Psychiatry and Clinical Neurosciences 2012; 66: 187–194 doi:10.1111/j.1440-1819.2011.02314.x

Regular Article

Relationships between exploratory eye movement dysfunction and clinical symptoms in schizophrenia

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Aim: Many psychophysiological tests have been widely researched in the search for a biological marker of schizophrenia. The exploratory eye movement (EEM) test involves the monitoring of eye movements while subjects freely view geometric figures. Suzuki *et al.* (2009) performed discriminant analysis between schizophrenia and non-schizophrenia subjects using EEM test data; consequently, clinically diagnosed schizophrenia patients were identified as having schizophrenia with high probability (73.3%). The aim of the present study was to investigate the characteristics of schizophrenia patients who were identified as having schizophrenia on EEM discriminant analysis (SPDSE) or schizophrenia patients who were identified as not having schizophrenia on EEM discriminant analysis (SPDNSE).

Methods: The data for the 251 schizophrenia subjects used in the previous discriminant-analytic study were analyzed, and the demographic or symptomatic characteristics of SPDSE and SPDNSE were investigated. As for the symptomatic features, a factor analysis of the Brief Psychiatric Rating Scale (BPRS) rating from the schizophrenia subjects was carried out.

Results: Five factors were found for schizophrenia symptoms: excitement/hostility; negative symptoms; depression/anxiety; positive symptoms; and disorganization. SPDSE had significantly higher factor scores for excitement/hostility, negative symptoms and disorganization than SPDNSE. Furthermore, the BPRS total score for the SPDSE was significantly higher than that for the SPDNSE.

Conclusion: SPDSE may be a disease subtype of schizophrenia with severe symptoms related to excitement/hostility, negative symptoms and disorganization, and EEM parameters may detect this subtype. Therefore, the EEM test may be one of the contributors to the simplification of the heterogeneity of schizophrenia.

Key words: biological marker, clinical symptoms of schizophrenia, exploratory eye movement, heterogeneity, schizophrenia.

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Received 4 September 2010; revised 29 August 2011; accepted 9 September 2011.

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MANY PSYCHOPHYSIOLOGICAL TESTS have been performed in the search for a biological marker for schizophrenia.[1,2] Event-related potentials (ERP), P300,[3] P50[4] and mismatch negativity (MMN),[5,6] prepulse inhibition (PPI),[7,8] saccadic and smooth pursuit eye movements[9–12] and working memory tasks[13,14] have been widely researched. Moreover, many researchers have focused on abnormalities of working memory as an endophenotype for schizophrenia in molecular genetic studies.[15,16]

We have studied eye movements while subjects freely viewed geometric figures; this is called the exploratory eye movement (EEM) test. In most previous studies, only schizophrenia patients have consistently shown disturbances of EEM.[17–25] Moreover, the parents and siblings of schizophrenia patients had EEM dysfunctions.[26,27] In addition, EEM demonstrated a significant linkage to chromosome 22q11.[28] Chromosome 22q11 is one of the most interesting regions in the genetic etiology of schizophrenia. Microdeletions at chromosome 22q11 cause velocardio-facial syndrome (VCFS/DiGeorage syndrome: DGS), and patients with VCFS have a high risk of schizophrenia.[29,30] Furthermore, there is strong evidence that this deletion is a risk factor for schizophrenia in a genome-wide association study (GWAS) using copy number variants (CNV).[31] Therefore, we believe that EEM disturbance may be a biological marker of schizophrenia, in addition to the aforementioned physiological defects.

On the basis of these findings, we considered that the EEM test might be useful for the clinical diagnosis of schizophrenia as well. Suzuki *et al.* carried out a discriminant analysis between schizophrenia patients and non-schizophrenia subjects in a large sample using EEM test data.[32] EEM performance was recorded in 251 schizophrenia patients and 389 non-schizophrenia subjects (111 patients with mood disorder; 28 patients with neurotic disorder; 250 normal controls). As a result, 184 of the 251 clinically diagnosed schizophrenia patients were identified as having schizophrenia (sensitivity, 73.3%); and 308 of the 389 clinically diagnosed non-schizophrenia subjects were identified as non-schizophrenic (specificity, 79.2%). Based on this finding, we propose that the EEM test might be useful for the clinical diagnosis of schizophrenia.

