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).

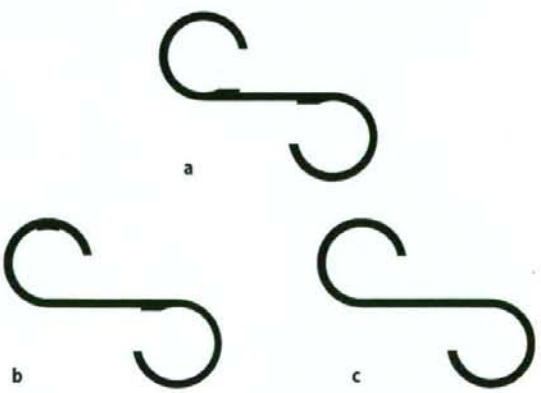

Fig. 2 The original target figure (**a**) and two figures slightly different from the target (**b**, **c**)

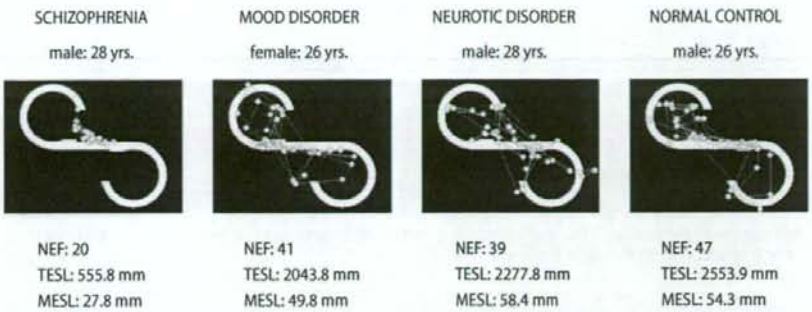

Fig. 3 The retention task, NEF, TESL and MESL in a schizophrenic patient, a mood disorder patient, a neurotic patient and a normal control

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

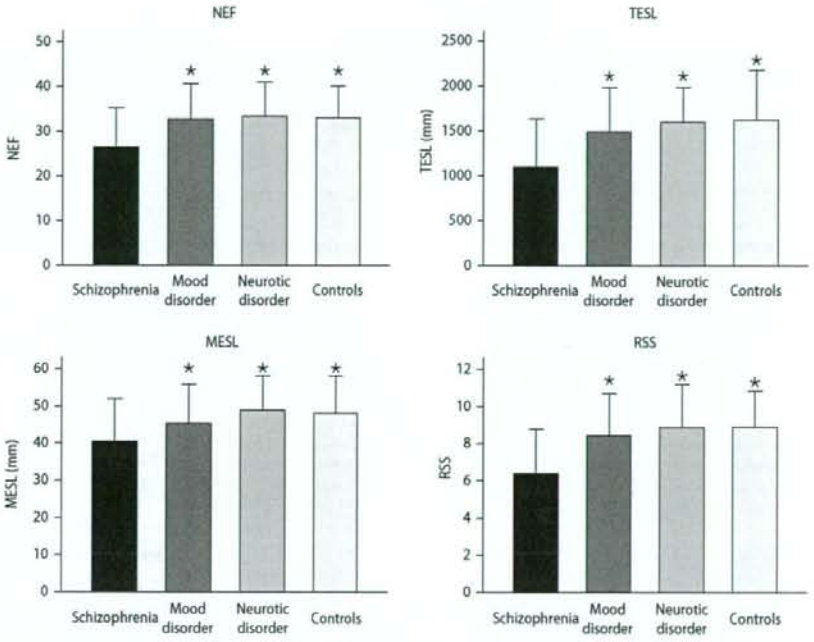

Fig. 4 The results of each parameter for schizophrenic patients, mood disorder patients, neurotic patients and normal controls
NEF number of eye fixations, *TESL* total eye scanning length, *MESL* mean scanning length, *RSS* responsive search scores
*$P < 0.01$ versus schizophrenia of Bonferroni

