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$GABA_A$/Benzodiazepine receptor binding in patients with schizophrenia using [^{11}C]Ro15-4513, a radioligand with relatively high affinity for α5 subunit

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Abstract

Dysfunction of the GABA system is considered to play a role in the pathology of schizophrenia. Individual subunits of $GABA_A$/Benzodiazepine (BZ) receptor complex have been revealed to have different functional properties. α5 subunit was reported to be related to learning and memory. Changes of α5 subunit in schizophrenia were reported in postmortem studies, but the results were inconsistent. In this study, we examined $GABA_A$/BZ receptor using [^{11}C]Ro15-4513, which has relatively high affinity for α5 subunit, and its relation to clinical symptoms in patients with schizophrenia.

[^{11}C]Ro15-4513 bindings of 11 patients with schizophrenia (6 drug-naïve and 5 drug-free) were compared with those of 12 age-matched healthy control subjects using positron emission tomography. Symptoms were assessed using the Positive and Negative Syndrome Scale. [^{11}C]Ro15-4513 binding was quantified by binding potential (BP) obtained by the reference tissue model. [^{11}C]Ro15-4513 binding in the prefrontal cortex and hippocampus was negatively correlated with negative symptom scores in patients with schizophrenia, although there was no significant difference in BP between patients and controls. $GABA_A$/BZ receptor including α5 subunit in the prefrontal cortex and hippocampus might be involved in the pathophysiology of negative symptoms of schizophrenia.

Keywords: γ-Amino-butyric acid; Schizophrenia; Negative symptoms; Prefrontal cortex; Hippocampus; PET

1. Introduction

γ-Amino-butyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system.

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$GABA_A$/Benzodiazepine (BZ) receptors are heteropentamiric GABA-gated chloride channels, and mediate fast synaptic inhibition (Moss and Smart, 2001). Benzodiazepines enhance the action of the neurotransmitter GABA at $GABA_A$/BZ receptors by interaction with their modulatory benzodiazepine sites.

Dysfunction of GABA neurotransmission in the brain is thought to play a role in the pathology of schizophrenia (Simpson et al., 1989; Reynolds et al., 1990). Postmortem studies using [^{3}H]muscimol showed that binding was increased in the hippocampal formation (Benes et al., 1996a), anterior cingulate cortex (Benes et al., 1992) and prefrontal cortex (Benes et al., 1996b; Dean et al., 1999) in patients with schizophrenia. The axon terminals of chandelier GABA neurons are reported to be reduced substantially in the middle layers of the prefrontal cortex in schizophrenia (Lewis et al., 1999).

$GABA_A$/BZ receptor chloride channel complex consists of two α subunits, two β subunits and one γ subunit (Barnard et al., 1998; Lüddens et al., 1995; Mehta and Ticku, 1999). It has been reported that the diversity of α subunits is responsible for various functional properties and ligand selectivity to the $GABA_A$/BZ receptor (Barnard et al., 1998; Low et al., 2000; Mehta and Ticku, 1999; Tobler et al., 2001). α1 subunit has been suggested to be related to hypnotic and sedative amnesic actions, whereas α2, α3 and α5 subunits to anxiolytic, anticonvulsant, and antipsychotic actions, and to the function of learning and memory (Crestani et al., 2001; Mohler et al., 2001; Serwanski et al., 2006).

Alterations in individual subunits of $GABA_A$/BZ receptor in schizophrenia have been the focus of recent postmortem studies. Expression of α1 subunit was reported to increase in the prefrontal cortex of patients with schizophrenia (Ohnuma et al., 1999; Ishikawa et al., 2004), α2 subunit was reported to increase in the prefrontal cortex (Volk et al., 2002), and α5 subunit expression was reported to show no significant change (Akbarian et al., 1995) or increase (Impagnatiello et al., 1998).

