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

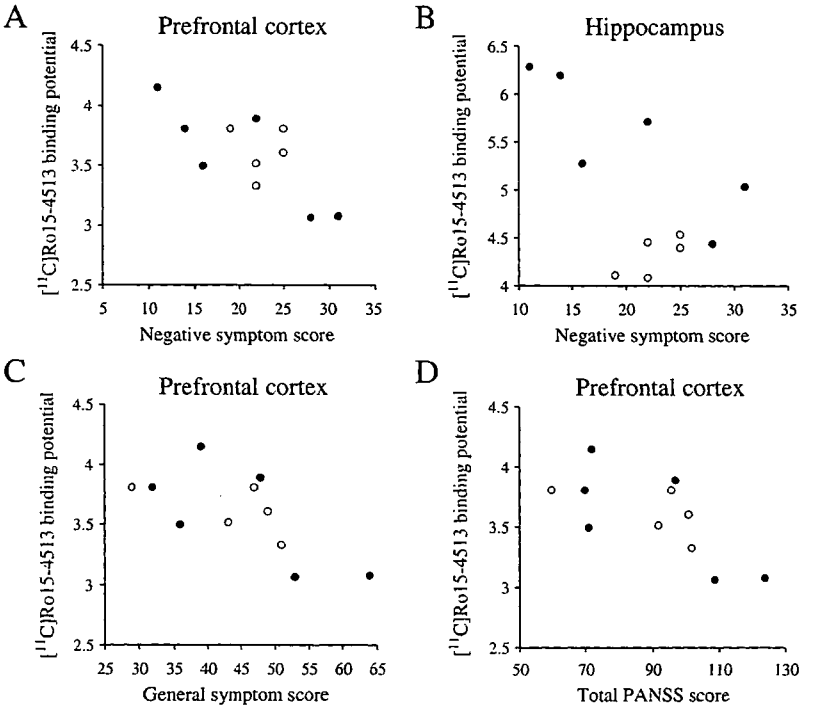

Fig. 1. Relationship between regional [^{11}C]Ro15-4513 binding potentials and PANSS scores in 11 patients with schizophrenia. Filled circles indicate neuroleptic-naïve patients ($N=6$). Open circles indicate drug-free patients ($N=5$). Total PANSS scores consist of positive symptom scores, negative 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.

Role of funding source

This study was supported by a consignment expense for Molecular Imaging Program on "Research Base for PET Diagnosis" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japanese Government. The Ministry had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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.

Acknowledgments

We thank Takashi Okauchi for his help with the statistical analysis of PET data, and all the PET members in National Institute of Radiological Sciences for their assistant.

References

Abadie, P., Baron, J.C., Bisserbe, J.C., Boulenger, J.P., Rioux, P., Travere, J.M., et al., 1992. Central benzodiazepine receptors in human brain: estimation of regional Bmax and KD values with positron emission tomography. Eur. J. Pharmacol. 213 (1), 107–115.

Abe, S., Suzuki, T., Ito, T., Baba, A., Hori, T., Kurita, H., et al., 2000. Differential expression of $GABA_A$ receptor subunit mRNAs and ligand binding sites in rat brain following phencyclidine administration. Synapse 38 (1), 51–60.

Abi-Dargham, A., Laruelle, M., Krystal, J., D'Souza, C., Zoghbi, S., Baldwin, R.M., et al., 1999. No evidence of altered in vivo benzodiazepine receptor binding in schizophrenia. Neuropsychopharmacology 20 (6), 650–661.

Abi-Dargham, A., Mawlawi, O., Lombardo, I., Gil, R., Martinez, D., Huang, Y., et al., 2002. Prefrontal dopamine D1 receptors and working memory in schizophrenia. J. Neurosci. 22 (9), 3708–3719.

Akbarian, S., Huntsman, M.M., Kim, J.J., Tafazzoli, A., Potkin, S.G., Bunney Jr, W.E., Jones, E.G., 1995. $GABA_A$ receptor subunit gene expression in human prefrontal cortex: comparison of schizophrenics and controls. Cereb. Cortex 5 (6), 550–560.

Asai Y., Ikoma Y., Takano A., Maeda J., Toyama H., Yasuno F., et al. in press. Quantitative analyses of [^{11}C]Ro15-4513 binding to subunits of $GABA_A$/Benzodiazepine receptor in living human brain. Nucl. Med. Commun.

Ball, S., Busatto, G.F., David, A.S., Jones, S.H., Hemsley, D.R., Pilowsky, L.S., et al., 1998. Cognitive functioning and GABAA/benzodiazepine receptor binding in schizophrenia: a ^{123}I-iomazenil SPET study. Biol. Psychiatry 43 (2), 107–117.

Barnard, E.A., Skolnick, P., Olsen, R.W., Mohler, H., Sieghart, W., Biggio, G., et al., 1998. Subtypes of gamma-aminobutyric acid A receptors: classification on the basis of subunit structure and receptor function. Pharmacol Rev. 50 (2), 291–313.

Benes, F.M., Vincent, S.L., Alsterberg, G., Bird, E.D., SanGiovanni, J.P., 1992. Increased $GABA_A$ receptor binding in superficial layers of cingulate cortex in schizophrenics. J. Neurosci. 12 (3), 924–929.

Benes, F.M., Khan, Y., Vincent, S.L., Wickramasinghe, R., 1996a. Differences in the subregional and cellular distribution of $GABA_A$ receptor binding in the hippocampal formation of schizophrenic brain. Synapse 22 (4), 338–349.

Benes, F.M., Vincent, S.L., Marie, A., Khan, Y., 1996b. Up-regulation of $GABA_A$ receptor binding on neurons of the prefrontal cortex in schizophrenic subjects. Neuroscience 75 (4), 1021–1031.

Busatto, G.F., Pilowsky, L.S., Costa, D.C., Ell, P.J., David, A.S., Lucey, J.V., Kerwin, R.W., 1997. Correlation between reduced in vivo benzodiazepine receptor binding and severity of psychotic symptoms in schizophrenia. Am. J. Psychiatry 154 (1), 56–63.

Chambers, M.S., Atack, J.R., Broughton, H.B., Collinson, N., Cook, S., Dawson, G.R., et al., 2003. Identification of a novel, selective $GABA_A$ alpha5 receptor inverse agonist which enhances cognition. J. Med. Chem. 46 (11), 2227–2240.

Collinson, N., Kuenzi, F.M., Jarolimek, W., Maubach, K.A., