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Original Article

Characteristics of Exploratory Eye Movements in Individuals with Attenuated Psychotic Syndrome

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ABSTRACT

Introduction: Patients with schizophrenia experience significant trouble with various symptoms and disabilities. Early detection and intervention are important to prevent such difficulties. We focused our attention on patients' exploratory eye movements (EEMs) as one of the physiological markers for early detection. The aim of this study was to examine the characteristics of the EEMs in patients with attenuated psychotic syndrome (APS).

Methods: We recruited 30 healthy controls, 25 patients with no family history of psychosis who were diagnosed as having APS, and 25 patients with schizophrenia. We performed the EEM test for all the participants, and four parameters were documented: number of eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL), and responsive search score (RSS).

Results: Of the four parameters, NEF, TESL, and RSS were significantly lower in the APS and schizophrenia groups than in the healthy controls. However, there were no significant differences in these three parameters between the APS and schizophrenia groups. The percentages of patients suspected as having schizophrenia using a discriminant function in the healthy control, APS, and schizophrenia groups were 13%, 56%, and 72%, respectively.

Conclusions: The characteristics of EEMs in APS were similar to those in schizophrenia. Individuals with APS did not have a family history; however, some ultra-high-risk individuals detected only with psychopathology may include risks associated with genetic factors, even though they do not have any obvious psychotic features yet. The EEM test seems useful in detecting individuals with APS and early schizophrenia.

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KEYWORDS: attenuated psychotic syndrome, early intervention, exploratory eye movements, psychophysiology, schizophrenia

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Introduction

Schizophrenia typically emerges in late adolescence or early adulthood. Many patients with schizophrenia experience significant trouble with various symptoms and disabilities of the disease. Although positive symptoms, such as delusions and hallucinations, which often occur during the acute phase, are more conspicuous, cognitive impairment, negative symptoms such as loss of motivation and emotional apathy, and anxiety symptoms likely decrease the everyday and social functioning in patients with schizophrenia.[1–4)]

A previous study reported that approximately 80% of schizophrenia patients relapse within 5 years of the initial diagnosis,[5)] and such patients then lose the chance to integrate into society. Some patients with schizophrenia are forced to be hospitalized for long periods of time.[6)] Therefore, the importance of early intervention for psychosis has recently been emphasized to prevent the decrease of patients' functioning and achieve better outcome.[7)]

The time interval from onset of the first psychotic symptom to initiation of treatment is defined as the duration of untreated psychosis (DUP), and many previous studies have demonstrated that the longer the DUP, the poorer the prognosis.[8–11)] Consequently, much attention has been paid to the early detection of schizophrenia, and criteria have been established for an at-risk mental state for psychosis (ARMS).[12)] While individuals with ARMS show subthreshold psychotic symptoms as well as nonspecific symptoms,[13)] they do not completely meet the diagnostic criteria for schizophrenia. The Structured Interview for Prodromal Syndrome and the Scale of Prodromal Symptoms (SIPS/SOPS) is often used to diagnose ARMS and determine its severity.[14)] SOPS consists of four subscales (Positive, Negative, Disorganization, and General symptoms), and the Criteria of Prodromal Syndromes include criteria for the diagnosis of 3 types of conditions: brief intermittent psychotic syndrome, attenuated psychotic syndrome (APS), and genetic risk and deterioration syndrome.[14)]

A meta-analysis of studies on ARMS revealed that 36% of patients with ARMS showed conversion to psychosis over a 3-year follow-up period.[15)] Early detection and treatment during the prodromal phase are expected to be effective in preventing the conversion to frank psychosis.[16)] However, predictors of the development of psychosis in patients with ARMS are still obscure.