In the discriminant-analytic study,[32] we were interested in characteristics of the schizophrenia patients who were identified as having schizophrenia on EEM discriminant analysis (SPDSE), or those who were identified as not having schizophrenia on EEM discriminant analysis (SPDNSE). Many researchers have indicated the potential heterogeneity of schizophrenia.[33–37] Hence, the EEM parameters may be able to detect different subtypes of schizophrenia. In the present study, to clarify the features of SPDSE and SPDNSE, we reanalyzed that data,[32] and focused on the demographic or symptomatic characteristics. If the characteristics of SPDSE and SPDNSE are clarified, further knowledge regarding the heterogeneity of schizophrenia may be yielded. Therefore, in the present study we discuss the features of SPDSE and SPDNSE and a further application of EEM for scientific research into schizophrenia.

METHODS

Subjects

Two hundred and fifty-one schizophrenia patients participated in the discriminant-analytic study (paranoid type, 65.3%; hebephrenic type, 15.9%; catatonic type, 1.2%; undifferentiated type, 5.2%; residual type, 9.6%; simple type, 1.6%; and unspecified type, 1.2%).[32] The patients were in/outpatients recruited from multiple centers, eight university hospitals and three affiliated hospitals. Diagnoses were made by one experienced psychiatrist according to the ICD-10 criteria for research at each university or hospital.[38] The demographic characteristics of the subjects were as follows: age, 37.9 ± 11.3 years; gender (M/F), 157/94; and duration of illness, 14.5 ± 13.1 years. The 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.

The clinical symptoms of the schizophrenia patients were assessed using the Brief Psychiatric Rating Scale (BPRS),[39] which yielded an average total score of 41.5 ± 13.3. All BPRS ratings were done by one experienced psychiatrist in each university or hospital. Of the 251 patients with schizophrenia, 249 received neuroleptic medication. The average daily dosage is expressed as a haloperidol equivalent of 13.9 ± 10.7 mg.[40] 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.

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Procedure

A standard test of the EEM using a digital eye-mark recording system (nac Image Technology, EMR-NS, Tokyo, Japan) was performed. An eye camera that detected corneal reflection of infrared light to identify eye movements, and a 15-in LCD monitor (1024 × 768 pixels) that displayed target figures for the EEM tasks (Fig. 1) were included in this system. According to the following method, 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. 1). First, the retention task: the subject was shown the original S-shaped figure (Fig. 1a) for 15 s. Next, the comparison task: the subject was instructed to compare a figure with the original figure (Fig. 1a); they were then shown a figure slightly different from the original one, which had one bump in a different position (Fig. 1b), for 15 s. 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. After the subject had replied and while the figure was still being shown, he/she was asked 'Are there any other differences?' The comparison task was then repeated with a figure without bumps (Fig. 1c).

In the digital eye-mark recording system, the detected eye movements were automatically analyzed by a digital computerized EEM analyzer. Consequently, 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 equipment and method are given in our previous studies.[17,20,32]

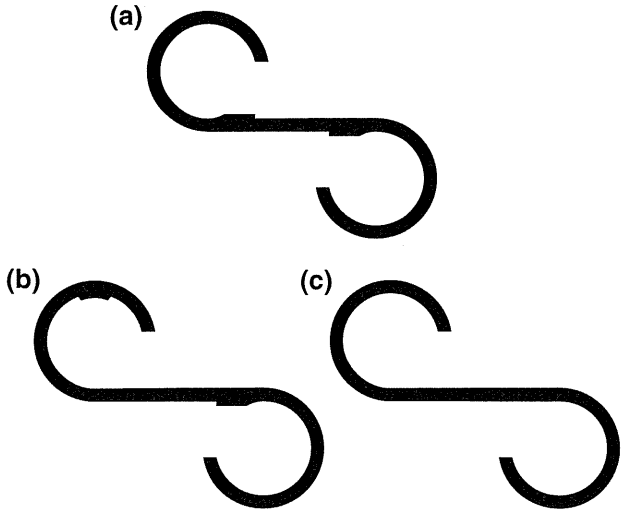

Figure 1. (a) Original target figure; (b,c) two figures slightly different from the target.

In our previous study, 184 of the 251 clinically diagnosed schizophrenia patients were identified as having schizophrenia on discriminant analysis using the EEM parameters (SPDSE).[32] The remaining 67 schizophrenia patients were identified as not having schizophrenia (SPDNSE). Table 1 lists the background data of the SPDSE and SPDNSE. In the present study we compared demographic and symptomatic characteristics of SPDSE with those of SPDNSE.

