dopamine D_2 receptor binding was observed in the frontal cortex (Kaasinen et al., 2001). Further studies to investigate gender differences in pre- and postsynaptic dopaminergic neurotransmission components using database would be required.

Thalamic dopaminergic system

The dopaminergic projections to the thalamus from neurons in the hypothalamus, periaqueductal gray matter, ventral mesencephalon, and the lateral parabrachial nucleus were reported (Sanchez-Gonzalez et al., 2005). Therefore, a dopaminergic system targeting the thalamus, which might be independent from the nigrostriatal dopaminergic system and the mesocorticolimbic dopaminergic system, has been proposed (Sanchez-Gonzalez et al., 2005). In the present study, relatively high binding to dopamine D_2 receptors was observed in the thalamus. In particular, anterior nuclei and dorsomedial nucleus showed higher binding in the present study, the same as reported by previous studies of the living human brain (Okubo et al., 1999) and human postmortem brain (Hall et al., 1996; Rieck et al., 2004). On the other hand, binding to dopamine D_1 receptors was very low (Hall et al., 1994). Binding to dopamine transporter was very low in the thalamus, the same as in the postmortem study (Hall et al., 1999), although dopamine D_2 receptors exist in this region. This means that released dopamine in the thalamic dopaminergic synapse might be inactivated by enzymatic degradation, the same as reported in other extrastriatal regions (Hall et al., 1999). Although aromatic L-amino acid decarboxylase activity in the thalamus has been reported to be very low (Lloyd and Hornykiewicz, 1972), dopamine synthesis in this region was observed in the living human brain, supporting the existence of dopaminergic innervation in the thalamus.

In conclusion, we have built a normal database of pre- and postsynaptic dopaminergic neurotransmission components in the living human brain using PET and the anatomic standardization technique. This database enables us to compare regional distributions of striatal and extrastriatal dopamine D_1 and D_2 receptor bindings, dopamine transporter binding, and endogenous dopamine synthesis. This database is expected to be useful for various researches to understand the physiology of dopaminergic functions in the living human brain. This database can also be used in the investigation of regional abnormalities of dopaminergic neurotransmission in neuropsychiatric disorders.

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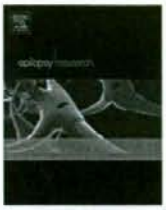

Difference in age of onset of psychosis between epilepsy and schizophrenia

Naoto Adachi[a,b,*], Tsunekatsu Hara[c], Yasunori Oana[d], Masato Matsuura[e], Yoshiro Okubo[f], Nozomi Akanuma[b], Masumi Ito[b], Masaaki Kato[b], Teiichi Onuma[b]

[a] *Adachi Mental Clinic, Kitano 7-5-12, Kiyota, Sapporo 004-0867, Japan*
[b] *National Center Hospital for Mental, Nervous, and Muscular Disorder, NCNP, Tokyo, Japan*
[c] *Komagino Hospital, Tokyo, Japan*
[d] *Department of Neuropsychiatry, Tokyo Medical University Hospital, Tokyo, Japan*
[e] *Department of Neuropsychiatry, Nihon University Hospital, Tokyo, Japan*
[f] *Department of Neuropsychiatry, Tokyo Medical and Dental University Hospital, Tokyo, Japan*

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Summary To clarify the nature of psychosis development in epilepsy patients, we studied differences in age of onset of psychosis between epilepsy patients with psychosis (epilepsy-psychosis) and schizophrenia patients. Subjects were 282 patients with epilepsy-psychosis (36 postictal, 224 interictal, and 22 bimodal psychoses) and 612 schizophrenia patients. Age of onset was compared between the schizophrenia group and the whole epilepsy-psychosis group as well as its subgroups. Effects of sex and family history of psychosis on age of onset were also evaluated. Epilepsy patients developed psychosis later (mean age 30.1) than schizophrenia patients (mean age 26.6). Among epilepsy-psychosis subgroups, postictal psychosis and interictal psychosis showed a later onset than schizophrenia. In interictal psychosis, while chronic schizophrenia-like psychosis occurred at similar age compared to schizophrenia, brief episodic psychosis occurred at later age. Epilepsy-psychosis patients showed no sex difference in age of onset, whereas female schizophrenia patients showed a later onset than male schizophrenia patients. Both the epilepsy and schizophrenia patients with family history of psychosis tended to develop psychosis at an earlier age, although this did not reach statistically significant level. The findings of the study suggest that the nature of epilepsy-psychosis is not fully equivalent to that of schizophrenia.

* Corresponding author at: Adachi Mental Clinic, Kitano 7-5-12, Kiyota, Sapporo 004-0867, Japan. Tel.: +81 11 8810325; fax: +81 11 8810325.
E-mail address: adacchan@tky2.3web.ne.jp (N. Adachi).

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Introduction

Psychosis is an important issue in the treatment of patients with epilepsy (Trimble, 1991; Mendez et al., 1993). Whereas similarities between the psychoses of epilepsy patients (epilepsy-psychosis) and schizophrenia have long been considered (Trimble, 1991; Sachdev, 1998), the detailed nature of the epilepsy-psychosis still remains unclear. With respect to age of onset of these two psychotic conditions, there have been few comparisons between epilepsy-psychosis and schizophrenia. Schizophrenia tends to develop during a specific age period and with a sex difference at age of onset of psychosis; men showed a single high peak during adolescence to early adulthood, while women showed a second peak of onset after age 40 (Weinbergar, 1987; Hafner et al., 1998). In addition, a family history of illness is often associated with age of onset in schizophrenia patients (Gorwood et al., 1995; Alda et al., 1996) as well as in several neuropsychiatric diseases (Ridley et al., 1986; Weissman et al., 1986). Conversely, epilepsy patients often exhibit psychosis in their late twenties or early thirties (Trimble, 1991; Adachi et al., 2002). Little is known about sex differences and effects of family history of psychosis on age of onset of psychosis. We conducted a large, multi-center, controlled study to compare age of onset of epilepsy-psychosis with that of schizophrenia.

Materials and methods

Definition of psychoses

Psychosis was defined as the presence of hallucinations, delusions, or a limited number of severe behavioral abnormalities in accordance with the ICD-10 (World Health Organization (WHO), 1992). The diagnosis of epilepsy-psychosis required distinct psychotic symptoms in a clear conscious state after the development of epilepsy. This definition of epilepsy-psychosis was originally described by Pond (1957) and has subsequently been used in most studies in epilepsy-psychosis (Slater et al., 1963; Bruens, 1974; Kristensen and Sindrup, 1978; Bredkjaer et al., 1998; Adachi et al., 2000, 2002; Rayport and Ferguson, 2001; Qin et al., 2005). This entity satisfied the ICD-10 criteria for organic hallucinosis (F06.0), organic catatonic disorder (F06.1), or organic delusional disorder (F06.2).

Epilepsy-psychoses were subclassified into three categories: postictal psychosis (PIP), interictal psychosis (IIP), and bimodal psychosis (BMP). (1) PIP was diagnosed when all psychotic episodes occurred within 7 days after a decisive seizure or a cluster of seizures (Logsdail and Toone, 1988; Kanemoto et al., 1996; Adachi et al., 2002, 2007). (2) IIP was diagnosed when all episodes occurred during seizure-free periods or between habitual seizures (Sachdev, 1998; Adachi et al., 2000, 2002). IIP included chronic schizophrenia-like psychosis (at least 1 episode lasted for 1 month or more) and brief interictal psychosis (all episodes disappeared within 1 month) (Slater et al., 1963; Bruens, 1974; Sachdev, 1998; Adachi, 2006). (3) If both postictal and interictal psychotic episodes were observed on different occasions in an individual patient, BMP was diagnosed (Tarulli et al., 2001; Adachi et al., 2003). Psychotic episodes during seizures, such as psychic seizures or nonconvulsive status epilepticus, were excluded.