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

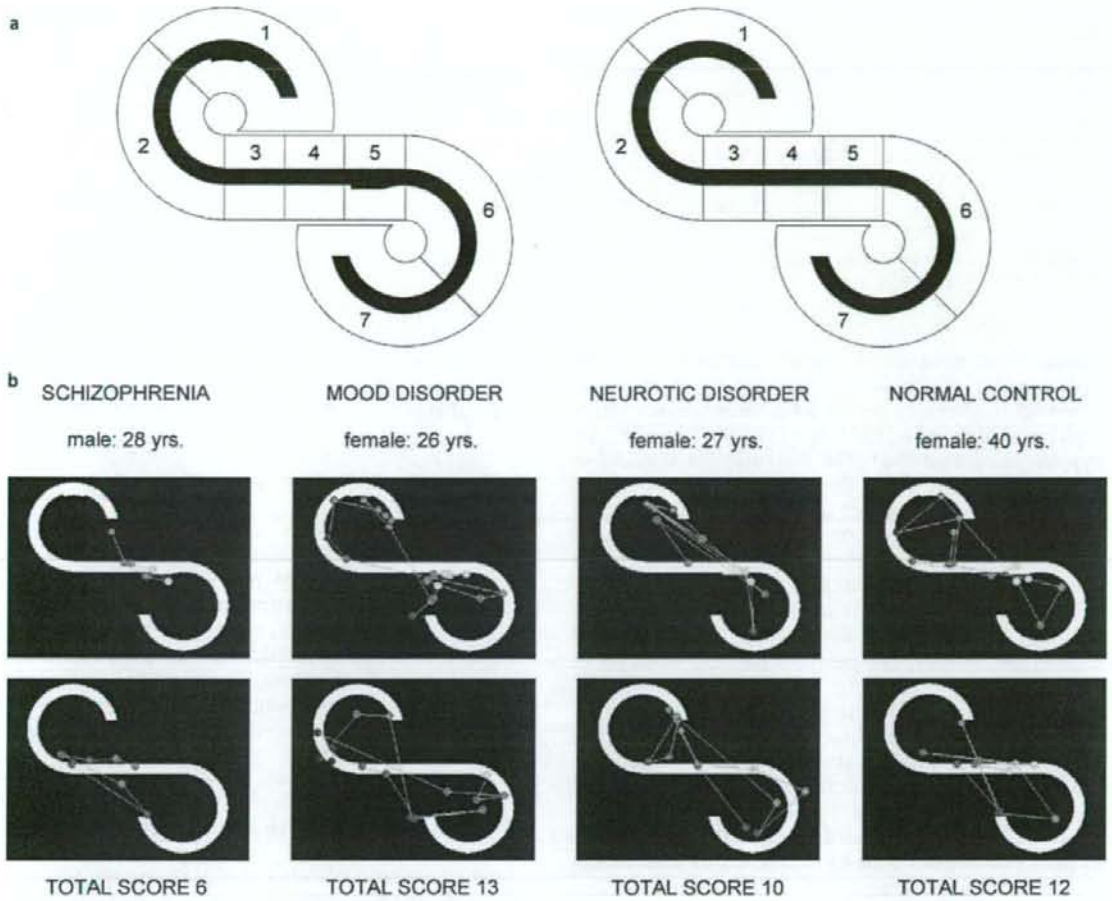

Fig. 5 **a** Seven sections for scoring the RSS. **b** The comparison task, RSS in a schizophrenic patient, a mood disorder patient, a neurotic patient and a normal control. When the RSS was scored, each horizontal S-shaped figure was divided into seven sections. If the eyes fixed on a section, the fixation 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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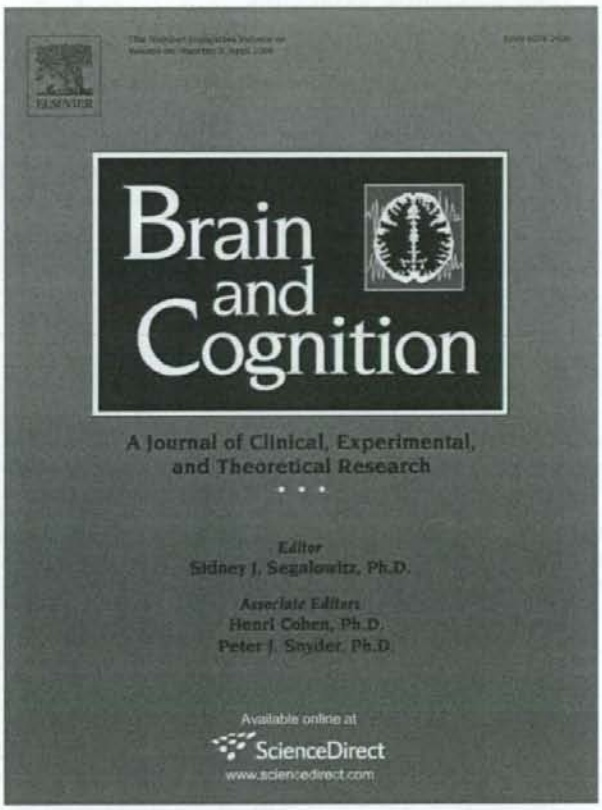

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Brief Communication

Superior fluid intelligence in children with Asperger's disorder

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Abstract

Asperger's disorder is one of autistic spectrum disorders; sharing clinical features with autism, but without developmental delay in language acquisition. There have been some studies of intellectual functioning in autism so far, but very few in Asperger's disorder. In the present study, we investigated abstract reasoning ability, whose form of intelligence has been labeled fluid intelligence in the theory of Cattell [Cattell, R. B. (1963). Theory of fluid and crystallized intelligence: A critical experiment. *Journal of Educational Psychology, 54*, 1–22.], in children with Asperger's disorder. A test of fluid intelligence, the Raven's Standard Progressive Matrices Test, was administered to 17 children with Asperger's disorder and 17 age-, gender-, and FIQ-matched normal children. The results showed that children with Asperger's disorder outperformed on the test of fluid reasoning than typically developing children. We suggest that individuals with Asperger's disorder have higher fluid reasoning ability than normal individuals, highlighting superior fluid intelligence.

Keywords: General fluid intelligence; Raven's progressive matrices test; Abstract reasoning ability

1. Introduction

Asperger's disorder is a pervasive developmental disorder characterized by impairments in social interaction, with restricted and repetitive patterns of behaviors and interests. This disorder is a subgroup on the autistic spectrum, sharing many clinical features with Autistic Disorder (American Psychiatric Association., 1994), but without clinically significant developmental delays in language acquisition. In Asperger's disorder, basic language skills are intact, although there are delays in nonverbal communication skills and pragmatics (Stein et al., 2004). There has been a report that individuals with Asperger's disorder often have a distinct profile on standard tests of intelligence such as the Wechsler Adult Intelligence Scale (WAIS) and Wechsler Intelligence Scale for Children (WISC), characterized by high verbal IQ and relatively low performance IQ (Klin, Volkmer, Sparrow, Cichetti, & Rourke, 1995).