Several ligands such as [^{11}C]flumazenil and [^{11}C]Ro15-4513 were developed to visualize $GABA_A$/BZ receptors by positron emission tomography (PET) (Inoue et al., 1992; Halldin et al., 1992; Pappata et al., 1988). Both [^{11}C]flumazenil and [^{11}C]Ro15-4513 have the imidazobenzodiazepine core structure. However, flumazenil is a $GABA_A$/BZ receptor antagonist while Ro15-4513 is known as a $GABA_A$/BZ receptor partial inverse agonist. A different distribution pattern has been reported for the binding of [^{11}C]Ro15-4513 compared to that of [^{11}C]flumazenil (Inoue et al., 1992; Halldin et al., 1992). Ro15-4513 was reported to have relatively higher affinity for the α5 subunit-containing $GABA_A$/BZ receptor *in vitro* (Lüddens et al., 1994; Wieland and Lüddens, 1994). [^{11}C]Ro15-4513 bindings in the cingulate and temporal cortical regions showed relatively higher binding to α5 subunit of $GABA_A$ receptor (Lingford-Hughes et al., 2002; Maeda et al., 2003).

A simplified method without arterial blood sampling for [^{11}C]Ro15-4513 in the living human brain has been evaluated recently, and it can be used in clinical studies (Asai et al., in press).

In this study, we measured [^{11}C]Ro15-4513 binding to examine $GABA_A$/BZ receptors with α5 subunit and their relation to clinical symptoms in patients with schizophrenia.

2. Methods and materials

2.1. Subjects

Eleven patients with schizophrenia (5 women, 6 men; 32.8±10.2 years old, mean±SD) meeting DSM-IV criteria for schizophrenia or schizophreniform disorder were enrolled in this study. Demographic and clinical data on subjects are shown in Table 1. Six of the patients (3 women, 3 men; 29.2±7.3 years old) were neuroleptic-naïve and five (2 women, 3 men; 37.2±12.2 years old) had been neuroleptic-free for at least one year before the PET measurement except one subject who took

Table 1
Demographic and clinical characteristics asstudy entry

						PANSS			
	N	Age (years)	Male/ female	Duration of illness (months)	Schizophrenia/ schizophreniform	Positive	Negative	General	Total
Patient	11	32.8±10.2	6/5	1–444	9/3	24.4±5.1	21.4±6.0	44.6±10.2	90.4±19.6
Drug-naïve	6	29.2±7.3	3/3	1–36	3/3	24.8±3.9	20.3±8.0	45.3±12.0	90.5±23.0
Drug-free	5	37.2±12.2	3/2	24–444	6/0	23.8±6.8	22.6±2.5	43.8±8.8	90.2±17.4
Normal controls	12	29.0±10.2	12/0	–	–	–	–	–	–

neuroleptics two weeks before the PET measurement. Three neuroleptic-naïve patients satisfying criteria for schizophreniform disorder (duration of illness 1 to 4 months at the time of PET measurement) met criteria for schizophrenia at 6-month follow-up. The patients were recruited from the outpatient units of university-affiliated psychiatric hospitals, psychiatric divisions of general hospitals, and a mental clinic in the urban environments of Tokyo and Chiba prefectures in Japan. Exclusion criteria were current or past substance or cannabis or alcohol abuse, mood disorders, organic brain disease, and medication of antipsychotics, antidepressants, or benzodiazepines or mood stabilizers within two weeks before PET measurement. Five out of 11 subjects were smokers.

Psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). PANSS was completed by three experienced psychiatrists on the same day as PET measurements was performed. They reviewed the ratings after the interviews, and disagreements were resolved by consensus; the consensus ratings were used in this study. The symptom scores were calculated as the total scores, positive symptom, negative symptom, and general symptom subscores of PANSS. The total PANSS score ranged from 60 to 124 (90.4±19.6, mean±SD), mean positive symptom scores were 24.4±5.1, negative symptom scores were 21.4±6.0, and general symptom scores were 44.6±10.2.

Normal control subjects (12 men, 29.0±10.2 years old) were recruited through notices on bulletin boards at the universities and among the staffs of the affiliated hospitals where the patients had been diagnosed. None of the controls had a history of psychiatric or neurological illness, brain injury, chronic somatic illness, or substance abuse. None had taken any drug including benzodiazepines within two weeks before PET measurements. Seven out of 12 subjects were smokers. All the subjects were examined by T1-weighted magnetic resonance image (MRI) using 1.5 T Philips Gyroscan NT to rule out organic brain diseases. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan. Written informed consent was obtained from all subjects.