Study subjects

A total of 282 epilepsy-psychosis patients, who were consecutively registered in our epilepsy-psychosis database in December 1996 were recruited for the study (Adachi et al., 2000, 2002). All patients met the criteria for epilepsy (International League Against Epilepsy (ILAE), 1989) and psychosis (World Health Organization (WHO), 1992). They were followed up regularly at an adult epilepsy clinic in one of five tertiary neuropsychiatry institutions: the National Center Hospital for Mental, Nervous, and Muscular Disorders; Nihon University Hospital; Tokyo Medical University Hospital; Tokyo Medical and Dental University Hospital; or Komagino Hospital. The detailed clinical characteristics of this cohort have been described elsewhere (Adachi et al., 2000, 2002).

We also recruited 612 schizophrenia patients diagnosed in accordance with the ICD-10 (WHO, 1992), who were consecutively enrolled after visiting a psychiatry clinic at one of the five hospitals during the period 1 and 14 November, 1996. Thus, this cohort represents the overall population of schizophrenia patients treated in the five hospitals.

Neither patient with epilepsy-psychosis nor with schizophrenia had evidence of dementing process, a history of substance abuse, or an expanding brain mass lesion during our follow-up periods.

Research items

In all subjects, the following items were investigated: (1) sex, (2) age at the time of the study, (3) age of onset of psychosis; age of onset was defined as the earliest age when a clear psychotic symptom was identified, regardless of whether or not it was preceded by prodromal non-psychotic symptoms and signs (Jablensky et al., 1992). To study differences in sex in late-onset psychosis, we compared the sex ratio in patients who developed psychosis at age 40 or later, and (4) family history of psychosis; any psychotic disorder of the ICD-10 (such as schizophrenia, paranoid disorders, or acute-transient psychosis) (WHO, 1992) in a first-degree relative was regarded as positive family history psychosis, in accordance with the Japanese version of the Family History Research Diagnostic Criteria (Kitamura et al., 1984).

In patients with epilepsy-psychosis, the following items were evaluated additionally: (1) age at onset of epilepsy, (2) epilepsy type (focal, generalized, and unclassified); diagnosed using observed seizure symptoms and EEG and neuroimaging findings in accordance with the International Classifications for Epilepsy (ILAE, 1989), and (3) psychosis subtypes (PIP, IIP, and BMP), as defined above.

Diagnoses and clinical assessments on epilepsy and all psychoses were made by neuropsychiatrists doubly qualified in epileptology and psychiatry. The patient and key informants were interviewed in accordance with the section of History of Onset and Hospitalization, the Japanese edition of the Comprehensive Assessment of Symptoms and History (Andreasen, 1994). Clinical notes were also used to confirm the first psychotic episode, since epilepsy patients had already been treated for epilepsy at the onset of psychosis. The study was approved by the ethics committees of the institutions.

Data analysis

Standard parametric regression analysis and analysis of variance (ANOVA) were used for continuous data. Post hoc Bonferroni test was used for subgroup comparisons; epilepsy-psychosis subtypes (IIP, PIP, and BMP) and IIP subtypes (chronic schizophrenia-like, brief, and unclassified). For comparison among study groups with different mean ages at the time of evaluation, the weighted least squares procedure (age at the examination as weight) was used to reduce the bias of age at the time of evaluation. Age at the time of evaluation correlated significantly with age at onset of psychosis in epilepsy patients ($r = 0.683$, $p = 0.000$) and in schizophrenia patients

($r = 0.542$, $p = 0.000$); the more advanced age at the observation the subjects are, the more advanced age at onset of psychosis was observed. This tendency may be partly due to a limitation of the operational diagnosis; since onset of psychosis in the future cannot be included, age of onset must be earlier than age of the time of evaluation. A Chi square test or Fisher's exact test was used for categorical data. The significance level was set as $p < 0.05$. SPSS 14.0 [SPSS Inc., Chicago, IL] was used for all statistical analyses.

Results

Characteristics of the subjects

The detailed clinical characteristics of the patients with epilepsy-psychosis have been described elsewhere (Adachi et al., 2000, 2002). In short, of the 282 epilepsy-psychosis patients (148 men and 134 women), age at the time of evaluation ranged 17–82 years (mean 40.4, S.D. 13.0); men, 39.9 years (S.D. 12.7) and women, 41.0 years (S.D. 13.2). Age of onset of epilepsy ranged 0–60 years (mean 13.6, S.D. 9.3). Two hundred and thirty patients had focal epilepsy (146 temporal lobe epilepsy, 33 frontal lobe epilepsy, 11 parietal lobe epilepsy, 6 occipital lobe epilepsy, and 34 multi- or undetermined-lobular epilepsy), 45 had generalized epilepsy (29 idiopathic generalized epilepsy and 16 symptomatic generalized epilepsy), and 7 had unclassifiable epilepsy. Two hundred and four patients had generalized tonic-clonic seizures and 186 had complex partial seizures. The epilepsy-psychosis subgroups consisted of IIP ($n = 224$, mean age at the time of evaluation 39.7 years, S.D. 12.7), PIP ($n = 36$, 46.3 years, 13.7), and BMP ($n = 22$, 38.5 years, 12.3). Of the IIP patients, 193 (mean age at the time of evaluation 39.1 years, S.D. 12.1) had chronic schizophrenia-like psychosis, 17 (45.5 years, 14.8) had brief interictal psychosis, and 14 (41.3 years, 16.8) had IIP with insufficient information of the durations. Fifteen patients (mean age 39.8 years, S.D. 12.9) had first-degree relatives with psychosis.

The 612 schizophrenia patients consisted of 310 men and 302 women. Age at the examination ranged 14–82 years (mean age at the time of evaluation 41.1, S.D. 13.4); men, 40.3 years (S.D. 13.0) and women, 42.0 years (13.7). Seventy patients (mean age 42.5 years, S.D. 13.1) had first-degree relatives with psychosis.

Ages of onset of psychosis

Ages of onset are shown for the entire study group and for the subgroups in Table 1. Mean age of onset was significantly later in epilepsy-psychosis than in schizophrenia ($F = 21.6$, $p = 0.000$). There were significant differences in age of onset between subgroups of epilepsy-psychosis and schizophrenia ($F = 16.1$, $p = 0.000$). PIP ($p = 0.000$) and IIP ($p = 0.018$) developed at a later age than did schizophrenia. Likewise, PIP developed later than did IIP ($p = 0.000$) or BMP ($p = 0.001$). Further analysis with subdivisions of IIP (chronic schizophrenia-like, brief episodic, and insufficient information) and schizophrenia showed significant differences in age of onset ($F = 6.9$, $p = 0.000$). Post hoc analysis showed that brief episodic IIP developed at later age than did schizophrenia-like IIP ($p = 0.006$) and schizophrenia ($p = 0.000$).

Age of onset is shown by sex and family history of psychosis for each group in Table 2. No significant difference was observed for all the epilepsy-psychosis patients ($F = 0.04$, $p = 0.834$). In contrast, for the schizophrenia patients, age of onset was significantly later in female than in male patients ($F = 12.4$, $p = 0.000$). Whereas epilepsy patients with late-onset psychosis showed no sex difference (20 men and 22 women, $\chi^2 = 0.27$, $p = 0.508$), late-onset schizophrenia patients showed a significant female preponderance (12 men and 38 women, $\chi^2 = 14.3$, $p = 0.000$). Age of onset in patients with family history of psychosis was slightly earlier than those without in the epilepsy-psychosis group ($F = 2.1$, $p = 0.148$) and in the schizophrenia group ($F = 3.0$, $p = 0.086$), although there was no statistically significant difference.