Numerous physiological and cognitive tests, such as event-related potential (ERP; P300,[17)] P50,[18)] and mismatch negativity[19)]), prepulse inhabitation,[20)] anti-saccade,[21)] eye tracking movement,[22)] working memory,[23)] and reaction time and attention,[24)] have been employed to identify the biological changes reflecting brain dysfunction in patients with schizophrenia. However, these biological changes are not always specific for schizophrenia, as patients with depression or bipolar disorder can also show abnormalities in these tests. Among these psychophysiological examinations, mainly the exploratory eye movement (EEM) test, which was developed to establish the specific biological changes in schizophrenia, has been employed in Japan since the 1960s. EEMs are one of the biomarkers related to visual cognitive function and are expected to be related to several regions of the brain, such as the thalamus, frontal cortex, or cingulate gyrus.[25)] Some abnormalities in the EEM test are considered to be characteristic of schizophrenia, and they are not recognized in other mental disorders such as depression, bipolar disorder, neurosis, methamphetamine psychosis, and temporal lobe epilepsy.[25–30)] Because both the sensitivity and the specificity of the EEM test for schizophrenia are over 70%,[25, 27, 30)] the EEM test is expected to be an effective clinical aid for the diagnosis of schizophrenia. Moreover, the EEM test has the advantage of being noninvasive, and the results can be automatically analyzed by a digital recorder. A previous study also revealed that siblings of patients with schizophrenia showed significantly higher rates of abnormalities on the EEM test as compared to healthy controls, even though they did not suffer from overt schizophrenia.[31)] It is thought that these abnormalities on the EEM test are genetic in origin and demonstrate an intermediate phenotype in schizophrenia.[32)]

If abnormalities on the EEM test were an intermediate phenotype of schizophrenia, we wondered what results of the EEM test would be obtained from individuals who did not have a family history of schizophrenia, but exhibited attenuated psychotic symptoms. Therefore, we focused on the characteristics of EEMs in patients with APS without a family history of schizophrenia in the present study. The aim of this study was to investigate the EEMs in APS patients without a family history as compared to those in patients with schizophrenia and in healthy control subjects. Furthermore, we examined the diagnostic contribution of EEMs in patients with APS, which might be useful for assessing the risk of development of schizophrenia together

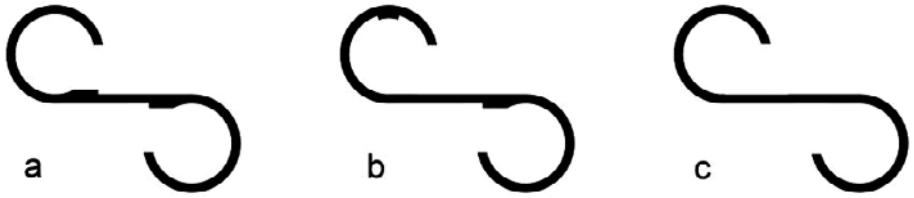

Fig. 1 Original target figure (a) and the two figures that were slightly different from the target figure (b, c).

with the criteria of ultra-high-risk patients.

Materials and Methods

Participants

We administered the Prevention Through Risk Identification, Management and Education (PRIME) Screen-Revised (PS-R) program for every individual who visited the Department of Psychiatry at the Toho University Omori Medical Center, Tokyo, for detecting potential APS candidates.[33] After this screening, we assessed patients with the SIPS Japanese version to determine if the subjects fulfilled the APS criteria.[13] Based on assessment by SIPS/SOPS, 27 individuals were diagnosed as having APS. Two of these subjects were excluded from this group, as they had a family history of schizophrenia. The mean age of patients with APS (7 men and 18 women) was 20.4 (SD = 5.7) years. Of the 25 patients with APS, 13 were receiving antipsychotic medication. The mean daily chlorpromazine (CPZ)-equivalent dosage of prescribed antipsychotics in these subjects was 119.2 (SD = 108.8) mg.[34]

For comparison, 25 patients with schizophrenia (11 inpatients and 14 outpatients) were also recruited from the medical center. The diagnosis was made by 2 experienced psychiatrists based on the International Statistical Classification of Disease and Related Health Problem Version 10 (ICD-10). The mean age of these patients with schizophrenia (14 men and 11 women) was 23.5 (SD = 5.5) years. The mean duration of illness was 4.6 (SD = 3.8) years. Six out of the 25 patients with schizophrenia had a family history of schizophrenia. Of the 25 patients with schizophrenia, only 1 was not receiving any antipsychotics. All the remaining were receiving antipsychotic agents at an average daily dosage of 500.7 (SD = 285.5) mg (CPZ-equivalent).

In addition, we administered the EEM test to 30 healthy control subjects (13 men and 17 women) who were recruited from independent sources in the community. None of these subjects had any past or family history of psychiatric disorders. The mean age of these subjects was 26.1 (SD = 2.4) years.