2.2. PET measurement

[^{11}C]Ro15-4513 was synthesized by *N*-methylation of a corresponding *N*-desmethyl precursor with [^{11}C] methyl iodide. The reaction mixtures were purified by liquid chromatography, eluted with CH_3CN/6mM-phosphoric acid=175/325. The radiochemical purities were more than 95%.

The PET system used was ECAT EXACT HR+(CTI-Siemens, Knoxville, TN, USA), which provides 63 planes and a 15.5-cm field of view and was used in 3-dimensional mode. After a 10-minute transmission scan, a bolus of 352.3±66.9 MBq (mean±SD) of [^{11}C] Ro15-4513 with high specific radioactivities (103.4±38.9 GBq/μmol; mean±SD) was injected into the antecubital vein with a 20-ml saline flush. Radioactivity in the brain was measured in a series of sequential frames up to 60 min (total 28 frames).

2.3. PET data analysis

All emission scans were reconstructed with a Hanning filter cut-off frequency of 0.4 (FWHM 7.5 mm). Regions-of-interest (ROIs) were delineated on PET/MRI coregistered images for ten target regions (anterior cingulate, hippocampus, amygdala, thalamus, temporal cortex, prefrontal cortex, insula, caudate, putamen, cerebellum) and the pons as a reference region. Regional binding potentials were calculated using a simplified reference tissue model (SRTM)(Lammertsma and Hume, 1996). In brief, based on the three-compartment model, regional radioactivities in a target region (C_T) can be described by the following equation:

$$C_T(t) = R_1 C_R(t) + (k_2 - R_1\theta_3) C_R(t) * e^{-\theta_3 t},$$

where C_R represents the radioactivity in the reference region, R_1 is the ratio of K_1 in a target region to the reference region, $\theta_3 = k_2/(1+BP)$, K_1 and k_2 are rate constants corresponding to the influx and efflux rates from plasma to the tissue compartments, and * is the

Table 2
Binding potentials for regions of interest

	BP values		*T* test (df=21)	
	Controls (*N*=12)	Patients (*N*=11)	*T* score	*p*
Anterior cingulated	6.08±0.72	6.14±0.63	−0.213	0.833
Hippocampus	5.43±0.77	4.95±0.80	1.432	0.167
Amygdala	5.49±0.56	5.25±0.48	1.118	0.276
Thalamus	2.00±0.28	1.83±0.24	1.534	0.14
Temporal cortex	4.20±0.52	4.12±0.38	0.438	0.666
Prefrontal cortex	3.60±0.35	3.59±0.34	0.09	0.929
Insula	5.79±0.63	5.56±0.46	1.011	0.324
Caudate	2.99±0.43	3.32±0.81	−1.199	0.249
Putamen	2.86±0.36	3.10±0.45	−1.445	0.165
Cerebellum	1.32±0.25	1.34±0.23	0.148	0.883

Values are mean±SD.

convolution operator. In this study, the pons was chosen as the reference tissue because this region is almost devoid of $GABA_A$/BZ receptor complex (Abadie et al., 1992).

2.4. Statistical analysis

Statistical analysis of the difference of regional BP or R_1 for each ROI between patients and controls was performed by repeated measures analysis of variance (ANOVA). When any interaction was found, post hoc Bonferroni correction was used for multiple comparisons. $p<0.05$ was considered significant.

Correlations between regional BP and PANSS scores were analyzed with Pearson's correlation method. $p<0.05$ was considered significant.

3. Results

Regarding regional BP values of [^{11}C]Ro15-4513, two-way repeated ANOVA revealed significant group-region interaction [$F_{4.3,90.6}=2.6$, $p=0.037$]. However, post hoc Bonferroni correction showed no significant differences of BPs for 10 ROIs between patients and controls (Table 2). As for R_1 values, two-way repeated ANOVA revealed no significant main effect of the groups [$F_{4.9,103.9}=1.613$, $p=0.164$] nor group-region interaction [$F_{1,21}=1.532$, $p=0.229$].

For the reference tissue, time activity curves of the pons between patients with schizophrenia and controls were compared with repeated-measures ANOVA with Green–Geisser correction. There was no significant main effect of groups [$F_{1,21}=1.027$, $p=0.323$] or no significant group by time interaction [$F_{2.09,43.9}=0.203$, $p=0.826$].