Discussion

Epilepsy patients developed psychosis at a later age compared to schizophrenia patients. Regarding the subgroups of epilepsy-psychosis, the both IIP and PIP tended to occur at

Table 1 Age of onset of psychosis in patients with epilepsy-psychosis or with schizophrenia

	Observed mean (S.D.)	Adjusted mean (S.E.)	95% CI
Epilepsy-psychosis ($n = 282$)	27.7 (0.7)	30.1 (0.6)[a]	28.9–31.3
Interictal ($n = 224$)	26.8 (10.3)	29.0 (0.7)[b]	27.6–30.3
Chronic schizophrenia-like ($n = 193$)	26.2 (9.8)	28.1 (0.7)[c]	26.7–29.6
Brief episodic ($n = 17$)	33.4 (12.1)	36.1 (2.3)[c]	31.6–40.6
Insufficient information for duration ($n = 14$)	27.4 (13.2)	31.1 (2.7)	25.9–36.3
Postictal ($n = 36$)	34.8 (10.3)	37.4 (1.6)[b]	34.3–40.6
Bimodal ($n = 22$)	25.0 (9.3)	26.8 (2.2)	22.4–31.2
Schizophrenia ($n = 612$)	25.1 (8.7)	26.6 (0.4)[a,b,c]	25.8–27.4

[a] Epilepsy-psychosis vs. schizophrenia by ANOVA (age at evaluation as weight), $F = 21.6$, $p = 0.000$.

[b] Epilepsy-psychosis subgroups vs. schizophrenia by ANOVA (age at evaluation as weight), $F = 16.1$, $p = 0.000$ (post hoc test: interictal psychosis vs. schizophrenia, $p = 0.018$, postictal psychosis vs. schizophrenia, $p = 0.000$).

[c] Interictal psychosis subgroups vs. schizophrenia by ANOVA (age at evaluation as weight), $F = 6.9$, $p = 0.000$ (post hoc test: schizophrenia vs. brief episodic, $p = 0.000$, chronic schizophrenia-like vs. brief episodic, $p = 0.006$).

Table 2 Effects of sex and family history of psychosis on age of onset of psychosis

Sex	Family history	Observed mean (S.D.)	Adjusted mean (S.E.)	95% CI
Epilepsy-psychosis[a]				
Men ($n=148$)		27.9 (10.3)	28.1 (1.7)	24.8–31.4
Women ($n=134$)		27.5(11.3)	27.8 (1.8)	24.3–31.4
	Positive ($n=15$)	24.9 (7.3)	25.7 (3.1)	19.6–31.8
	Negative ($n=267$)	27.9 (10.9)	30.3 (0.7)	28.9–31.7
Men	Positive ($n=10$)	25.8 (8.4)	25.8 (3.1)	19.6–31.9
Men	Negative ($n=138$)	28.1 (10.4)	30.5 (1.0)	28.5–32.4
Women	Positive ($n=5$)	23.0 (4.8)	25.5 (3.1)	19.6–31.9
Women	Negative ($n=129$)	27.7 (11.5)	30.2 (1.0)	28.1–32.3
Schizophrenia[b]				
Men ($n=310$)		24.1 (7.3)	24.5(0.7)	23.1–25.9
Women ($n=302$)		26.1(9.9)	27.2(0.7)	25.8–28.5
	Positive ($n=70$)	24.1 (7.2)	24.8 (1.1)	22.6–27.0
	Negative ($n=542$)	25.2 (8.9)	26.9 (0.4)	26.1–27.7
Men	Positive ($n=36$)	23.2 (5.7)	23.5 (1.2)	21.2–25.8
Men	Negative ($n=274$)	24.2 (7.5)	25.5 (0.6)	24.4–26.6
Women	Positive ($n=34$)	25.0 (8.5)	26.2 (1.2)	23.9–28.5
Women	Negative ($n=268$)	26.2 (10.1)	28.2 (0.6)	27.1–29.3

ANOVA with age at evaluation as weight.

[a] Sex, $F=0.04$, $p=0.834$; family history, $F=2.14$, $p=0.145$; sex × family history, $F=0.121$, $p=0.729$.

[b] Sex, $F=12.4$, $p=0.000$; family history, $F=2.9$, $p=0.088$; sex × family history, $F=0.03$, $p=0.858$.

a later age than did schizophrenia. Only the patients with BMP had a comparable onset to the schizophrenia patients. Our findings are concordant with most uncontrolled studies reporting similar age range of onset of epilepsy-psychosis, late twenties or early thirties (Slater et al., 1963; Trimble, 1991). These age ranges appear to be slightly later than the first peak of onset of schizophrenia (early twenties) (Hafner et al., 1998). Although Mendez et al. (1993) showed a comparable age of onset between 62 epilepsy patients (mean 23.6 years) and 62 age-matched schizophrenia patients (mean 24.6 years), they found a later age of onset (mean 28.4 years) in their expanded sample cohort (146 epilepsy-psychosis patients). Epilepsy patients often have multiple risks for developing psychosis, i.e., distinct brain insults, repetitive seizures, and antiepileptic drugs (Adachi et al., 2000; Trimble, 1991), while few schizophrenia patients have these risks. If the congenital vulnerability for developing psychosis was the same for both groups, the acquired risks associated with epilepsy or organic brain damage would be expected to predispose these patients to the development of an early onset of psychosis. However, our findings did not support this notion, suggesting that the underlying vulnerability to psychosis in epilepsy patients does not completely equivalent to that in schizophrenia patients.

With respect to the further subdivisions, chronic schizophrenia-like psychosis occurred at earlier age. Age of onset was similarly slightly earlier in BMP patients. Kanemoto et al. (1996) also reported that chronic IIP occur at an earlier age than do either PIP or episodic IIP. In accordance with the ICD-10 (WHO, 1992), most patients with chronic schizophrenia-like psychosis can be diagnosed as having schizophrenia unless epilepsy was considered. Patients categorized in these narrow diagnostic entities may have high vulnerabilities towards development of psychosis. According to the neurodevelopmental hypothesis, similar age of onsets, regardless of their etiologies, could exhibit similar psychiatric symptoms (Weinbergar, 1987). Thus, it is possible that these patients with high vulnerabilities have common liabilities to schizophrenia patients. However, this should be argued with cautions. Several studies (Mellers et al.,1998; Maier et al., 2000) has demonstrated some pathophysiological differences between schizophrenia-like psychosis in epilepsy and schizophrenia. The reliability of subdivision with clinical course has not yet been thoroughly confirmed; an individual epilepsy-psychosis patient often shows both episodic and chronic psychoses on different occasions in the course of their illness (Onuma et al., 1992; Cockerell et al., 1996; Adachi et al., 2003; Adachi, 2006). If our patients with brief IIP were to develop chronic schizophrenia-like psychosis afterwards, the mean age of onset might shift later than that observed in the current study.

Epilepsy-psychosis patients showed no sex difference in age of onset. This appeared to be due partially to the smaller proportion of late-onset psychosis in female epilepsy patients, as opposed to the female preponderance for late-onset schizophrenia. A protective effect of estrogen in the brain has been proposed to explain the sex difference in the development of schizophrenia (Hafner et al., 1998). In epilepsy patients, several factors, such as seizure frequency, duration of epilepsy, and antiepileptic drugs, are correlated with neuroendocrine levels (Leiderman et al., 1990) and may account for the difference. The serum luteinizing hormone level is elevated after seizures in both men and women with epilepsy (Dana-Haeri et al., 1983). Furthermore, in epilepsy patients with psychopathology, baseline serum gonadotrophine levels were lower than those in epilepsy patients without psychopathology, and levels were

more volatile after seizures (Dana-Haeri and Trimble, 1984). These epilepsy-related factors may disrupt endocrinologic regulation, thus diminishing any sex effect. However, this is not entirely clear, as these factors have also been reported to be associated with the development of psychosis in epilepsy patients (Adachi et al., 2000, 2002; Trimble, 1991).

The both epilepsy and schizophrenia patients with family history of psychosis developed psychosis at an earlier age, although there was no statistical difference. Whether family history of psychosis is a risk factor to psychosis in epilepsy patients has long been discussed (Trimble, 1991; Adachi, 2006). In contrast to the Slater's negative observations (Slater et al., 1963), several large control studies (Adachi et al., 2000, 2002; Qin et al., 2005) have recently shown the possibility of genetic vulnerability to psychosis in epilepsy-psychosis patients. Whereas effects of family history on age of onset are controversial in schizophrenia studies (Kendler et al., 1996), our findings may be in line with some studies showing that schizophrenia patients with a family history had an earlier onset than those without (Gorwood et al., 1995; Alda et al., 1996). It is concordant that individuals with a high familial liability to various neuropsychiatric diseases develop their first symptom at a young age (Ridley et al., 1986; Klein et al., 1999). Patients with the genetic vulnerability to psychosis, regardless of having epilepsy, are likely to develop their psychotic episode at an earlier age.