Some studies have indicated that children with Asperger's disorder have high performances on the Vocabulary and Comprehension verbal subtests of the WISC, while their performances on nonverbal subtests, including Block Design and Object Assembly, are impaired (Ehlers et al., 1997). These findings at first sight suggest that individuals with Asperger's disorder have superior verbal crystallized intelligence, rather than nonverbal fluid intelligence. However, Wechsler-type intelligence scale is not considered as a test of fluid intelligence but rather an example of tests that typically measure skills and knowledge, crystallized intelligence (Gray & Thompson, 2004). General fluid intelligence (gF) is a major dimension of individual differences and refers to reasoning and novel problem-solving ability (Cattell, 1963; Gray & Thompson, 2004). Empirically, fluid intelligence is strongly associated with frontal executive function (Duncan, Burgess, & Emslie, 1995), attentional control and working memory (Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Gray, Chabris, & Braver, 2003; Kane & Engle, 2002), and the core function of fluid intelligence is the abstract reasoning ability, which has been a component of most formal theories of intelligence (Stern-

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berg, 1985; Thurstone, 1938). On the other hand, general crystallized intelligence is distinct from gF, referring to overlearned skills and static knowledge such as vocabulary, and there is empirical evidence for a distinction between the psychological processes and the neural substrates that subserve fluid reasoning and crystallized knowledge (Cattell, 1963; Duncan et al., 1995). As a test of fluid intelligence, the Raven Progressive Matrices test (Raven, Raven, & Court, 1993) is regarded as one of the best measurements, because it provides an optimal domain-independent measure of the abstract reasoning processes relevant to the management of novel problem-solving goals in working memory (Carpenter, Just, & Shell, 1990; Duncan et al., 2000; Gray & Thompson, 2004; Gray et al., 2003).

In cognitive research with autism, IQ is the most frequent matching variable in use, and Wechsler scales, British Picture Vocabulary Scale (BPVS) and the Raven's Coloured Progressive Matrices test (RCPM) are the frequently used instruments to determine IQ. Mottron (2004) claimed that there is a high probability of overestimating the level of intelligence in percentile vales of BPVS and RCPM score as compared to those of Wechsler scale, recommending a replacement to Wechsler scale as a basis of IQ matching.

Thus, the RCPM is frequently used to assess intelligence in individual with pervasive developmental disorders. However, the RCPM was developed to assess young children (5 to 10 1/2 years), whereas the Raven's Standard Progressive Matrices (RSPM) was developed for use with older children and adults (Raven et al., 1993). The colored backgrounds on which the problems are printed attract attention and make the test spontaneously interesting (Raven et al., 1993), and so the way to solve the problems on the RCPM is closely tied to the perceptual and analytical processes. By contrast, most of the problems on the RSPM are not as closely tied to the perceptual format and require a more abstract characterization in terms of dimensions and attributes (Carpenter et al., 1990). Therefore, the RSPM is widely accepted as a measure of high level analytical reasoning and of fluid intelligence (Carpenter et al., 1990; Dawson, Soulieres, Gernsbacher, & Mottron, 2007).

It is possible to assume that individuals with Asperger's disorder would show low fluid intelligence, as in the case of autistics who showed poor fluid reasoning (Blair, 2006; Pennington & Ozonoff, 1996) and poor performance on the tests of high-level integration or abstraction (Courchesne & Pierce, 2005; Just, Cherkassky, Keller, & Minshew, 2004). However, a recent study by Dawson and colleagues (2007) provided us with empirical evidence that autistic children showed high scores on the test of fluid intelligence using the RSPM. Such an empirical study has never been documented in Asperger's disorder or high-functioning autism. Here, we aimed to examine fluid intelligence in children with Asperger's disorder, using the Raven's Standard Progressive Matrices test (RSPM).

2. Methods

2.1. Participants

Seventeen participants with Asperger's disorder (10 boys and 7 girls, ages 6 to 12 years) were recruited from the outpatient's clinic of one children's hospital and took part in this study. These participants all were found to meet DSM-IV (American Psychiatric Association, 1994) criteria for a diagnosis of Asperger's disorder and were screened for psychiatric disorders through an in-depth clinical investigation performed by two of us (M.K., a psychiatrist and K.I., a child neuropsychologist) at the time of passing a standardized diagnostic instrument. Exclusion criteria included epileptic disorder, severe head trauma, the other neurological illness, or serious medical problems. In particular, those who had attention deficit/hyperactivity disorder, learning disability and developmental dyslexia were excluded from this study. None of them were on medication or showed signs of gross neurological abnormalities at the time of testing.

Although all participants with Asperger's disorder showed clinical symptoms including abnormal social interaction, and restricted and repetitive patterns of behaviors, they could use single words by the age of two years and communicative phrases by the age of three, and had no echolalia, pronoun reversal, nor stereotyped language.

Participants with Asperger's disorder showed a mean full-scale IQ of 96.7 (SD = 15.3) as measured with the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), and their mean verbal IQ (VIQ) (101.7 ± 13.7) was higher than their mean performance IQ (PIQ) (91.5 ± 19.3) [$t(16) = 2.29$, $p < .05$].