Regarding the relation to clinical symptoms, there were significant negative correlations between [^{11}C]Ro15-4513 binding in the prefrontal cortex and negative symptom scores ($R=-0.733$, $p=0.010$)(Fig. 1A), general symptom scores ($R=-0.655$, $p=0.029$) (Fig. 1C), and total PANSS scores ($R=-0.690$, $p=0.019$) (Fig. 1D). There was also a negative correlation between [^{11}C]Ro15-4513 binding in the hippocampus and negative symptom scores ($R=-0.605$, $p=0.048$) (Fig. 1B). No other regions

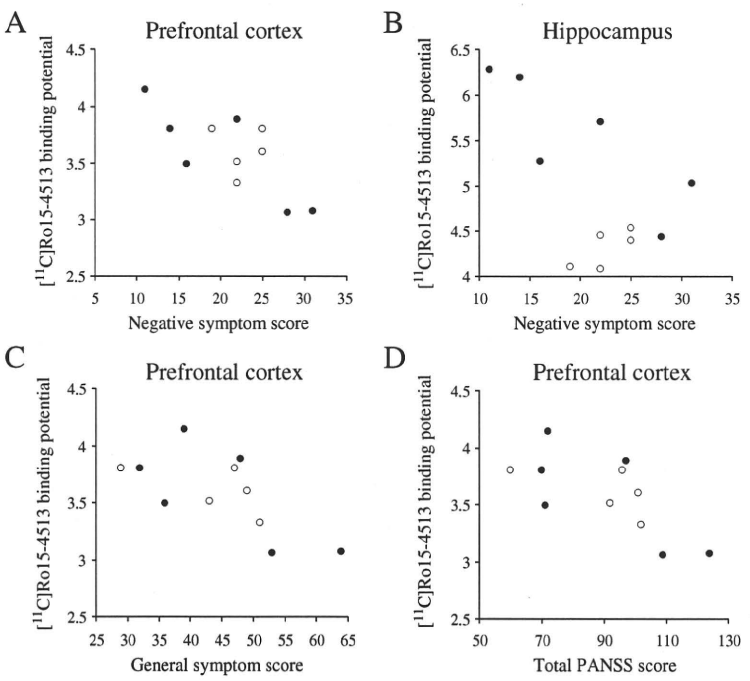

Fig. 1. Relationship between regional [^{11}C]Ro15-4513 binding potentials and PANSS scores in 11 patients with schizophrenia. Filled circles indicate neuroleptic-naïve patients ($N=6$). Open circles indicate drug-free patients ($N=5$). Total PANSS scores consist of positive symptom scores, negative symptom scores, and total symptom scores. There were significant negative correlations between [^{11}C]Ro15-4513 binding in the prefrontal cortex and negative symptom scores ($R=-0.733$, $p=0.010$)(A), general symptom scores ($R=-0.655$, $p=0.029$) (C), and total PANSS scores ($R=-0.690$, $p=0.019$) (D). There was also a negative correlation between [^{11}C]Ro15-4513 binding in the hippocampus and negative symptom scores ($R=-0.605$, $p=0.048$) (B).

Table 3
Correlation between regional [11C]Ro15-4513 binding potentials and PANSS scores

	Positive symptoms		Negative symptoms		General symptoms		Total scores	
Region	*R*	*p*	*R*	*p*	*R*	*p*	*R*	*p*
Anterior cingulate	−0.123	0.718	−0.312	0.350	−0.079	0.817	−0.169	0.620
Hippocampus	−0.008	0.982	−0.605	0.048*	−0.221	0.513	−0.302	0.367
Amygdale	−0.394	0.231	−0.307	0.359	−0.282	0.401	−0.343	0.302
Thalamus	−0.298	0.373	−0.163	0.633	0.005	0.987	−0.125	0.714
Temporal cortex	−0.415	0.205	−0.594	0.054	−0.564	0.070	−0.583	0.060
Prefrontal cortex	−0.485	0.131	−0.733	0.010*	−0.655	0.029*	−0.690	0.019*
Insula	−0.146	0.668	−0.541	0.085	−0.281	0.403	−0.349	0.292
Caudate	−0.164	0.630	−0.118	0.729	0.031	0.929	−0.063	0.854
Putamen	−0.383	0.245	−0.287	0.393	−0.184	0.587	−0.283	0.398
Cerebellum	0.057	0.868	−0.120	0.725	−0.010	0.976	−0.027	−0.937

showed significant correlation with clinical symptom scores (Table 3).