Our significant findings of differences in age of onset between epilepsy-psychosis and schizophrenia need to be interpreted with caution to our definition of epilepsy-psychosis. In the current study, we studied patients who developed psychosis after the onset of epilepsy in accordance with the most popular definition of epilepsy-psychosis. Since Pond's initial description (1957), most large studies on epilepsy-psychoses have dealt subjects which developed epilepsy prior to psychosis (Slater et al., 1963; Kristensen and Sindrup, 1978; Mendez et al., 1993; Bredkjaer et al., 1998; Adachi et al., 2000, 2002; Qin et al., 2005). It can ensure the specificity of diagnosis for causal relation between epilepsy and psychosis, rather than psychosis simply related to brain damage or concurrence of non-organic psychosis (Pond, 1957; Slater et al., 1963; Bruens, 1974; Trimble, 1991; Rayport and Ferguson, 2001). However, this definition is rather operative based on limited observations in the early periods (Pond, 1957; Slater et al., 1963; Bruens, 1974). The significance of epileptic process on the development of epilepsy-psychosis has not been fully demonstrated (Adachi, 2006). Further studies are required to clarify as to whether patients who developed psychosis, either organic or functional, after the onset of epilepsy are equivalent to our subjects.

Other limitations may also be considered in the current study. First, the subclassification for epilepsy-psychosis, in particular IIP, remain controversial (Adachi, 2006). We employed the diagnostic criteria covering different characteristics of epilepsy-psychosis subgroups. We believe they are the most comprehensive criteria among those used in previous studies. Thus, our finding may be partially inconsistent with those that resulted from studies using narrow criteria. Second, because our study subjects were looked after in specialist clinics, they were inevitably patients who suffer from difficult-to-manage epilepsy, psychosis, or both. Thus our findings may not directly apply to those in more general settings. Third, the WHO 10-country study (Jablensky et al., 1992) showed that age of onset of schizophrenia is influenced by multiple interacting factors including sex, premorbid personality traits, family history of psychosis, and marital status. Premorbid personality and marital status were not considered in the present study. Although we have no reason to believe that they would significantly bias our data, this remains a limitation in our study. Further analyses based on our findings are required to clarify the nature of epilepsy-psychosis.

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Regular Article

Relationship between exploratory eye movement, P300, and reaction time in schizophrenia

Sakae Takahashi, MD, PhD,[1]* Eiichi Tanabe, MD, PhD,[1] Teiichiro Sakai, MD, PhD,[1] Masato Matsuura, MD, PhD,[2] Eisuke Matsushima, MD, PhD,[3] Shigeru Obayashi, MD, PhD[4] and Takuya Kojima, MD, PhD[1]

[1]*Department of Neuropsychiatry, Nihon University School of Medicine,* [2]*Section of Biofunctional Informatics, Graduate School of Allied Health Sciences, Tokyo Medical and Dental University,* [3]*Section of Liaison Psychiatry and Palliative Medicine and* [4]*Section of Psychiatry and Behavioral Sciences, Graduate School of Tokyo Medical and Dental University, Tokyo, Japan*

Aims: Exploratory eye movement (EEM), P300 and reaction time (RT) tests may relate to the important parts of information processing in the human brain. Therefore the aim of the present study was to compare EEM, P300 and RT test data in schizophrenic and normal control groups to investigate whether schizophrenic patients have information processing abnormalities. In addition, the potential correspondence between the three tests was examined in order to investigate the information processing dysfunctions seen in schizophrenic patients.

Methods: The EEM, P300 and RT performances were recorded in 34 schizophrenic and 36 normal control subjects. Ten parameters were measured: four from the EEM test (number of eye fixations, total eye scanning length, cognitive search score and responsive search score [RSS]); two from the P300 test (amplitude and latency); and four from the RT test (simple reaction time, index of reaction time crossover [IRT-crossover], set index and coefficient of variation).

Results: These parameters in the schizophrenic patients differed significantly from those in the control group. Additionally, there was a significant correlation between the RSS and the IRT-crossover in the schizophrenic patients.

Conclusion: The present group comparisons (schizophrenia vs normal controls) are consistent with previous studies in that the abnormalities in EEM, P300 and RT tests in schizophrenic patients were able to be replicated. Moreover, based on the former psychological theory, it is reasonable to propose that the RSS is associated with the IRT-crossover. The present results may contribute to elucidation of the pathophysiological signature of schizophrenia.

Key words: exploratory eye movement, P300, reaction time, schizophrenia.

DISTURBANCES IN INFORMATION processing in the brain have played a central role in understanding schizophrenia since early in the 20th century.[1,2] Cognitive dysfunction in schizophrenia has been the subject of in-depth empirical analysis. Abnormalities in eye movement, event-related potentials (ERP), reaction time (RT), continuous performance task and skin conductance orienting response have been proposed to reflect disturbances in information processing.[3]

Our group has studied eye movements while subjects freely view stationary horizontal S-shaped figures. This method is called the exploratory eye movement (EEM) test. We have demonstrated that disturbances in EEM test were usually found in schizophrenic patients.[4] Abnormalities in ERP, especially the P300, are among the most robust biologic

**Correspondence: Sakae Takahashi, MD, PhD, Nihon University School of Medicine Department of Neuropsychiatry, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan. Email: sakae@med.nihon-u.ac.jp*

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observations in schizophrenia.[5] The P300 has been performed frequently in many laboratories worldwide. RT disturbances are another replicable finding in schizophrenia. Several studies have verified that schizophrenic patients have RT test disturbances.[3,6] Based on these findings, we considered that EEM, P300 and RT were putative biological indicators of liability to schizophrenia. Moreover, with regard to the three tests, it has been reported that EEM may reflect the information processing in relation to Neisser's anticipatory schemata; P300 may index the updating of memory systems; and RT may link cognitive function with reference to Shakow's major set. Precisely, it is possible that these three tests relate the important parts of information processing in the human brain. Therefore, the aim of the present study was to conduct EEM, P300 and RT tests in schizophrenic patients and normal controls, to investigate whether schizophrenic patients have information processing abnormalities. In addition, we examined the potential correspondence between the three tests to investigate the information processing dysfunctions seen in schizophrenic patients.

METHODS

Subjects

Thirty-four subjects with schizophrenia and 36 normal controls were included in the present study. The schizophrenia subjects (21 male, 13 female) had a mean age of 26.9 ± 4.9 years; mean duration of illness was 4.2 ± 3.9 years; mean age at onset was 22.8 ± 5.4 years; mean years of education was 12.8 ± 2.2 years. All schizophrenic subjects met the DSM-IV criteria for schizophrenia.[7] The diagnosis was based on structured clinical interviews for DSM-IV. Each interview was administered by two experienced psychiatrists. All schizophrenic patients were receiving an average daily dosage of 10.8 ± 9.0 mg of a haloperidol equivalent neuroleptic medication. No schizophrenia subjects had ever undergone electroconvulsive shock treatment. Classifying the schizophrenic patients into DSM-IV subtypes, there were seven disorganized types, 17 paranoid types, four residual types and six undifferentiated types. We performed the exploratory eye movement, P300 and RT tests on the schizophrenic subjects after they recovered from acute symptoms. All subjects in the present study understood the investigator's instructions clearly. The normal control subjects (18 male, 18 female; mean age 26.7 ± 3.6 years; mean years of education 16.4 ± 2.2 years) were age- and sex-matched with the schizophrenic subjects. With regard to the mean years of education, there was a significant difference between schizophrenic patients and normal controls. The normal controls were drawn from healthy volunteers who consisted of hospital staff, students from Nihon University and members of Tokyo-based drug companies. The normal controls had no specific history of mental illness according to DSM-IV criteria and were taking no psychiatric medications. None of the schizophrenic patients or normal controls had any evidence of substance or alcohol abuse or organic brain pathology. The present study was approved by the Ethics Committees of Nihon University, Tokyo, Japan. Informed consent was obtained from each patient and normal control subjects after the nature of study had been fully explained.