All subjects were under 40 years of age and native Japanese, and none had any history of substance dependence or neurological disease. We carefully explained the procedure of this study and obtained written informed consent from each of the subjects for participation in the study. For subjects who were under 20 years, we also explained the contents of this research to their parents or legal representatives and obtained written informed consent from them. This study was performed in accordance with the World Medical Association's Declaration of Helsinki and with the approval of the Ethics Committee of the Toho University Omori Medical Center (26-239).

Measures

We used a digital eye-mark recording system (Nac Image Technology, EMR-NS, Tokyo, Japan) for this study. This device includes an eye camera that detects the corneal reflection of infrared light to identify eye movements, and a 15-inch LCD monitor displaying figures for the EEM tasks. The subjects' eye movements were automatically recorded and analyzed by the computer. We focused on four parameters: number of eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL), and responsive search score (RSS).

First, the original S-shaped figure (Fig. 1a) was displayed on the LCD monitor, and the subject taking the test was instructed to view it carefully for 15 s. Next, the subject was asked to "Please draw the next figure after finishing this test" and shown the original S-shaped figure again for 15 s. The eye movements were recorded while the subject was gazing at the figure, and the fixation points were recorded if the eye movement stopped in any specific areas for more than 0.1 s. The number of eye fixations was recorded as NEF, the total eye scanning length as TESL, and the average eye scanning length as MESL.

For comparison, the subjects were asked to look at a slightly different figure, which had one bump in a different position (Fig. 1b), for 15 s. After 15 s had passed, the sub-

Table 1 Comparison of EEM test parameters

	Healthy controls (n = 30)	APS (n = 25)	Schizophrenia (n = 25)		Post hoc		
EEM test parameters	Mean (SD)	Mean (SD)	Mean (SD)	p value	HCs vs APS	APS vs Sz	HCs vs Sz
NEF	35.57 (8.56)	28.44 (8.22)	29.04 (8.21)	0.004	0.022	0.969	0.011
TESL (mm)	1828.76 (630.55)	1312.31 (673.06)	1363.76 (652.76)	0.008	0.020	0.963	0.040
MESL (mm)	51.27 (14.84)	44.22 (14.84)	46.94 (14.99)	0.231	0.241	0.581	0.822
RSS	8.23 (2.19)	6.08 (2.53)	5.84 (1.85)	<0.001	0.003	0.931	<0.001
Positive / Negative	4 / 26	11 / 14	18 / 7	<0.001	<0.001	0.218	<0.001

One-way ANOVA with post hoc comparisons (Scheffe's *F*-test).
EEM: exploratory eye movement; SD: standard deviation; HCs: healthy controls; APS: attenuated psychotic syndrome; Sz: schizophrenia; NEF: number of eye fixations; TESL: total eye scanning length; MESL: mean eye scanning length; RSS: responsive search score; Positive: schizophrenia suspected; Negative: schizophrenia not suspected

jects were asked whether it differed from the original figure. If the subject responded with a "Yes," he/she was asked what was different. Then, the subject was asked if there were any other differences. After this question was asked, RSS was automatically recorded based on the number of areas where the eye movement stopped during a 5-s period. The figure was divided into seven sections, and the best score for RSS was 7 in this task.

The same procedure was repeated for the next figure, which was not different from the original figure (Fig. 1a). The subject was expected to reply that there was no difference.

The comparison task was repeated with a figure without the bumps (Fig. 1c). Similar to the first comparison task, the eye movements were automatically recorded after the question, and RSS was calculated. The maximum possible RSS score of this whole test added up to 14. Finally, the subject was asked to draw the target figure on a piece of paper.

TESL and RSS have already been reported as valid variables for discriminating between "schizophrenia suspected" and "schizophrenia not suspected." In a previous study, the following discriminant function was derived for the discriminant analysis: $D = 4.100 + (0.001 \times TESL + 0.332 \times RSS)$.[25] The results of RSS and TESL were applied to this discriminant function, and if the result was over 0 ($D > 0$), the subject was classified as "schizophrenia suspected." We called them positive subjects. If the result was under 0 ($D < 0$), the subject was classified as "schizophrenia not suspected." We called them negative subjects. We also calculated the sensitivity and specificity of this test based on these results.