Statistical analysis

Group differences on the demographic and symptomatic data were assessed using the *t*-test or the χ^2 test. For group comparison of the symptomatic data, scores for factors extracted by factor analysis of BPRS ratings and BPRS total scores were used. In the factor analysis, we conducted a principal component analysis with orthogonal rotation (Varimax method) according to previous studies.[41–43] Moreover, based on prior studies, factors with eigenvalues >1.0 were considered to be meaningful.[41,43] All statistical analyses were performed using SPSS for Windows version 17.0. The statistical significance was set at $P < 0.05$ (two-tailed).

RESULTS

Group comparisons (SPDSE vs SPDNSE) of demographic characteristics

There were no significant differences for age, sex, duration of illness or drug dosage between SPDSE and SPDNSE.

Group comparisons (SPDSE vs SPDNSE) of subtypes and clinical symptoms

There were no significant differences for the subtypes between SPDSE and SPDNSE.

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Table 1. Subject characteristics

	SPDSE ($n = 184$)	SPDNSE ($n = 67$)
Age (years), mean ± SD	38.0 ± 12.6	37.7 ± 12.0
Gender (M/F)	112/72	45/22
Duration of illness (years), mean ± SD	14.6 ± 13.9	14.3 ± 10.8
Equivalent dose of haloperidol (mg), mean ± SD†	14.4 ± 11.1	12.5 ± 9.7
Subtype, *n* (%)		
Paranoid	120 (65.3)	44 (65.6)
Hebephrenic	30 (16.3)	10 (14.9)
Catatonic	3 (1.6)	0 (0)
Undifferentiated	9 (4.9)	4 (6.0)
Residual	18 (9.8)	6 (9.0)
Simple	3 (1.6)	1 (1.5)
Unspecified	1 (0.5)	2 (3.0)

†In each group (SPDSE or SPDNSE), one patient did not receive neuroleptic medication, respectively.
SPDSE, schizophrenia patients identified as having schizophrenia on exploratory eye movement (EEM) discriminant analysis; SPDNSE, schizophrenia patients identified as not having schizophrenia on EEM discriminant analysis.

Factor analysis of BPRS items

Table 2 lists the factors and factor loadings derived using principal component analysis of BPRS rating. The principal component analysis extracted five factors that accounted for 70.0% of the variance. Based on previous studies, BPRS items with factor loadings >0.5 were considered to load on the

Table 2. Factors and factor loadings derived in BPRS principal component analysis

	Factor				
	1	2	3	4	5
BPRS items					
Somatic concern	0.033	0.080	0.615	0.505	−0.074
Anxiety	0.184	0.123	0.727	0.272	−0.126
Emotional withdrawal	0.070	0.879	0.139	0.043	0.140
Conceptual disorganization	0.401	0.298	0.113	0.356	0.629
Guilt feelings	0.091	−0.085	0.670	−0.157	0.487
Tension	0.416	0.404	0.543	0.106	−0.126
Mannerisms and posturing	0.383	0.457	0.178	0.339	0.393
Grandiosity	0.736	−0.115	0.133	0.124	0.158
Depressive mood	0.192	0.287	0.722	0.041	−0.058
Hostility	0.783	0.077	0.213	0.210	−0.118
Suspiciousness	0.477	0.126	0.273	0.546	−0.111
Hallucinatory behavior	0.246	0.171	0.045	0.805	0.067
Motor retardation	0.004	0.850	0.179	0.159	0.083
Uncooperativeness	0.677	0.432	−0.057	0.122	0.086
Unusual thought content	0.276	0.170	0.133	0.734	0.322
Blunted affect	0.021	0.857	0.083	0.168	0.160
Excitement	0.778	−0.023	0.195	0.218	0.153
Disorientation	−0.034	0.241	−0.241	0.056	0.659
Variance explained (total = 70.0%)†	17.5	17.5	14.1	12.6	8.4

†Cumulative or percentage of variance explained is rounded off; therefore, the cumulative percentage is not identical to the sum of each percentage. Underline, BPRS items with factor loadings >0.5.
BPRS, Brief Psychiatric Rating Scale.