Exploratory eye movement

A standard test of EEM using an NAC V-type eye mark recorder (NAC, Tokyo, Japan) was carried out. Three horizontal S-shaped figures were projected on to a screen (Fig. 1). The method is briefly described as follows.

1) The subject was shown the original S-shaped figure (Fig. 1a) for 15 s. Immediately after viewing it, he/she was asked to draw the original S-shaped figure.

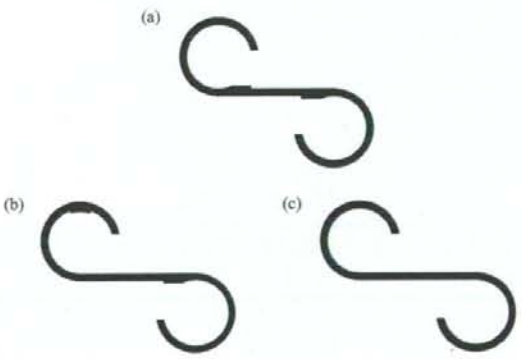

Figure 1. Three horizontal S-shaped figures in the exploratory eye movement (EEM) test. More detailed descriptions of these figures (a, b and c) have been presented in our previous studies.[4,8,9]

2) (i) The subject was instructed to compare a figure with the original figure (Fig. 1a) and was then shown a figure slightly different from the original one, which had one bump in a different position (Fig. 1b), for 15s; (ii) 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; (iii) after the subject had replied and while the figure was still being shown, he/she was asked 'Are there any other differences?'.
3) Step 2(i–iii) was repeated with a figure without bumps (Fig. 1c).

We analyzed the subject's eye movements while they were viewing the horizontal S-shaped figures. Based on the analysis, we obtained four parameters: number of eye fixations (NEF), total eye scanning length (TESL), cognitive search score (CSS) and responsive search score (RSS). We consider that the RSS may be the most specific parameter of schizophrenia in the EEM test. We obtain the RSS based on the data of eye movements during the 5 s immediately after the question 'Are there any other differences?' is asked in step 2(iii). More detailed descriptions of the EEM test methods have been presented in our previous studies.[4,8,9]

P300

ERP were recorded based on the standard auditory odd-ball paradigm. Tone pips were delivered binaurally through headphones at a stimulus intensity of 60 dB and a tone duration of 100 ms, with a rise and fall time of 10 ms. Subjects were asked to count silently, with eyes closed, infrequent high-pitched tones (2000 Hz) pseudo-randomly presented with a series of frequent low-pitched tones (1000 Hz). Two hundred and fifty tones were presented with interstimulus intervals of 0.6/s, and the ratio of high- to low-pitch tones was 1:4 (50:200).

ERP recordings were obtained using three silver/silver chloride disc electrodes with a linked-ear reference according to the international 10–20 system (Fz, Cz, Pz). The electroencephalogram was filtered using a bandpass of 0.5–60 Hz. Horizontal electrooculogram (EOG) was recorded from electrodes placed at the right and left external canthi. Vertical EOG was recorded using right eye supra- and infraorbital electrodes. Horizontal and vertical EOG were used to monitor and control eye movement and blink artifacts. In addition, these were used to reject EOG artifacts, and trials were excluded when the voltage exceeded ±100 μV.

Fifty trials with the high-pitched tones were averaged with a sweep time of 700 ms including a 100 ms prestimulus baseline. The P300 peak latency and amplitude were measured from baseline to peak and were defined as the data point at the Pz electrode with the largest positive voltage from 250 to 550 ms. The sampling time was 6 ms.

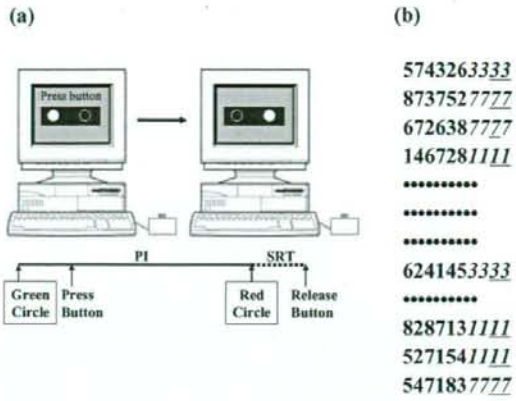

Figure 2. (a) Reaction time test apparatus and (b) preparatory interval (PI) array. SRT, simple reaction time.

Reaction time

RT was calculated based on the methods of Steffy and Galbraith.[10] As shown in Fig. 2(a), the RT task apparatus consisted of a computer linked to a control button. The subject reclined in a chair in front of the display monitor. When the subject pressed the button, a green circle immediately appeared on the left side of the display. The subject held it down, and after a preparatory interval (PI), the green circle disappeared and a red circle appeared on the right side of the display. The subject was required to release the button as quickly as possible after the appearance of the red circle. The lag time between the appearance of the red circle and the release of the button was measured as the simple reaction time (SRT). This RT task consisted of a series of 120 trials that included a regular series and an irregular series (Fig. 2b). The regular series consisted of 12 sets of four isotemporal

trials with 1, 3 or 7 s PI (Fig. 2b, italic font). The irregular series consisted of 12 sets of six anisotemporal trials with eight PI, from 1 to 8 s (Fig. 2b, plain font). These eight PI were given in pseudo-random order. As can be seen in Fig. 2(b), the regular and irregular series were presented alternately.

According to DeAmicis and Cromwell, we calculated the index of reaction time crossover (IRT-crossover) utilizing mean SRT with formula (1) given here.[11] Rodnick and Shakow reported that reaction time crossover (RT-crossover) phenomenon may be a marker for process schizophrenia.[12] This phenomenon was transformed to the index (IRT-crossover: difference between the average SRT for regular trials and for irregular trials at the 7 s PI) using the DeAmicis and Cromwell method.[11] They found that 25 ms was the optimal cut-off point between schizophrenic patients and normal controls from the inspection of the data in individual subjects. Since then, some investigators have indicated that the optimal cut-off point is 10 ms or 25 ms.[13,14] Thus, it has been considered that the optimal cut-off point of IRT-crossover between schizophrenic patients and normal controls is still not determined. Using a DeAmicis and Cromwell method,[11] we inspected the present data and found that the maximum difference between schizophrenia patients and normal controls was obtained using a cut-off point of 15 ms. For this reason, if the IRT-crossover score was ≥15 ms, we defined it as abnormal.

On the basis of the procedures of Rodnick and Shakow, we calculated the set index (SI) utilizing mean SRT with formula (2) given here.[12] They found that this single criterion of mean RT level differentiated most of the schizophrenia patients from the normal controls, but there was still some overlap despite the fact that a significant difference existed between the two groups. They attempted to create an index using the data from the RT to achieve more satisfactory differentiation between patients and normal controls, and finally obtained the SI. There was no overlap between schizophrenia patients and normal controls with SI in their study. In the present study the construction of the trial arrangement differentiated from their method. The task procedure in the present study followed the Steffy and Galbraith method, which was modified to show the RT-crossover most frequently. Steffy and Galbraith did not calculate the SI.[10] In the present study, in order to calculate the SI based on the data of the trial arrangement of Steffy and Galbraith, we slightly adjusted the Rodnick and Shakow formula. Therefore, although we tried to stay as close to this as possible, our SI formulas differed slightly from the original Rodnick and Shakow work.[12]

To investigate intra-trial response variability, we calculated the coefficient of variation (CV) of data from all trials with formula (3) given here. If the CV was >95% upper of confidence interval of the normal control group, we defined it as abnormal.

$$\text{IRT-crossover} = \text{M7R} - \text{M7I} \quad (1)$$

where M7R is the mean RT for each trial on regular condition with a PI of 7 s, the regular condition is the last two trials of the regular series were defined as the regular condition (Fig. 2b, underlined italic font); M7I, is the mean RT for each trial on irregular condition with a PI of 7 s, the irregular condition is all trials of the irregular series, and the first trial of the regular series were defined as the irregular condition (Fig. 2b, plain and italic font).

$$\text{SI} = \text{MH} \times (\text{M7R} + \text{M7I}) + \text{M1R}^2 + \text{M3R} \quad (2)$$

where MH is the highest of several RT means for each trial obtained at any PI (1, 2, 3, 4, 5, 6, 7 or 8) under either condition (regular or irregular). M7R and M7I are the same as defined above. M1R is the mean RT for each trial on regular condition with a PI of 1 s, M3R is the mean RT for each trial on a regular condition with a PI of 3 s.

$$\text{CV} = \text{SD7I} + \text{M7I} \quad (3)$$

where SD7I is the standard deviation of RT for each trial on irregular condition with a PI of 7 s. M7I is same as defined above.

It is possible that these three tests may have been effected by the time of day. To ensure consistency, all three tests were done for each subject on the same day. Further, each of the three tests was performed for each subject at the same time of day. The order of test performances was as follows: (i) RT, (ii) EEM, and (iii) P300. These three tests were done according to this order in almost all subjects.

Statistical analysis

All EEM, P300 and RT measurements failed to meet the criteria for normality (Wilks–Shapiro test). Therefore, these data were examined using a non-parametric method. Group differences (schizophrenia group vs normal control group) on all EEM

and P300 parameters and the SRT of the RT test were assessed using the Mann–Whitney *U*-test. Because the IRT-crossover and the CV in the RT test data were converted to categorical data, these data were compared using the 2×2 contingency table. Moreover, because the RT-crossover table included cells that had a low expected frequency, the RT-crossover was compared using Fisher's exact test. In contrast, because the CV table did not include cells that had a low expected frequency, the CV was compared using the χ^2 test. Statistical significance was set at $P < 0.01$. Relationships between EEM, P300 and RT variables were tested using the Spearman rank-order correlation test. In order to examine these relationships, we used numerical variables as opposed to categorical variables with regard to RT-crossover and CV parameters. This is primarily due to the fact that numerical variables yield a more detailed outcome.

RESULTS

Schizophrenic patients versus normal controls

Table 1 shows the results of EEM, P300 and RT tests for the two groups.

Exploratory eye movement

The NEF and TESL were significantly lower in the schizophrenic group compared to that of the normal control group. The schizophrenic group had significantly lower CSS and RSS than the normal control group.

P300

There was a significant increase in the latency and a reduction in the amplitude of P300 in the schizophrenic group compared with that in the normal control group.

Reaction time

The SRT and SI in the schizophrenic group were significantly higher than those in the normal control group. There were nine patients (25.7%) in the schizophrenic group who had an abnormal RT-crossover, but there was only one subject (3%) in the normal control group who had an abnormal RT-crossover. Concerning CV, 24 schizophrenic patients (70.6%), but only nine normal controls (25.0%) demonstrated any abnormality. There was a significant difference between the schizophrenic patients and the normal controls with regard to RT-crossover and CV.

EEM, P300 and RT tests

Tables 2,3 illustrate the rank-order (Spearman) correlation between EEM, P300 and RT in schizophrenia and normal controls. As can be seen, the RSS of the

Table 1. EEM, P300 and RT parameters in schizophrenia and normal controls

		Schizophrenic patients ($n = 34$)	Controls ($n = 36$)
EEM	NEF	28.1 ± 7.5	36.8 ± 6.7*
	TESL (cm)	434.3 ± 167.2	619.8 ± 146.4*
	CSS	4.5 ± 1.0	6.2 ± 0.9*
	RSS	7.4 ± 1.4	10.4 ± 1.9*
P300	LAT (ms)	373.3 ± 32.6	346.7 ± 24.0*
	AMP (μV)	6.6 ± 2.8	9.1 ± 2.9*
RT	SRT (ms)	229.7 ± 48.4	164.0 ± 23.7*
	SI	465.3 ± 121.2	349.1 ± 88.4*
	RT-Cross	9 (26.5%)	1 (2.8%)†
	CV	24 (70.6%)	9 (25.0%)‡

*$P < 0.01$ (Mann–Whitney *U*-test), †$P < 0.01$ (Fisher's exact test), ‡$P < 0.01$ (χ^2 test).
Mean ± SD.
AMP, amplitude; CSS, cognitive search score; CV, coefficient of variation; EEM, exploratory eye movement; LAT, latency; NEF, number of eye fixations; RSS, responsive search score; RT, reaction time; RT-Cross, reaction time crossover; SI, set index; SRT, simple reaction time; TESL, total eye scanning length.

Table 2. EEM, P300 and RT tests (Spearman's δ) in schizophrenia

		P300		RT			
		LAT	AMP	SRT	SI	IRT-cross	CV
EEM	NEF	−0.29	0.15	−0.37	−0.33	−0.11	−0.08
	TESL	−0.18	0.32	−0.39	−0.33	−0.43	0.02
	CSS	0.02	0.01	−0.23	−0.17	−0.04	−0.10
	RSS	−0.09	0.19	−0.16	−0.08	−0.56*	0.26
P300	LAT			0.12	0.14	0.26	0.18
	AMP			−0.22	−0.23	−0.15	−0.30

*$P < 0.01$.

AMP, amplitude; CSS, cognitive search score; CV, coefficient of variation; EEM, exploratory eye movement; IRT-cross, index of reaction time crossover; LAT, latency; NEF, number of eye fixations; RSS, responsive search score; RT, reaction time; SI, set index; SRT, simple reaction time; TESL, total eye scanning length.

EEM test was significantly negatively correlated with the IRT-crossover of the RT test in the schizophrenia group ($\delta = -0.56$, $n = 34$, $P = 0.00066$). There was no significant correlation with respect to other parameters of the three tests (EEM, P300 and RT) in the schizophrenic patients. In reference to the normal controls, we also found no significant correlations between the results of the three tests.

EEM, P300, RT and medications

Relationships between EEM, P300, RT variables and the dosage of a haloperidol equivalent neuroleptic medication were tested using Spearman rank-order correlation test to investigate the medication effects. There were no significant correlations between the parameters of EEM, P300 and RT and the dosage of a haloperidol equivalent neuroleptic medication.

DISCUSSION

Schizophrenic patients and normal controls

In the present study all EEM, P300 and RT tests parameters in the schizophrenic group differed significantly from those in the control group. The present findings are consistent with previous studies in that we were able to replicate abnormalities in EEM, P300 and RT tests in schizophrenic patients.[3–5,8,9] As already noted, we inspected our data in detail and set an optimal cut-off point between schizophrenic patients and normal controls. Hence, it is reasonable to propose that the schizophrenic group was significantly different from the normal control group in the RT-crossover. Moreover, concerning the mean years of education, the schizophrenic group education level was significantly lower than that of the normal

Table 3. EEM, P300 and RT tests (Spearman's δ) in normal controls

		P300		RT			
		LAT	AMP	SRT	SI	IRT-cross	CV
EEM	NEF	0.21	0.02	−0.07	−0.09	0.12	0.21
	TESL	0.40	−0.28	0.13	0.12	0.04	0.06
	CSS	0.18	0.06	−0.22	−0.18	0.24	−0.07
	RSS	0.14	0.11	−0.34	−0.15	−0.08	−0.21
P300	LAT			−0.08	0.02	0.03	−0.15
	AMP			−0.24	−0.20	0.04	0.03

AMP, amplitude; CSS, cognitive search score; CV, coefficient of variation; EEM, exploratory eye movement; IRT-cross, index of reaction time crossover; LAT, latency; NEF, number of eye fixations; RSS, responsive search score; RT, reaction time; SI, set index; SRT, simple reaction time; TESL, total eye scanning length.

control group. Thus, it is possible that the mean years of education may affect the comparisons between schizophrenic patients and normal controls.