Statistical analysis

The differences in the values of each of the parameters (NEF, TESL, MESL, and RSS) among the 3 groups were analyzed by one-way analysis of variance (ANOVA), followed by post hoc comparisons (Scheffe's *F*-test). Whether subjects were positive or negative was assessed using the χ^2-test. The statistical significance was set at $p < 0.05$ (two tailed). All statistical analyses were performed using SPSS for Windows version 23.0 (IBM Corp., Armonk, NY).

Results

The values of the 4 EEM parameters (NEF, TESL, MESL, and RSS) in the healthy control, APS, and schizophrenia groups, and the number of subjects classified as positive or negative by the discriminant function are shown in Table 1. The dot plots of the distribution of the 4 parameters (NEF, TESL, MESL, and RSS) are shown in Fig. 2.

One-way ANOVA revealed significant differences among the 3 groups in NEF, TESL, and RSS. Subsequent post hoc testing (Scheffe's *F*-test) revealed significantly higher values of NEF, TESL, and RSS in the APS and schizophrenia groups as compared to the healthy controls. However, the values of these 3 parameters were not significantly different between the APS and schizophrenia groups. MESL was also not significantly different among the 3 groups.

The scatter diagram of TESL and RSS is shown in Fig. 3. The discriminant function is also described in this diagram. The plots under the discriminant function represent subjects who were classified as "schizophrenia suspected" (positive subjects). The percentages of positive subjects identified by the discriminant function in the healthy con-