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Table 3. Mean factor scores and BPRS total score (mean ± SD)

	SPDSE ($n = 184$)	SPDNSE ($n = 67$)	t (d.f. = 249)	z
Factor				
1 Excitement/hostility	0.09 ± 1.07	−0.25 ± 0.74		−2.16*
2 Negative symptoms	0.10 ± 1.01	−0.27 ± 0.93	−2.57*	
3 Depression/anxiety	−0.03 ± 1.03	0.07 ± 0.92	0.70	
4 Positive symptoms	0.03 ± 1.03	−0.07 ± 0.92	−0.71	
5 Disorganization	0.08 ± 1.03	−0.21 ± 0.89	−2.06*	
BPRS total score (mean ± SD)	43.08 ± 13.48	37.51 ± 12.10	−2.98*	

*$P < 0.05$.

BPRS, Brief Psychiatric Rating Scale; SPDSE, schizophrenia patients identified as having schizophrenia on exploratory eye movement (EEM) discriminant analysis; SPDNSE, schizophrenia patients identified as not having schizophrenia on EEM discriminant analysis.

respective factor.[41,43] Consequently, we summarized the five factors as follows: factor 1 loaded heavily in grandiosity, hostility, uncooperativeness and excitement; factor 2 had heavy loadings in emotional withdrawal, motor retardation and blunted affect; factor 3 loaded heavily in somatic concern, anxiety, guilt feelings, tension and depressive mood; factor 4 had heavy loadings in somatic concern, suspiciousness, hallucinatory behavior and unusual thought content; factor 5 loaded heavily in conceptual disorganization and disorientation. Accordingly, we interpreted the five factors as having the following dimensions: factor 1, excitement/hostility (17.5% of total variance); factor 2, negative symptoms (17.5%); factor 3, depression/anxiety (14.1%); factor 4, positive symptoms (12.6%); and factor 5, disorganization (8.4%).

Group comparisons (SPDSE vs SPDNSE) of factor scores

Table 3 lists the mean factor scores of the five factors for SPDSE and SPDNSE. SPDSE had significantly higher scores of excitement/hostility ($P = 0.005$), negative symptoms ($P = 0.011$) and disorganization ($P = 0.040$) than SPDNSE. Furthermore, the BPRS total score of SPDSE was significantly higher than that of the SPDNSE ($P = 0.003$). For the excitement/hostility factor, the Levene test for equality of variance did not show homoskedasticity between the two groups. Therefore, the P-value for the excitement/hostility factor was based on an unequal-variance t-value. In order to confirm the result of the excitement/hostility factor, we also performed the non-parametric test, Mann–Whitney U-test. Consequently, SPDSE also demonstrated significantly higher scores of excitement/hostility than SPDNSE on non-parametric analysis ($P = 0.031$).

DISCUSSION

Suzuki *et al.* performed discriminant analysis between schizophrenia patients and non-schizophrenia subjects using the EEM test data.[32] As a result, 184 of the 251 clinically diagnosed schizophrenia patients were identified as having schizophrenia (sensitivity, 73.3%). In the present study, results of the factor analysis of BPRS ratings from the aforementioned 251 schizophrenia subjects produced five factors of symptoms (excitement/hostility; negative symptoms; depression/anxiety; positive symptoms; and disorganization). Excitement/hostility, negative symptoms and disorganization were more predominant in the 184 SPDSE subjects compared to the SPDNSE subjects. Furthermore, the BPRS total score of the SPDSE was significantly higher than that of the SPDNSE. Consequently, the SPDSE group may consist of patients with severe schizophrenia, and the severity of symptoms in SPDSE was found to be due mainly to excitement/hostility, negative symptoms and disorganization.

Evidence for five dimensions in schizophrenia symptoms was found in the present study. Many studies have proposed similar five-factor structures.[41–47] In these studies, the Positive and Negative Syndrome Scale (PANSS) has been used as the symptom rating scale. In contrast, the present data were based on the BPRS. All items of the BPRS, however, are included in the PANSS.[39,48] Therefore, it

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is possible that the present findings reflect the past studies of the factor analysis using PANSS items. Consequently, although items included for each factor in previous studies and the present study were not identical, the present findings of the factor analysis are distinctly similar to previous factor-analytic study results. Thus, we consider that the present five-factor structure may be meaningful for the symptomatology of schizophrenia. The PANSS, however, is more informative than the BPRS, therefore the present study may be limited by this issue.