RSS and RT-crossover

In the data from our previous and present work, we did not identify any patients with psychiatric disease in which the RSS was similar to that of schizophrenic patients.[4,8,9,15] Not only chronic and acute schizophrenic patients but also those in remission can be distinguished on RSS from patients with depression, neurosis, methamphetamine psychosis, temporal lobe epilepsy, frontal lobe lesions and normal controls. Thus, we consider that the RSS in the EEM test may be specific to schizophrenia.

In the EEM test the RSS is obtained from eye movements that occur in response to an examiner's question 'Are there any other differences?'. The subjects explore the figure again and try to search for differences. The RSS may reflect the visual behavior of a subject who wants to check or confirm their response induced by the interaction between the subject and the examiner, and therefore, the RSS may be an indicator of an interpersonal response. As for the RSS, Kojima *et al.* described the following.[4] According to Neisser's theory of the perceptual cycle, at each moment the viewer has expectations of certain kinds of information, which are readily accepted if they are available. It is postulated that the subject must frequently and actively explore the visual field by moving the eyes or head to make the information in the field available. These explorations are dictated by the anticipatory schemata. The anticipatory schemata are considered to be related to mental attitude: the desire to obtain more information from the visual field.[16] The lower RSS in schizophrenic patients seems to indicate a dysfunction of the anticipatory schemata. We propose that the RSS may reflect the information processing of the brain in relation to the anticipatory schemata in the interpersonal response.

Data from several studies are consistent with the assertion that RT-crossover abnormalities are found in the majority of process schizophrenic patients. Almost all of the available literature suggests that a high rate of process schizophrenic patients shows the RT-crossover.[6,10,11,14,17] These findings suggest that the crossover phenomenon may be a marker for process schizophrenia.

Shakow accounted for this mechanism using his segmental set theory.[18] RT-crossover is the phenomenon in which schizophrenic patients have slower RT in a regular series than in an irregular series. Ordinarily, the consistency of the preparatory intervals in the regular series should give an individual an advantage and lead to faster RT than in the irregular series. Schizophrenic patients, however, are not able to take advantage of such regularity information, and thus they perform poorly. Schizophrenic patients have difficulty in keeping up a state of readiness for response to a coming stimulus. In order to deliver the optimal response to the stimulus, an individual has to focus on the relevant aspects of the defined situation; that is, the individual must maintain a high readiness to respond. But schizophrenic patients are affected by irrelevant aspects of the stimulus surroundings, which prevent focusing on the main stimulus. Schizophrenia patients cannot extract the relevant aspects for optimal response; hence they have difficulty in maintaining a readiness to respond. The mechanism for maintaining this readiness is directed by the major set. The major set reflects the readiness of subjects to recognize stimuli, and is the primary and principal layer of information processing. Shakow proposed that schizophrenic patients are characterized by a failure to maintain an adequate major set.[18]

There is one point we would like to emphasize. According to the Neisser theory, it appears that the anticipatory schemata are similar to the readiness reflected by the major set.[16] Therefore, we consider that these two theories (Neisser's perceptual cycle and Shakow's major set) are similar in concept. In the present study, associations were found between the RSS of the EEM test and the RT-crossover score of the RT test in the schizophrenic group. If the assumption that the RSS of the EEM test reflects the anticipatory schemata and that the crossover phenomenon of the RT test reflects the major set, is correct, it is reasonable to propose that the RSS is associated with the crossover phenomenon. Moreover, based on our previous data, we consider that the EEM test parameters except for the RSS may not relate to the anticipatory schemata in the interpersonal response.[4] Thus it is also reasonable to consider that the EEM test parameters except for the RSS are not strongly associated with the crossover phenomenon. But from the psychological explanation of the P300 amplitude, it may also relate to the anticipatory schemata or the major set.[3,5] In the present study there was no association between the P300 amplitude and the crossover phenomenon. The P300 amplitude also did not relate to the RSS.

Hence the information processing reflected by the P300 amplitude may be distinct from that of the RSS or the cross-over phenomenon. These findings, however, should be interpreted cautiously, and additional studies are needed to confirm these considerations for the P300 amplitude.

In the present study we detected two fundamental information processing abnormalities in schizophrenic. These two abnormalities are in accordance with the former theory. Because it is considered that abnormalities of information processing are among the most important symptoms of schizophrenia, the present results may contribute to elucidation of the pathophysiological signature of schizophrenia. But the present sample size was not very large; thus the present findings should be interpreted cautiously; and additional studies with a larger sample are needed to confirm the findings. Moreover, we did not estimate psychiatric symptoms of patients using a scale for assessment of symptoms. Thus, further limitation of the study are that we were not able to present the severity of subjects or a relationship between the physiological tests and psychiatric symptoms.

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Regular Article

Impairment of exploratory eye movement in schizophrenia patients and their siblings

Sakae Takahashi, MD, PhD,[1]* Eiichi Tanabe, MD, PhD,[1] Kazuo Yara, MD, PhD,[1] Masato Matsuura, MD, PhD,[2] Eisuke Matsushima, MD, PhD[3] and Takuya Kojima, MD, PhD[1]

[1]*Department of Neuropsychiatry, Nihon University, School of Medicine,* [2]*Section of Biofunctional Informatics, Graduate School of Allied Health Sciences, Tokyo Medical and Dental University and* [3]*Section of Liaison Psychiatry and Palliative Medicine, Graduate School of Tokyo Medical and Dental University, Tokyo, Japan*

Aims: Previous family, adoption and twin studies of schizophrenia have shown that genetic factors contribute significantly to the risk of schizophrenia. The aim of the present study was therefore to investigate whether exploratory eye movement (EEM) abnormalities are related to the genetic markers linked to schizophrenia.

Methods: Twenty-three probands with schizophrenia, 23 of their healthy siblings (23 proband–sibling pairs), and 43 unrelated normal controls performed EEM tasks. Two parameters were measured: (i) number of eye fixations in responsive search (NEFRS) and (ii) responsive search score (RSS).

Results: Abnormalities in NEFRS and RSS were more frequent in schizophrenia probands than in their unaffected siblings and in normal controls, and were also more frequent in the healthy siblings than in normal controls. Thus, the EEM test performances of the healthy siblings were intermediate between those of the probands with schizophrenia and those of normal controls.

Conclusion: Abnormalities of the EEM test parameters may be related to the genetic etiology of schizophrenia. The use of EEM parameters as an endophenotype for schizophrenia may facilitate linkage and association studies in schizophrenia.

Key words: etiology, exploratory eye movement, genetic factors, schizophrenia, siblings.

PREVIOUS FAMILY, ADOPTION and twin studies of schizophrenia have indicated that genetic components contribute significantly to the development of schizophrenic disorder. The mode of inheritance in schizophrenia, however, is complex. In addition, schizophrenia probably has etiologic heterogeneity, including locus heterogeneity, in genetic-associated cases of schizophrenia.[1–4] The conflicting results of recent linkage studies involving schizophrenia as the phenotype may be due to the complexity of genetic transmission.[5,6] Current findings of genetic studies in schizophrenia cannot completely account for the genetic factors of schizophrenia. One approach to resolving this issue is to search for a biological marker that fulfils the following criteria: (i) characteristic of schizophrenia; and (ii) related to the genetic predisposition to schizophrenia. Such an indicator may facilitate linkage analysis of schizophrenia.[7] Linkage analysis with such a biological marker of schizophrenia may lead to identification of chromosomal loci for susceptibility to schizophrenia.