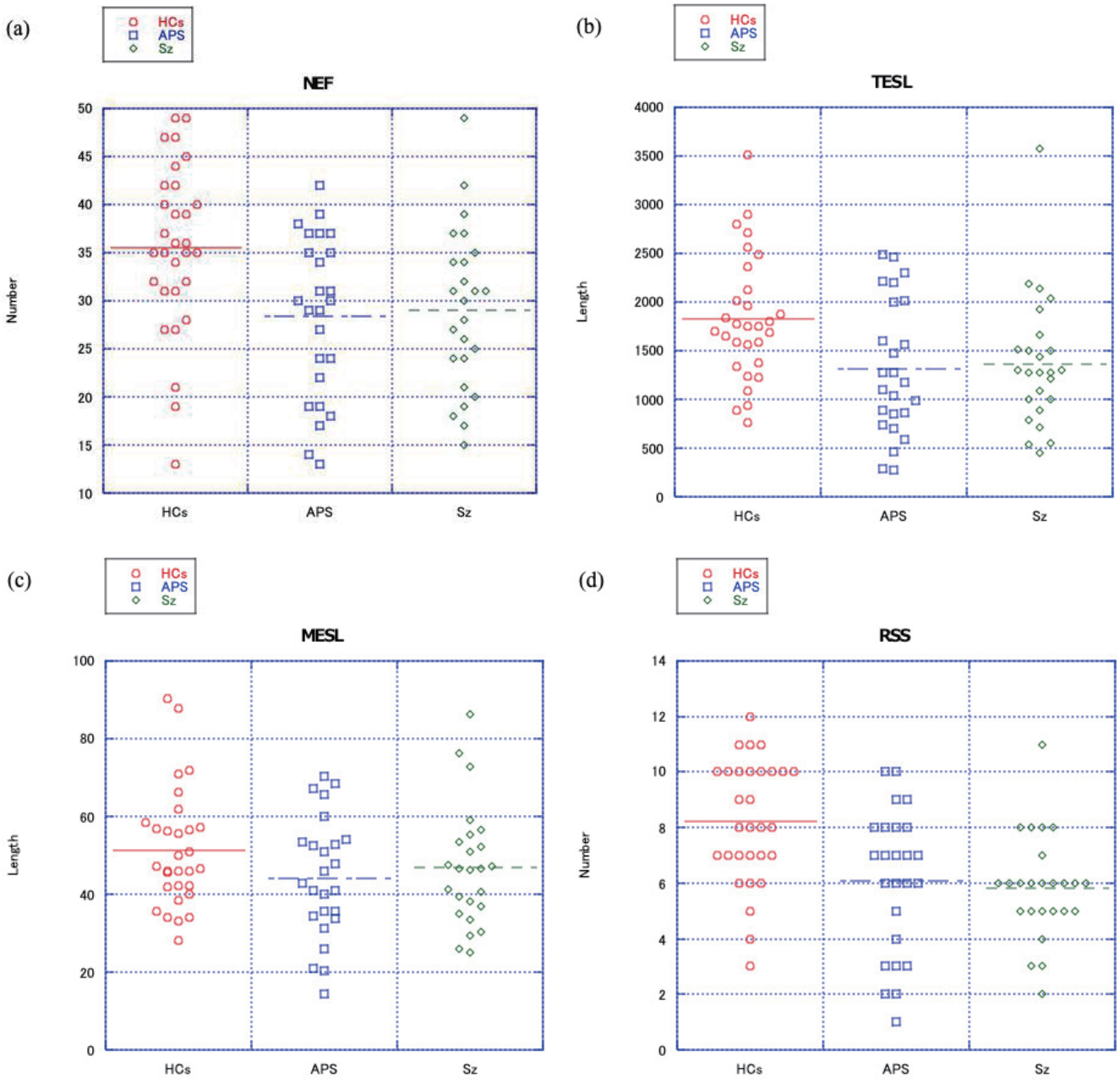

Fig. 2 Distribution of (a) number of eye fixations (NEF), (b) total eye scanning length (TESL), (c) mean eye scanning length (MESL), and (d) responsive search score (RSS) in the healthy control, attenuated psychosis syndrome (APS), and schizophrenia (Sz) groups. The bars represent mean values.

trol, APS, and schizophrenia groups were 13.3%, 56.0%, and 72.0%, respectively. Although the percentage of positive subjects among the healthy controls was significantly lower than that in the APS and schizophrenia groups, it did not differ significantly between the APS and schizophrenia groups.

Based on these results, the sensitivity of this test was 72.0%: that is, 72.0% of patients with schizophrenia were correctly discriminated as "schizophrenia suspected." On the other hand, the specificity of this test was 86.7%: that is, only 13.3% of healthy controls were wrongly discriminated as "schizophrenia suspected."

Discussion

In this study, we examined the EEMs of healthy control subjects, of patients with APS without a family history, and of patients with schizophrenia. The results revealed significantly lower values of NEF, TESL, and RSS in pa-

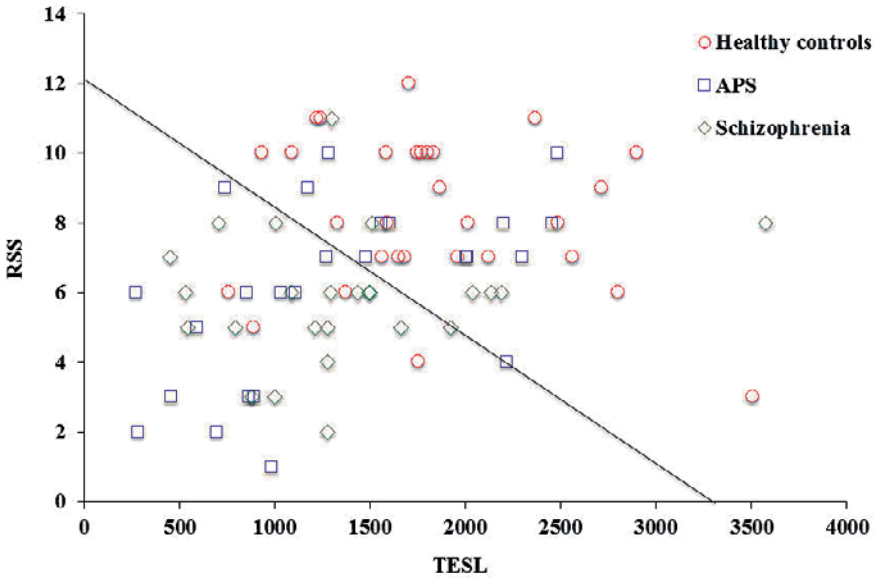

Fig. 3 Scatter diagram of total eye scanning length (TESL) and responsive search score (RSS) in the healthy control, attenuated psychosis syndrome (APS), and schizophrenia groups. The discriminant line is also shown in the graph. Data under the line show subjects discriminated as "schizophrenia suspected."

tients with APS and schizophrenia than in healthy control subjects. However, there were no differences in the values of any of these 3 parameters between patients with APS and those with schizophrenia.

In previous studies, NEF was lower in patients with schizophrenia or depression than in healthy controls.[30, 35] As the diagnosis of APS was supposed to be determined only by the positive symptoms score on SOPS, some patients with APS possibly had a depressed mood. Therefore, the results can be influenced by these 2 factors.