4. Discussion

In this study, significant negative correlation between clinical symptoms (especially negative symptoms) and $GABA_A$/BZ receptor binding in the prefrontal cortex (Fig. 1A, C, D) and the hippocampus (Fig. 1B) of the patients with schizophrenia was found. The significant relation between $GABA_A$/BZ receptor binding and clinical symptoms would suggest dysfunctions of the GABA system in schizophrenia.

Our results showed no significant difference of $GABA_A$/BZ receptor binding between patients with schizophrenia and controls (Table 2). This is consistent with some of the previous postmortem studies (Akbarian et al., 1995; Impagnatiello et al., 1998). However, inconsistent results have also been reported (Benes et al., 1996a, 1996b; Dean et al., 1999). Inconsistency can be attributed to methodological differences between PET study and postmortem study, as well as to the effects of prolonged antipsychotic and benzodiazepine administration. None of the patients in this study had taken any antipsychotics or benzodiazepines for at least two weeks before PET measurement. On the other hand, most of the subjects investigated in the postmortem studies had taken antipsychotics and/or benzodiazepines on a long-term basis. Recently, it was suggested from an animal experiment that antipsychotic drug administration would result in a "reshuffling" of $GABA_A$ receptor subtypes (Skilbeck et al., 2007).

Although there was no significant difference in [^{11}C] Ro15-4513 binding between patients and controls, [^{11}C] Ro15-4513 binding was found to be negatively correlated with clinical symptom scores. Although some previous SPECT studies using [^{123}I]iomazenil showed no significant difference of benzodiazepine binding between patients and controls (Abi-Dargham et al., 1999, Verhoeff et al., 1999), some reported that there were significant negative correlations between benzodiazepine binding and the severity of negative symptoms (Busatto et al., 1997), or cognitive impairment (Ball et al., 1998) in patients with schizophrenia. Our results were consistent with those studies, despite [^{11}C]Ro15-4513 having relatively high affinity for α5 subunit of $GABA_A$/BZ receptor while [^{123}I]iomazenil binds to $GABA_A$/BZ receptor non-selectively.

α5 subunit-containing $GABA_A$ receptors are reported to be concentrated in the apical dendrites of pyramidal neurons (Akbarian et al., 1995). In a postmortem study, α2 subunit of GABA in the axonal initial segment of pyramidal neurons was reported to be increased in patients with schizophrenia (Volk et al., 2002). The expression of subunits of $GABA_A$/BZ receptor was reported to be changed following chronic administration of phencyclidine, which induces schizophrenia-like symptoms in rats (Abe et al., 2000). Combining our results with these reports, the imbalance among α subunits in pyramidal neurons could be expected in patients with schizophrenia.

Dopamine receptors in the prefrontal cortex have been suggested to be involved in the pathophysiology of schizophrenia. Dopamine D1 receptor plays a key role in negative symptoms and cognitive dysfunctions of schizophrenia (Abi-Dargham et al., 2002; Okubo et al., 1997). Reduced prefrontal pyramidal neuron output could change the activity of dopamine neurons in the prefrontal cortex in schizophrenia (Lewis and Gonzalez-Burgos, 2006). The possible change of α5 subunit in the prefrontal cortex might cause the change of pyramidal neuron output, which might interact with dopamine D1 receptor.

Not only the prefrontal cortex but also the hippocampus was found to be correlated negatively with negative symptoms of patients with schizophrenia in this study (Fig. 1B). Hippocampal-dependent spatial learning was improved in α5 subunit of $GABA_A$ receptor-knockout mice (Collinson et al., 2002), or by systemic treatment of an inverse agonist selective for α5 $GABA_A$ receptors (Chambers et al., 2003). The change of α5 subunit of $GABA_A$ receptors in the prefrontal cortex in patients with schizophrenia might affect hippocampal function because of the plastic neuronal connections between the hippocampus and prefrontal cortex (Goldman-Rakic et al., 1984; Laroche et al., 2000; Maccotta et al., 2007; Tierney et al., 2004; Takahashi et al., 2007).