Our group previously developed a method to study eye movements while subjects viewed geometric figures, called the exploratory eye movement (EEM) test.[8–10] We have obtained responsive search scores (RSS) for the EEM test. In previous studies we did not identify any patients with psychiatric diseases in

**Correspondence: Sakae Takahashi, MD, PhD, Nihon University School of Medicine Department of Neuropsychiatry, 30-1 Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan. Email: sakae@med.nihon-u.ac.jp*
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whom the RSS was similar to that of schizophrenia patients. RSS abnormalities were found only in schizophrenia patients.[8–10] Moreover, we conducted a worldwide collaborative EEM study to analyze the stability of parameters of EEM. The EEM tests were performed at seven World Health Organization collaborative centers in six countries. The RSS of patients with schizophrenia were significantly lower than those of depressed patients or healthy controls in all centers.[10] Thus, we believe that RSS may be a candidate indicator of schizophrenia.

The aim of the present study was to investigate whether EEM abnormalities are related to genetic vulnerability to schizophrenia. For that purpose, this project was designed to compare EEM test data between schizophrenia probands, their healthy siblings, and normal controls. We investigated the possibility that the EEM test can assist with the clarification of genetic components in schizophrenia.

METHODS

Subjects

Twenty-three probands with schizophrenia, 23 of their healthy siblings (23 proband–sibling pairs), and 43 unrelated normal controls participated in this study. All probands met the DSM-IV criteria for schizophrenia. The schizophrenia probands (14 men and nine females) had a mean age of 29.3 ± 9.1 years; mean duration of illness was 5.2 ± 4.6 years; mean age at onset was 24.0 ± 5.8 years. All probands were receiving an average daily dosage of 9.3 ± 7.1 mg of a neuroleptic medication equivalent to haloperidol, and were also taking anti-cholinergic drugs. The probands were 10 inpatients and 13 outpatients at Nihon University Hospital in Tokyo or one of three affiliated hospitals (two in Tokyo; one in Chiba Prefecture close to Tokyo). The schizophrenia probands were subclassified into DSM-IV categories: disorganized type ($n = 3$), paranoid type ($n = 15$), residual type ($n = 2$), and undifferentiated type ($n = 3$). We performed the EEM test on the probands during a period when they were not suffering from acute symptoms. All probands in the present study cooperated with the tests and understood the investigator's instructions clearly.

The normal siblings (10 men and 13 women) had a mean age of 30.9 ± 12.3 years. The goal of this project was to research one non-psychotic sibling for each proband. Whenever possible, the healthy sibling chosen was of the same sex and nearest in age to the proband from each family. The unrelated normal controls (22 men and 21 women) had a mean age of 34.7 ± 12.2 years. The controls were selected from healthy volunteers among hospital staff, students from Nihon University, and members of Tokyo-based drug companies. The healthy siblings and normal controls had no specific history of mental illness according to DSM-IV criteria and had never received psychiatric medications. In addition, the normal controls had no history of psychotic illness in their first-degree family members.

The schizophrenia probands, their healthy siblings, and the normal controls were matched for age and sex. None of the probands, their healthy siblings, or the normal controls had evidence of substance or alcohol abuse or organic brain pathology. The diagnosis of the probands, their healthy siblings, and the normal controls was based on structured clinical interviews for DSM-IV. Each face-to-face interview was conducted by two experienced interviewers. After the nature of the study had been fully explained, written informed consent was obtained from the probands, their siblings, and the normal controls.

Exploratory eye movement

The EEM procedure followed that used by Kojima *et al.*[8] The subjects were asked to sit on a stool equipped with a nac VIII-type Eye Mark Recorder (nac, Tokyo, Japan), a device that detects corneal reflection of infrared light. Three repeats of an original horizontal S-shaped motifs (Fig. 1a,c,e) and two S-shaped motifs that differed slightly from the original one (Fig. 1b,d) were projected individually onto a screen positioned 1.5 m directly in front of the subject's eyes. The width of each of these projected geometric figures was 90 cm, and the height was 75 cm (angle of sight was 33° horizontally and 27.5° vertically). Figure 1 illustrates the sequence of events in the EEM test, which was done in the following steps. First, each subject was directed to view the motif carefully because he/she would be asked to draw it later. The subject was then shown the original S-shaped motif (original motif: OM, Fig. 1a) for 15 s. Immediately after viewing it, the subject was asked to draw the OM from memory. Second, the subject was instructed to compare the OM (Fig. 1a) with a subsequent motif and was then shown a slightly different motif with one bump in a different position (bump in different position motif: BDPM, Fig. 1b) for 15 s;

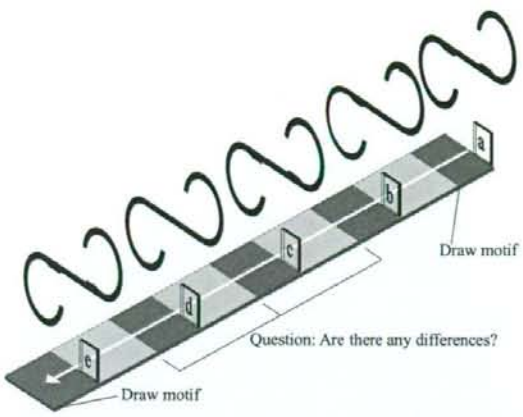

Figure 1. Sequence of events in the exploratory eye movement (EEM) test. (a,c,e) Repeats of the original motif; (b,d) slightly different motifs from the original one (motif b has one bump in a different position; motif d has no bumps). The EEM test proceeded from motif (a) to motif (e).

after 15 s had elapsed and with the BDPM still visible, the subject was asked whether it differed from the OM and if it did, how it differed; after the subject had replied and while the BDPM was still being shown, he/she was asked, 'Are there any other differences?' This question was repeated until the subject stated there were no further differences. Step 2 was repeated with the OM (Fig. 1c) and with a motif without bumps (no bump motif: NBM, Fig. 1d). Third, the subject was told to look at a projection of the OM (Fig. 1e) again for 15 s and to draw it again.

EEM tests during all steps were recorded on videotape with the eye mark recorder. These tapes were analyzed with a computerized system (eye movement analyzing software for Windows developed by our group). Eye fixations that focused on the same position for at least 200 ms were taken as real eye fixations. Movements of two degrees or more of sight were considered eye movements. In the present study we ascertained the following two measures: number of eye fixations in responsive search (NEFRS) and responsive search score (RSS). The actual NEFRS and RSS of a normal control subject are presented in Fig. 2.

Number of eye fixations in responsive search

The NEFRS is the number of eye fixations during the first 5 s immediately after the final question ('Are there any other differences?') when the subjects look at the BDPM (Fig. 1b) and the NBM (Fig. 1d). The NEFRS is the total number: BDPM result (Fig. 2a) + NBM result (Fig. 2b). In Fig. 2 the NEFRS of one control subject is shown: 30 (15 + 15).

Responsive search score

The BDPM and NBM were each divided into seven sections. Figure 2 shows the seven sections relevant to RSS scoring. The number of sections upon which the subject's eye fixed at least once was counted during

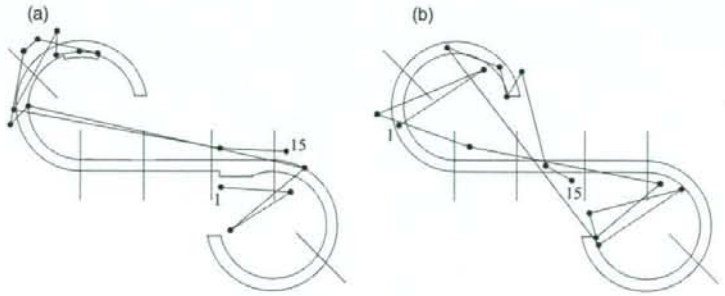

Figure 2. Number of eye fixations in responsive search (NEFRS) and the responsive search score (RSS) of a normal control subject. (a) and (b) are slightly different from the original motif (Fig. 1a). Figure 2(a) has a bump in a different position motif (BDPM). Figure 2(b) has no bump motif (NBM). The fixation points and movement sequences are represented by closed circle dots and lines. First and last fixation points are numbered 1 and 15 respectively. The NEFRS of this subject is 30 (15 + 15). These motifs are separated into seven sections for scoring of RSS. The RSS of this subject is 11 (5 + 6).