In the present study, demographic data, age, sex, duration of illness and drug dosage for SPDSE and SPDNSE were not significantly different. But there were significant differences for symptom, excitement/hostility, negative symptoms and disorganization between SPDSE and SPDNSE. In our previous study, EEM parameters were not influenced by the demographic data.[27,32] Moreover, one of the EEM parameter, RSS, which was principally used in the discriminant analysis of SPDSE, was associated with negative symptoms.[17] Altogether, we believe that differences between SPDSE and SPDNSE in the EEM may relate to symptoms of schizophrenia, but not demographic data, sex, age, course of illness or medication.

With regard to the ICD-10 subtypes, we also did not find significant differences between SPDSE and SPDNSE. This finding seems to conflict with the significant differences of the BPRS scores between the two groups. Lykouras *et al.* investigated relationships between the DSM-III-R schizophrenia subtypes and the PANSS scores.[49] As a result, paranoid type was associated with positive symptoms, and disorganized type linked to negative symptoms. In addition to disorganized type, however, catatonic type related to negative symptoms. Moreover, based on the DSM-IV-TR, the schizophrenia symptoms have been divided into three dimensions.[50] However, past reports and the present study propose that schizophrenia may be symptomatically more complex.[41–47] This has also been indicated by Wolthaus *et al.*[47] In this way, subtypes and dimensions of the diagnostic criteria are often not consistent with those of the symptomatic rating scales. There is, however, a possible limitation to the present study. Although we discussed diagnoses using the ICD-10 criteria and the BPRS scores in detail, inter-rater and intra-rater reliabilities for those were not formally assigned. Consequently, if they were formally assigned, the ICD-10 subtypes might coincide with the BPRS scores.

Based on the present findings, SPDSE may be associated with excitement/hostility, negative symptoms and disorganization in the present five symptomatic dimensions. Accordingly, SPDSE may have three different dimensions; but it can also be said that SPDSE may be a schizophrenia subtype characterized by these three dimensions. The present findings may indicate that there is a putative subtype of schizophrenia with severe symptoms related to excitement/hostility, negative symptoms and disorganization. Furthermore, the EEM abnormality may be a biological marker for this subtype of schizophrenia. There is another point worth making. As mentioned here, the EEM parameter, RSS was associated with negative symptoms.[17] Thus, negative symptoms may be the most specific of the three dimensions to the subtype.

In addition to the schizophrenia patients, their parents and siblings also had EEM dysfunction.[26,27] Therefore, we considered that the EEM abnormality may be an intermediate phenotype of schizophrenia, and may be useful for linkage studies of schizophrenia. Indeed, we found a significant linkage to chromosome 22q11.2–12.1 in our previous linkage study using EEM impairment as an endophenotype of schizophrenia.[28] Chromosome 22q11 is one of the most interesting regions for the etiology of schizophrenia. Moreover, in this area, there are several candidate genes for schizophrenia, for example COMT, PRODH and ZDHHC8, and so on.[29,30]

Many researchers have presented positive linkage and association findings with schizophrenia, but initial findings have often not been replicated.[30] One of the most significant causes of conflicting results in the present molecular genetic studies of schizophrenia may be the potential heterogeneity of schizophrenia. Several investigators have suggested that schizophrenia is not a single disease entity but may reflect common symptomatology caused by several distinct genetic abnormalities.[33–37] As mentioned here, the EEM deficits are linked to chromosome 22q11. If the EEM parameters are associated with a schizophrenia subtype with severe symptoms related to excitement/hostility, negative symptoms and disorganization, chromosome 22q11 and genes of 22q11 may relate to this subtype. In this manner, if we are able to find a new subtype using the EEM disturbances, and clarify the heterogeneity of schizophrenia, then linkage or association studies for schizophrenia using the subtype may yield further knowledge regarding the genetic influences on schizophrenia.

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In conclusion, we have found evidence for the existence of five dimensions of schizophrenia symptoms: excitement/hostility; negative symptoms; depression/anxiety; positive symptoms; and disorganization. Schizophrenia patients with EEM abnormalities (SPDSE) may have severe symptoms related to excitement/hostility, negative symptoms and disorganization. In light of the heterogeneity of schizophrenia, SPDSE may be a disease subtype of schizophrenia with the aforementioned symptomatic features; and the EEM parameters may detect this subtype. Therefore, EEM may be one of the contributors to the simplification of the heterogeneity of schizophrenia. Consequently, we may apply EEM to other scientific studies as an endophenotype for schizophrenia.

ACKNOWLEDGMENT

The present study was supported by a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health (H16-KOKORO-003) from the Ministry of Health, Labor and Welfare, Japan.

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