There has been some interest in treating negative symptoms and cognitive dysfunctions in schizophrenia with GABA-modulating drugs (Guidotti et al., 2005; Lewis et al., 2004; Menzies et al., 2007). Imidazenil, which selectively allosterically modulates cortical $GABA_A$ receptors containing α5 subunit, was reported to contribute to amelioration of the behavioral deficits without producing sedation or tolerance liability in mice (Guidotti et al., 2005), and it increased locomotor activity in a social isolation mouse model (Pinna et al., 2006).

There were several limitations to this preliminary study. The number of subjects was small, and five of the eleven patients were previously treated. Further study would be needed with a larger population of drug-naïve patients. Although age correction was not performed, we previously reported no significant age effect of [^{11}C] Ro15-4513 binding (Suhara et al., 1993). We also compared with age-matched subgroup of drug naïve paitents (N=6) with controls (N=12) and two-way repeated ANOVA revealed no significant group-region interaction of [^{11}C]Ro15-4513 binding.

Sex was not matched between patients and controls, but sex differences of [^{11}C]Ro15-4513 binding have not been reported.

In conclusion, the present study showed that [^{11}C] Ro15-4513 binding was negatively correlated with negative symptom scores in schizophrenia. $GABA_A$/BZ receptor including α5 subunit might be involved in the pathophysiology of schizophrenia with negative symptoms.

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Contributors

Y Asai, T Takano and T Suhara designed the study and wrote the protocol. Y Okubo, M Matsuura, A Otsuka, H Takahashi, T Ando, and S Ito recruited the subjects and made psychiatric evaluations. Y Asai, T Takano, and R Arakawa performed the data analysis. Y Asai wrote the first draft of the manuscript. H Ito gave fruitful comments to finalize the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors have no conflict of interest.

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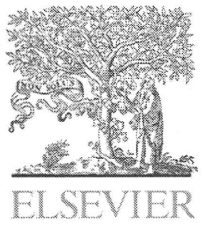

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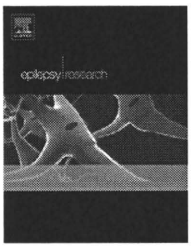

Difference in age of onset of psychosis between epilepsy and schizophrenia

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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.

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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

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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

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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.

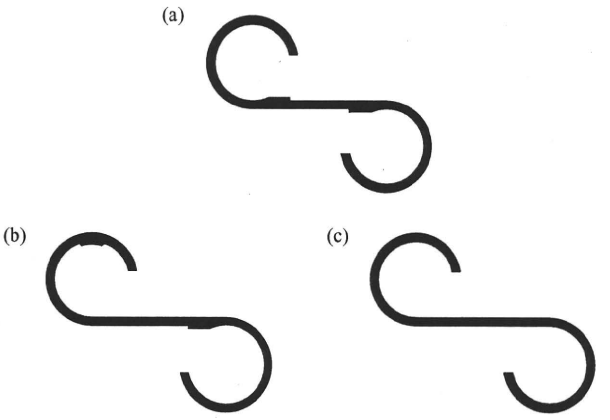

Figure 1. Three horizontal S-shaped figures in the exploratory eye movement (EEM) test. More detailed descriptions of these figures (a, b and c) have been presented in our previous studies.[4,8,9]

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.

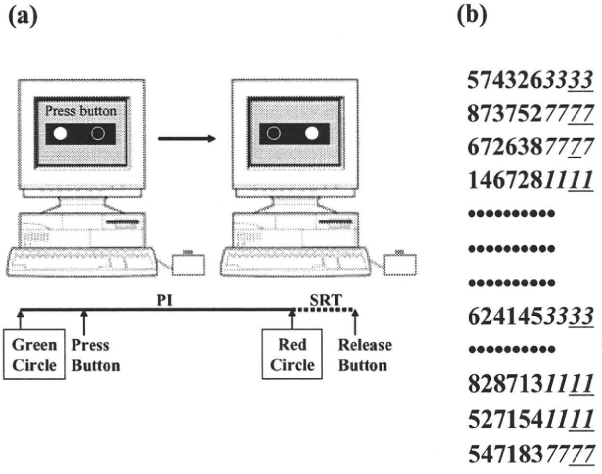

Figure 2. (a) Reaction time test apparatus and (b) preparatory interval (PI) array. SRT, simple reaction time.

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.

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 $\geq$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).

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

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.

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

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.