RSS in a schizophrenic patient, a mood disorder patient, a neurotic patient and a normal control. When the RSS was scored, each horizontal S-shaped figure was divided into seven sections. If the eyes fixed on a section, the fixation points were highlighted by *unique colors*. For example, when the eyes fixed in fourth section, the fixation points were highlighted by green (see fourth section in **a** and *green* fixation points of schizophrenia in **b**). Fixation points highlighted by *gray* are out of the scoring area

between the three groups. As a result, ANOVA showed no significant main effect in any parameter (NEF: $P = 0.71$, TESL: $P = 0.65$, MESL: $P = 0.12$ and RSS: $P = 0.96$).

Discriminant analysis

In the discriminant analysis, TESL and RSS were selected as the valid parameters for discriminating between schizophrenics and non-schizophrenics. Using these as predictive parameters, we performed a discriminant analysis between schizophrenics and non-schizophrenics. As a result, we obtained the following discriminant formula: $D = 4.100 - (0.001 \times \text{TESL} + 0.332 \times \text{RSS})$. Utilizing this formula, we discriminated between 251 schizophrenics and 389 non-schizophrenics (111 patients with mood disorders, 28 patients with neurotic disorders and 250 normal controls). Consequently, 184 of the 251 clinically diagnosed schizophrenics were discriminated as having schizophrenia (sensitivity 73.3%); and 308 of the 389 clinically diagnosed non-schizophrenic subjects were discriminated as non-schizophrenics (specificity 79.2%) in the discriminant analysis (Table 5).

Discussion

In most previous studies, there were no normal individuals or patients with non-schizophrenic psychiosis in whom the parameters of the EEM test were similar to those of schizophrenic patients. Only schizophrenic

Table 5 Results of discriminant analysis for each group

	Schizophrenic	Non-schizophrenic
Schizophrenics	184/251 (73.3%)	67/251 (26.7%)
Non-schizophrenics		
Patients with mood disorders	33/111 (29.7%)	78/111 (70.3%)
Patients with neurotic disorders	5/28 (17.9%)	23/28 (82.1%)
Healthy controls	43/250 (17.2%)	207/250 (82.8%)
Total non-schizophrenics	81/389 (20.8%)	308/389 (79.2%)

Schizophrenics were discriminated from non-schizophrenics with a sensitivity of 73.3% and a specificity of 79.2%

patients have consistently shown disturbances of the EEM [16–20, 24, 25, 30, 43]. Moreover, we discriminated schizophrenics from non-schizophrenics with a high probability using EEM data [19, 26]. Therefore, we hypothesized that the EEM test may be specific to schizophrenia. However, the samples used in our previous studies were not very large. Thus, the findings of those studies required cautious interpretation and additional studies with larger samples were needed to confirm our findings. In our previous studies, one of the most important reasons that we initially used smaller samples was based on the prevailing method and existing technology. The previous method relied on an offline analog system, thus we devoted a substantial amount of time to performing the test and analyzing the data. Furthermore, the data analysis method was not completely standardized; it was also not automatic. In the present study, the authors developed a digital computerized version of the EEM test. This newly developed system handles the online detection of eye fixation points during the EEM task. Using this system, we yielded the following benefits: (1) automatic detection of eye movement data, (2) automatic standardized data analyzing system, and (3) accordingly, the time required to perform the test and analyze the data was drastically reduced. Consequently, we did the first large sample study to confirm our previous findings.

Parameters of the EEM test

The NEF, TESL and MESL, parameters of the retention task, were significantly lower in schizophrenic patients than in the other three groups. None of the retention task parameters showed statistically significant differences between the patients with mood disorders, patients with neurotic disorders and healthy controls. These results indicate that eye movements were less frequent and two-dimensional spatial distributions of the eye movements were much more limited in schizophrenics than in other groups.