Among the 4 parameters of the EEM test, the values of only MESL were not significantly different among the 3 groups in this study. MESL reportedly reflected the chronicity of schizophrenia.[29] As the mean age and duration of illness in the schizophrenia group were 23.5 years and 4.6 years, respectively, their illness stage was not necessarily chronic. This could explain why there were no significant differences in MESL among the 3 groups.

In a previous study, both TESL and RSS were specifically lower only in patients with schizophrenia as compared to healthy controls and patients with other psychiatric disorders.[30] In the present study, both TESL and RSS were lower in patients with APS as compared to healthy controls. The characteristics of the EEMs in patients with APS were similar to those of patients with schizophrenia. Moreover, in a study of the relationship between EEMs and brain morphology in patients with schizophrenia spectrum disorders, the decrease in RSS was correlated with dysfunction of the neural network in the right frontal eye field, right supplementary eye field and parietal eye field, and right inferior frontal region.[36] Another study demonstrated a significant positive correlation of RSS with gray matter volume in the left supplementary motor area, left superior frontal cortex, bilateral precentral gyri, bilateral postcentral gyri, and bilateral middle frontal cortices in patients with schizophrenia.[37] In addition, longitudinal research of ultra-high-risk individuals revealed that they had reduced white matter and increased cortical thinning in the left middle temporal gyrus as compared to healthy controls.[38] The results of the present study and these other studies suggest that the biological changes associated with EEMs already exist at the stage of APS.

It has been revealed in a previous study that abnormal EEMs indicate an intermediate phenotype and a trait marker of schizophrenia.[32] We recruited APS patients without a family history in this present study to focus on individuals who were recognized as being at an ultra-high risk of psychosis only on the basis of psychopathology. Nevertheless, the EEMs of patients with APS were similar to those of patients with schizophrenia. This result indicates that some patients with subthreshold psychotic symptoms possibly have genetic risk factors even if none

of their siblings suffer from psychosis/schizophrenia. There are two types of ultra-high-risk states for schizophrenia: genetic and symptomatic. The results of the present study suggest that these two high-risk types are closely related to each other. Family history is recognized only by the existence of a proband suffering from frank psychosis. None of the APS individuals in the present study had such a family history; however, some ultra-high-risk individuals detected only with psychopathology may include risks associated with genetic factors, even though they do not have any obvious psychotic features yet.

The sensitivity and specificity of EEMs in the present study for the diagnosis of schizophrenia were 72.0% and 86.7%, respectively. This result is consistent with previous reports.[23, 25, 28] In recent years, other examination modalities, such as fMRI and biomolecule examinations, have been developed for the diagnosis of schizophrenia.[39] The present results suggest that we can utilize the EEM test to estimate the risk of psychosis more precisely. A careful follow-up of individuals with APS by the EEM test can lead to early detection, prompt treatment, and adequate support in the future.

Limitations

A few limitations in this study should be mentioned. First, how many subjects with APS will actually develop schizophrenia could not be estimated because this study is a cross-sectional study. Therefore, we should continue to observe these subjects longitudinally to prove the relationship between the results of EEM parameters and the risks of developing psychosis in individuals with APS. Besides, the results of sensitivity and specificity in individuals with APS are not obtained without the onset rate of them. Second, the present study adopted SIPS/SOPS, in which the diagnosis of APS was determined only by the positive symptoms score. Accordingly, other evaluations such as negative symptoms were not considered in this study. The previous study revealed that EEM parameters were associated with negative symptoms in schizophrenia;[28] therefore, the score of negative symptoms may also influence the results in APS.

Conclusion

The characteristics of EEMs in patients with APS were similar to those in patients with schizophrenia. Individuals with APS in the present study did not have a family history; however, some ultra-high-risk individuals detected only with psychopathology may include risks associated with genetic factors, even though they do not have any obvious psychotic features yet. The EEM test seems useful in detecting individuals with APS and early schizophrenia.

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Conflicts of interest: None declared.

Author Contributions: Y.S., T.N., J.S., and M.M. conceived the idea and methodology of this study. E.M. and T.K. were involved in the conceptualization level of the study. Y.S. collected the data. Y.S. and T.N. analyzed the data. Y.S. wrote the first draft of the manuscript. T. N. revised the manuscript. All authors contributed to the preparation of the final manuscript and have approved its submission.

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