Seventeen typically developing children (10 boys and 7 girls) participated in this study as age- and sex matched controls (NC). They were recruited from public primary schools in Tokyo. All participants were initially screened by teachers and were evaluated further by a structured psychiatric interview of two independent child psychiatrists and medical assessment. The exclusion criteria were a history of DSM-IV psychiatric disorders including attention deficit / hyperactivity disorder, learning disability and evidence of any other organic diseases. These control children had a mean FIQ of 99.8 (SD = 9.8) as measured with WISC-III, and their mean verbal IQ (VIQ) (101.3 ± 9.2) did not differ from their mean performance IQ (PIQ) (99.1 ± 10.2) [$t(16) = .96$, $p > .05$]. There were no significant differences on the mean of age and FIQ score between the participants with Asperger's disorder and the control participants ($p > .05$, Table 1.). The parents of each group were mostly from upper middle-class social status. Written informed consent was obtained from all participants and their parents.

2.2. Measures

The Raven's Standard Progressive Matrices test (RSPM) (Raven, Court, & Raven, 1992) was administered

Table 1
Descriptive characteristics of participants in control (NC) and Asperger's disorder (AD) groups

	Groups	
	NC	AD
N (boys/girls)	17 (10/7)	17 (10/7)
Age (years)	9.5 (2.5)	9.2 (1.9)
WISC-III		
FIQ	99.8 (9.8)	96.7 (15.3)
VIQ	101.3 (9.2)	101.7 (13.7)
PIQ	99.1 (10.2)	91.5 (19.3)*

Data are expressed as group mean and standard deviation in parentheses. WISC-III, Wechsler Intelligence Scale for Children-Third Edition.
* The mean PIQ score was significantly lower than the mean VIQ in AD group ($p < .05$).

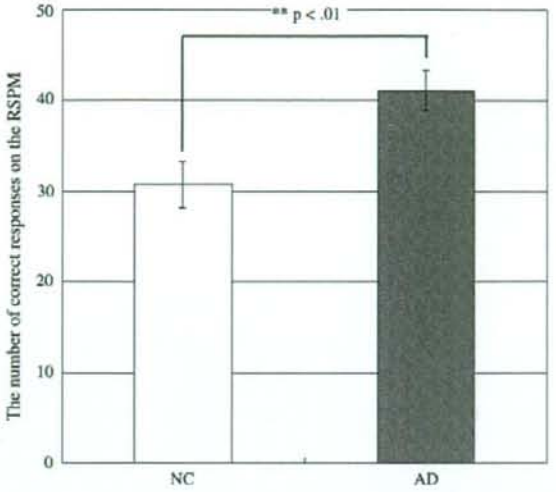

Fig. 1. Mean numbers of correct responses on the RSPM for control (NC) and Asperger's disorder (AD) groups. Open (left) and filled (right) columns represent numbers of correct responses in NC and AD groups, respectively. Vertical bars represent the standard error of the mean.

to the participants. The RSPM comprises 60 problems, divided into five sets (A–E) of increasing difficulty, and the each set begins with easy problems and ends with difficult ones. Each item contains a matrix of geometric design with one cell of the matrix removed, and there are six or eight alternatives given to insert in place of the missing cell, one of which fits correctly.

All participants were tested individually, and the RSPM was administered without time limit.

3. Results

Mean numbers of correct responses on the RSPM in the Asperger's disorder (AD) and normal controls (NC) groups are shown in Fig. 1. The number of matrices correctly solved in both groups were analyzed as a dependent variable, and two-tailed t tests revealed that the AD group (41.1 ± 9.3) made significantly more correct responses than the NC group (30.7 ± 10.3) [$t(32) = -3.08$, $p < .01$, Cohen's $ds = 1.05$].

Furthermore, a two-way ANOVA with groups and gender as variables, revealed significant main effects of groups [$F(1,30) = 8.69$, $p < .01$] and group × gender interaction [$F(1,30) = 17.37$, $p < .01$]. Regarding the boys, the AD group (46.0 ± 2.6) outperformed the NC group (26.0 ± 2.6) [$ds = 2.48$]. On the other hand, the girls in the AD group (34.0 ± 3.0) showed the equivalent number of correct responses to the girls in the NC group (37.4 ± 3.0) [$ds = 0.42$].

There was no significant correlation between the number of correct responses on the RSPM, and FIQ ($r = .24$, $p > .05$), VIQ ($r = .27$, $p > .05$) and PIQ ($r = .16$, $p > .05$) on the WISC-III for all children combined.

4. Discussion

The present study demonstrates that participants with Asperger's disorder made more correct responses on the RSPM than did normal controls. The results of this study suggest that Asperger's disorder involves superior abstract reasoning ability or higher general fluid intelligence. A theoretical account in the literature regarding the processing of the Raven test (Carpenter et al., 1990) proposes that the RSPM involves abstraction and goal management processes. In order to solve the problems on the RSPM, it is necessary to induce rules from the relationship between elements in matrices, and to generate and maintain goals in working memory until a target satisfies a theorem as a whole. As compared to normally developing children, the performance on the RSPM in children with Asperger's disorder was critically different and was significantly better, implying the superiority in fluid intelligence in Asperger's disorder.

Moreover, from clinical case records of children with Asperger's disorder diagnosed by Hans Asperger and his team, it was revealed that some individuals with Asperger's disorder had a special gift for abstract thinking and logical reasoning (Hippler & Klicpera, 2003). Hans Asperger contended, in his original paper, that the traits of this disorder were in fact necessary for high achievement in the arts and sciences (Wing, 2005). Logical reasoning ability is a premise for conducting scientific research, and in fact there have been some outstanding scientists who were the cases of Asperger's disorder (Asperger, 1944; Frith, 2004). Such clinical characteristics could be in correspondence to the superior performance on abstract reasoning problems of the RSPM in the present study.

Recently, an interesting study of autistic intelligence has been published (Dawson et al., 2007). In this study, autistic children showed high scores on the RSPM. However, the percentile score on the RSPM were higher than the percentile scores on the Wechsler scales of intelligence in autistic

children, while typically developing children did not show such discrepancy. The results of this study suggested that intelligence has been underestimated in autistics. Although this study was conducted to children with autism, and some autistics included IQ score below the average, indicating 'low-functioning' autism (i.e., in the range of mental retardation), our participants included children with Asperger's disorder who had average or high IQ scores. Nevertheless, the results of our study were in line with those of the study by Dawson and colleagues (2007), since Asperger's disorder shares the same clinical features to autism in poor social communication and is considered as one of autistic spectrum disorders (Wing, 1981).

Recent cognitive neuroscience studies showed that analytic reasoning activates the left frontal cortex (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997; Wharton et al., 2000). Moreover, general fluid intelligence reflects the function of a specific neural system, including the lateral frontal cortex as one major part (Duncan et al., 2000; Gray et al., 2003). Thus, the left lateral frontal function may play an important role for fluid reasoning, and our results of superior fluid intelligence in Asperger's disorder may imply the unique involvement in the left frontal lobe functioning. Future research should explore the neural substrates for fluid intelligence in Asperger's disorder.

Although we demonstrated new cognitive characteristics in Asperger's disorder, there are some limitations in our study. The major one is the small number of participants with Asperger's disorder. The results of this study suggested that boys with Asperger's disorder particularly performed better on the RSPM. It might be because that males are better at 'systemizing', that is, 'to predict and to respond to the behavior of nonagentive deterministic systems by analyzing rules that govern such systems' (Baron-Cohen, 2002). Hans Asperger himself even noted that autistic mind is an extreme variant of male intelligence (Asperger, 1944; Frith, 2004; Wing, 2005). However, unfortunately, it would be too early to reason from such a small number of participants. The comparison of boys versus girls in Asperger's disorder with more cases would be of importance and should be carefully examined. Another limitation is the lack of multiple measures of general fluid intelligence in this study. Although we suppose that the RSPM would be a good and convincing enough measure, it would be hard to clearly articulate the types of cognitive processes that the RSPM taps into. Future study is expected to investigate general fluid intelligence with some other cognitive tests in Asperger's disorder. Thirdly, the children participated in this study were diagnosed as Asperger's disorder. This diagnosis was made only for autistic children without relevant delay or deficits in language development. It would be interesting and necessary to compare the performance on the tests of fluid intelligence in Asperger's disorder with high-functioning autism. Finally, what is the most puzzling for us is why persons with Asperger's disorder have such a special abstract reasoning ability? We should explore what cognitive factors associated with Asperger's disorder would contribute to high fluid intelligence in future research.

In conclusion, we demonstrated that individuals with Asperger's disorder are able to perform better on the RSPM than normally developing individuals, and highlights superior abstract reasoning ability and high general fluid intelligence in this disorder. This study provides new insight into the cognitive strengths associated with Asperger's disorder.

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CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Case Report: Adult Phenotype of Mulvihill–Smith Syndrome

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Mulvihill–Smith syndrome (MSS) is characterized by premature aging, multiple pigmented nevi, decreased facial subcutaneous fat, microcephaly, short stature, mental retardation and recurrent infections, however the adult phenotype of MSS has yet to be delineated. We report a 28-year-old woman with Mulvihill–Smith syndrome, who had a solid pseudopapillary cystic tumor of her pancreas at age 17 years. Her distinctive sleep pattern includes severe insomnia with disappearance of sleep spindles and K-complexes, persisting muscle tone, and loss of slow wave sleep. The clinical and neurophysiological studies are compatible with agrypnia excitata, a sleep disorder attributable to a dysfunction of the thalamo-limbic system. Brain magnetic resonance imaging and single photon emission computed tomography revealed structural and functional deficits in the dorsomedial region of the thalamus and indicated that an alteration in the thalamo-limbic system may underlie the sleep disturbances in MSS. Furthermore, the rapid and severe decline in acquired cognitive function showed the distinct cognitive impairments resembling dementia, including intellectual deficits, memory disorder and executive dysfunction. We posit that an early onset tumor, sleep disorder and cognitive decline are adult manifestations of Mulvihill–Smith syndrome. © 2009 Wiley-Liss, Inc.

Key words: Mulvihill–Smith syndrome; solid pseudopapillary cystic tumor; sleep disorder; agrypnia excitata; dementia

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INTRODUCTION

Mulvihill–Smith syndrome (MSS) is characterized by premature aging, multiple pigmented nevi, lack of facial subcutaneous fat, microcephaly, short stature, and mental retardation [de Silva et al., 1997]. Immunodeficiency may also be a critical feature [Ohashi et al., 1993].

Since its recognition by Mulvihill and Smith [1975], eight patients have been reported [Shepard, 1971; Elliott, 1975; Wong et al., 1979; Baraitser et al., 1988; Ohashi et al., 1993; Bartsch et al., 1994; de Silva et al., 1997; Ferri et al., 2005]. Because both male and female patients have been described, as well as a patient born to a consanguineous couple has been reported [Ohashi et al., 1993], the mode of inheritance is likely to be autosomal recessive. The causative gene has not been identified so far.

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The adult phenotype of MSS has yet to be delineated. Two adult MSS patients presented with tumors, and one patient exhibited cognitive decline and sleep disorder [Bartsch et al., 1999; Ferri et al., 2005]. Whether or not these conditions represent characteristic adult features of MSS has not been clarified. We report a patient with MSS who developed tumors, a sleep disorder with severe insomnia and cognitive decline and suggest that these features are indeed unique adult manifestations of MSS.

CLINICAL REPORT

A Japanese girl was born by a spontaneous vaginal delivery at 38 weeks gestation after an unremarkable pregnancy. The parents were nonconsanguineous and phenotypically normal. The birth weight was 2,570 g (10–25th centile), the head circumference (OFC) 31.5 cm (10–25th centile), and the crown heel length 45.6 cm (10–25th centile). She was hospitalized for a month because of feeding difficulties.

During infancy and early childhood, she had multiple episodes of infections, including recurrent otitis media and a severe varicella infection that required hospitalization for 2 weeks. At age 1 year, multiple pigmented nevi became noticeable on the trunk. The number of nevi increased with age, and when the patient was 3 years old, a dermatologist diagnosed her as having LEOPARD syndrome because of multiple pigmented nevi, short stature, and mild hearing loss. She also had delayed motor development. She exhibited tonic postures of the upper limbs at age 3 months. With physical therapy, she was able to walk at age 1 year. She also started to speak meaningfully around the same time, and her speech development has been age-appropriate since then. She attended elementary school from age 6 years and achieved average grades. At age 13 years after entering the seventh grade, she developed bilateral sensory neural hearing impairment. Then her social interaction including personal contacts with her peers became poor and her scholastic achievement also declined.

At age 17 years, Werner syndrome was suspected because of a premature senile appearance; however, a Western blot for WRN protein showed a normal pattern. Her G-banded karyotype was normal. At age 20 years, she developed diabetes mellitus and started oral hypoglycemics. At age 24 years, band keratopathy and cataract developed; she had bilateral corneal transplantations at age 26 years and an intraocular lens placement at age 27 years.

At age 25 years, she was referred to our genetics clinic. She weighed 24.5 kg and was 138.4 cm tall; her OFC was 50.0 cm (<3rd centile), medians for 7 6/12, 10 0/12, and 4 3/12 years, respectively. She had a triangular face, a lack of facial subcutaneous fat, multiple pigmented nevi, a low posterior hairline, alopecia, bifid uvula, and a high pitched-voice (Fig. 1). Her external genitalia were normal. A bone radiograph showed brachydactyly with a shortening of the distal phalanges. The results of immunological studies including IgG, IgA, and IgM levels, PHA stimulation test, and lymphocyte subpopulation analysis were unremarkable. The patient's specific features (the progeria-like appearance, short stature, microcephaly, diffuse pigmented nevi, and metacarpophalangeal pattern [Bartsch et al., 1994]) allowed us to diagnose MSS.

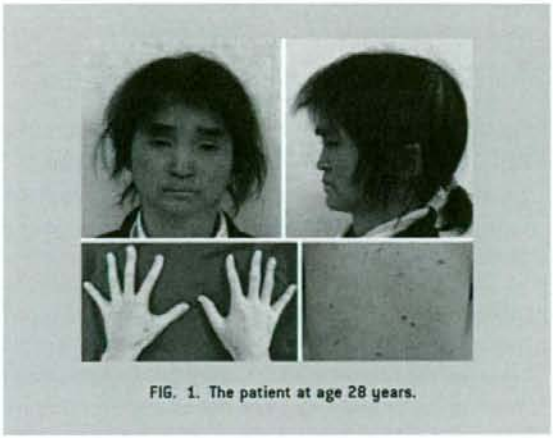

FIG. 1. The patient at age 28 years.

Development of Tumors

At age 17 years, the number of pigmented nevi increased. Abdominal ultrasonography revealed an asymptomatic pancreatic mass, which was resected surgically. The post-operative diagnosis was a solid pseudopapillary cystic tumor of the pancreas.

At age 25 years, she developed paresis and hyperesthesia of the right thumb and index finger. A head MRI showed nothing that could account for the findings; however, a 2.0 cm mass was incidentally identified in the right cerebellum. A re-evaluation performed 3 years later revealed that the size of the mass was unchanged, so the lesion was considered to be a benign tumor or cyst.

At age 27 years, she underwent surgical removal of a tongue tumor; the histopathologic diagnosis was an ulcer of the tongue with chronic inflammation, in which no evidence of malignancy was disclosed.

Sleep Disturbances and Neurophysiological Examinations

At age 26 years, she developed excessive daytime sleepiness and nighttime insomnia with hypnagogic hallucinations. However, these symptoms had been mild and had not interfered with her normal activities until age 28 years, when she became emotionally unstable and irritable. She had paresis and hyperesthesia of the right thumb and index finger and a slightly ataxic gait with myoclonic jerks. Her insomnia and emotional disturbances gradually deteriorated, and she began to experience visual hallucinations in the daytime.

The patient underwent polysomnography, comprising electooculography, electroencephalography (EEG), electromyogram of the submentalis and the tibialis anterior muscles, ECG and nasal airflow. The EEG background findings with the eyes closed showed a posterior dominant rhythm of 9–10 Hz with intermittent 3–6 Hz slow waves. Sleep recordings revealed a complete loss of sleep spindles and K-complexes, which indicated an alteration of the physiological transitional process from being awake to falling

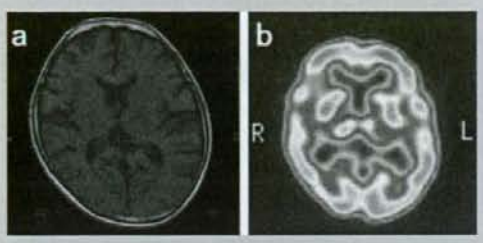

FIG. 2. Brain imaging at age 28 years. a: MRI. Note the bilateral atrophy of the dorsomedial nucleus of the thalamus and pulvinar, and the mild enlargement of the cortical sulci. b: Brain single photon emission computed tomography (^{99m}ECD-SPECT). Note the focal reduction of regional cerebral blood flow in the left thalamus (b).

asleep, and further demonstrated a remarkable decrease in slow-wave sleep stages characterized by 1–2 Hz slow-waves, low chin muscle tone and the absence of motor activity in the four limbs. Furthermore, these polysomnographic recordings documented an absence of typical REM sleep episodes, with a low-voltage fast background and hypotonia. During sleep, intermittent myoclonic jerks often appeared with the persistence of chin muscle tone. The overall polysomnographic recordings were characterized by the loss of sleep spindles and K-complexes, sleep fragmentation as a result of increased arousals and persisting muscle tone, and an especially marked loss of slow wave sleep.

Neuropsychological and Neuroimaging Examinations

Clinical neuropsychological tests were performed at age 28 years. The patient's full-scale intelligence quotient (FIQ) on the Wechsler Adult Intelligence Scale III was 51 (verbal IQ = 55; performance IQ = 54), indicating global intellectual impairment. The Wechsler Memory Scale-Revised (WMS-R) revealed that she had severe memory deficits (general memory index 53, visual memory index 74, verbal memory index 54). On executive function, she showed poor performances on the Trail-making Test parts A and B, the Wisconsin Card Sorting Test and the Word Fluency Test. Taken together, the neuropsychological assessments demonstrated her cognitive deficits including intellectual disability, memory disorder and executive dysfunction.

Brain MRI at age 28 years revealed bilateral atrophy of the dorsomedial nucleus of the thalamus and pulvinar, and mild enlargement of the cortical sulci (Fig. 2a). Brain single photon emission computed tomography (^{99m}ECD-SPECT) demonstrated a focal reduction of regional cerebral blood flow in the left thalamus (Fig. 2b).

DISCUSSION

The patient reported herein exhibited all of the shared features of previously reported MSS patients: short stature, senile appearance, and pigmented nevi [de Silva et al., 1997; Ferri et al., 2005]. In addition, she had many of the common features of MSS: a high-pitched voice, alopecia, chronic and recurrent infections, hearing loss, cataract, mental retardation and a distinctive metacarpophalangeal pattern (Table I). Based on this recognizable phenotype, we diagnosed the patient as having MSS.

As this syndrome is characterized by premature aging, the development of tumors at an unusually young age is significant. Solid-pseudopapillary tumor of the pancreas, which developed in the present patient at age 17 years, is a relatively rare low-grade malignant tumor that seldom metastasizes. The tumor is commonly found in women of child-bearing age. Thus, the onset age of the solid-pseudopapillary tumor in the present patient was substantially lower than average [Papavramidis and Papavramidis, 2005]. Two previously reported MSS patients also exhibited the early onsets of tumors: signet ring cell carcinoma of the stomach in a 23-year-old patient [Bartsch et al., 1999] and squamous cell carcinoma of the tongue in a 20-year-old patient [Ferri et al., 2005]. We suspect that early onset tumors may represent an important adult MSS phenotype that needs attention. Since two of the three tumors arose in the epithelial cells of the gastrointestinal tract, MSS patients may be susceptible to specific type(s) of tumors of the gastrointestinal tract. The development of an abnormal mass in the tongue of the present patient is also noteworthy. Although pathological examination did not reveal tumor cells in the abnormal tongue mass, the report by Ferri et al. [2005] of squamous cell carcinoma of the tongue may indicate that the tongue or oral mucosa of patients with MSS are susceptible to tumors. The significance of the cerebellar mass in the patient reported herein remains undetermined.

We posit that cognitive deterioration in adults, in addition to the developmental delay, is an underappreciated feature of MSS. The rapid and severe cognitive decline observed in our patient cannot be accounted for by neural alterations arising from simple premature aging. The patient herein reported started the decline in acquired cognitive function around age 26 years, and showed the distinct cognitive impairments resembling dementia, including intellectual deficits, memory disorder and executive dysfunction at age 28 years. A similar clinical course suggesting a progressive decline in cognitive function was also described in a patient with MSS who exhibited mental retardation (IQ56) at age 25 years [Ferri et al., 2005].

The cognitive decline in the patient was further aggravated by a distinctive sleep pattern abnormality resembling agrypnia excitata, which is ascribed to a dysfunction of the thalamo-limbic system [Lugaresi and Provini, 2001; Montagna and Lugaresi, 2002]. Agrypnia excitata is observed in patients with fatal familial insomnia, Morvan fibrillary chorea, and delirium tremens, and is characterized by peculiar polysomnographic findings, including the absence of sleep spindles and K-complexes, the complete loss of slow-wave sleep, and abnormal REM sleep with lack of muscle atonia. The distinctive features of the sleep pattern in the patient also include severe insomnia with marked disappearance of sleep spindles and K-complexes, persisting muscle tone, and loss of slow wave sleep. Since the same sleep pattern abnormality has been reported in another adult MSS patient [Ferri et al., 2005], agrypnia excitata could be a feature of MMS. The fact that brain MRI and SPECT studies in the present patient revealed structural and

TABLE I. Clinical and Laboratory in Nine Cases of Mulvihill–Smith Syndrome

	Mulvihill and Smith [1975]	Shepard [1971] and Elliott [1975]	Wong et al. [1979]	Baraitser et al. [1988]	Ohashi et al. [1993]	Bartsch et al. [1994, 1999]	de Silva et al. [1997]	Ferri et al. [2005]	Present case
Sex	M	M	F	M	F	M	M	F	F
Age	17	3, 4	14	7	30	20, 23	4	25	28
Low birth weight	+	+	+	+	−	−	−	NR	−
Short stature	+	+	+	+	+	+	−	+	+
Microcephaly	+	+	+	+	+	+	+	+	+
High pitched voice	+	NR	NR	+	−	+	+	+	+
Lower facial hypoplasia	+	+	+	+	+	+	+	+	+
Hypertelorism	NR	+	+	−	+	+	−	−	−
Pigmented nevi	+	+	+	+	+	+	+	+	+
Facial fat reduced	+	NR	+	+	+	+	+	+	+
Alopecia	+	+	NR	NR	−	−	−	−	+
Deafness	+	+	+	+	+	+	−	+	+
Cataract	−	−	−	NR	−	+	−	+	+
Brachydactyly	+	+	NR	NR	+	+	−	NR	+
Diabetes	+	−	−	−	−	−	−	−	+
Recurrent infections	+	+	+	−	+	+	+	+	+
T cell dysfunction	NR	NR	NR	NR	+	+	+	NR	−
Abnormal Ig levels	+	NR	−	+	+	+	+	+	−
Development of tumor	−	−	−	−	−	Gastric	−	Tongue	Pancreas tongue cerebellum?
Mental retardation	Borderline	Moderate	−	Mild	Severe	Mild	−	Mild	Mild
Psychological findings	NR	NR	NR	NR	NR	Depression	NR	Depression hallucination	Depression hallucination
Sleep disorder	NR	NR	NR	NR	NR	NR	NR	+	+

NR, not recorded; Ig, immunoglobulin.

functional deficits in the dorsomedial region of the thalamus further support the notion that the alterations in the thalamo-limbic system may underlie sleep disturbances with MSS, because the thalamus is a structure involved in the regulation of sleep.

In summary, we suggest that early onset tumors, cognitive deterioration, and severe insomnia accompanied by agrypnia excitata may represent an emerging phenotype of adults with MSS.

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Gaze-triggered orienting is reduced in chronic schizophrenia

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Abstract

Patients with schizophrenia have been reported to demonstrate subtle impairment in gaze processing, which in some cases indicates hypersensitivity to gaze, while in others, hyposensitivity. The neural correlate of gaze processing is situated in the superior temporal sulcus (STS), a major portion of which is constituted by the superior temporal gyrus (STG), and may be the underlying dysfunctional neural basis to the abnormal gaze sensitivity in schizophrenia. To identify the characteristics of gaze behavior in patients with chronic schizophrenia, in whom the STG has been reported to be smaller in volume, we tested 22 patients (mean duration of illness 29 years) in a spatial cueing paradigm using two central pictorial gaze cues, both of which effectively triggered attentional orienting in 22 age-matched normal controls. Arrow cues were also employed to determine whether any compromise in schizophrenia, if present, was gaze-specific. Results demonstrated that schizophrenic subjects benefit significantly less from congruent cues than normal subjects, which was evident for gaze cues but not for arrow cues. This finding is suggestive of a relatively gaze-specific hyposensitivity in patients with chronic schizophrenia, a finding that is in line with their clinical symptomatology and that may be associated with a hypoactive STS.

Keywords: Ambiguous stimulus; Arrow; Biological motion; Spatial cueing; Superior temporal gyrus; Superior temporal sulcus

1. Introduction

Schizophrenia is a neuropsychiatric disorder that can be disabling due to a variety of socio-cognitive impairments. One of its most intriguing symptoms is an abnormal sensitivity to gaze. In a typical course of schizophrenia, the acutely ill patient often expresses complaints of 'always being watched', reflecting heightened sensitivity to gaze. As the course becomes chronic, however, the patient tends to be more and more withdrawn, and hyposensitivity to gaze takes place. This is often observed through the patient's gaze behavior; he/she becomes very reluctant to engage in mutual eye contact. Some previous studies have highlighted this hyper/hyposensitivity to gaze. For example, schizophrenic subjects have been demonstrated to be impaired in the discrimination of whether gaze is looking at self or not (Rosse et al., 1994; Hooker and Park, 2005) in the face of an intact right/left discrimination (Franck et al., 1998); to have reduced fixation on prominent facial features such as the eyes when viewing faces (Phillips and David, 1997); and to show very early attentional orienting in response to

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