The RSS, parameter of comparison task, was significantly lower for the patients with schizophrenia than for the other three groups and no significant differences were found between the other three groups. Nemoto et al. [29] investigated brain activation during a visual exploration task that was similar to the comparison task using the functional MRI in schizophrenics and normal controls. The normal control subjects showed activations at the bilateral thalamus and the left anterior medial frontal cortex. In contrast, the schizophrenic subjects had activations at the right anterior cingulate gyrus, but no activations at the thalamus and the left anterior medial frontal cortex. These findings indicate that the RSS abnormality of schizophrenia may be associated with the dysfunctions of the thalamus, frontal cortex or cingulate gyrus. In all of our studies, only schizophrenic patients have shown the RSS abnormalities [16–20, 24, 25, 30, 43]. Therefore, the dysfunction of neuronal networks involving the thalamus, frontal cortex or cingulate gyrus may be associated with schizophrenia.

The medication effect for the EEM test

Almost all patients with schizophrenia were taking neuroleptic medication. Consequently, the effect of these drugs on the EEM test should be discussed. Kojima et al. [20] investigated the effect of neuroleptics on the EEM test in schizophrenics. They contrasted a neuroleptic-medicated performance with a non-medicated performance for the EEM test in the same subjects. They found that the EEM performances were not influenced by the use of neuroleptics.

Eye movement research of schizophrenia

As eye movement research of schizophrenia, saccadic or smooth pursuit eye movement has been conducted in many laboratories on a worldwide basis [8, 11, 21, 37]. However, abnormalities of saccadic or smooth pursuit eye movement were shown in non-schizophrenic patients [9, 12, 14, 22, 39]. However, as mentioned above, the EEM abnormalities may be specific to schizophrenia, and not influenced by medication. Therefore, we used the EEM parameters for discriminating schizophrenics from non-schizophrenics.

Discriminant analysis

By using the TESL and RSS as the valid variables, we discriminated schizophrenics from non-schizophrenics with a sensitivity of 73.3% and with a specificity of 79.2%. This result was essentially consistent with our previous study [19, 26]; however, the sample size of the previous study was not very large. In this study, we replicated our previous findings with higher probability in a larger sample.

To date, there have been several studies that attempted to discriminate between schizophrenics and non-schizophrenics using psychophysiological or

neurophysiological measures. Shagass et al. [38] quantified a basic EEG activity in unmedicated patients with schizophrenia, depression, mania, neuroses and personality disorders, and performed the discriminant analyses between schizophrenics and non-schizophrenics using quantified EEG data. They discriminated schizophrenic patients from non-schizophrenic patients with a sensitivity over 50% and a specificity from 68.0 to 86.2%. Ogura et al. [31] recorded ERP, N200 and P300, to discriminate between 37 schizophrenics and 29 normal controls. They discriminated schizophrenics from normal controls with a sensitivity of 88.2% and a specificity of 85.2%. Pfefferbaum et al. [34] tried to diagnose schizophrenia, depression and dementia using P300 measures but was unsuccessful. Mather et al. [23] investigated the pursuit eye movements in 24 schizophrenics, 10 patients with unipolar depression and 16 normal controls. They correctly classified schizophrenics in 84% of cases. Price et al. [36] recorded MMN, P50, P300, and antisaccade in 60 schizophrenics and 44 normal controls; and they investigated association between the multivariate endophenotype and diagnostic groups with logistic regression. In a logistic regression using all four features, the diagnostic grouping had a sensitivity of 81.7% and a specificity of 72.7% in predicting group membership.

Discrimination between schizophrenics and non-schizophrenics using the EEM data demonstrated the following characteristics: (1) both sensitivity and specificity were higher than 70%, (2) schizophrenia was compared with other psychiatric disorders, and (3) the sample was large enough to confirm the results. Based on our findings and other studies, no other study using a physiological measure for discrimination meets all of the above criteria. Therefore, we believe that the EEM may be useful for discriminating between schizophrenics and non-schizophrenics. Thus, the EEM measures may show promise as a biological marker for the clinical diagnosis of schizophrenia. However, in order to apply the EEM to the clinical diagnosis of schizophrenia, higher sensitivity and specificity values are needed. Hence, we need a more detailed contrivance for the application of the EEM for the diagnosis of schizophrenia. Moreover, when discriminant analysis is used in this type of study, the following approach is recommended: (1) the discriminant analysis should be performed among subjects, and a discriminant function with excellent sensitivity and specificity should be obtained; and (2) to test the external validity of the discriminant function, it should be applied to a group that is separate from the study group. However, we did not use the above recommended approach because we were eager to have a prominent function by using a large sample in this study. The findings of this study can be applied to other samples in the future.

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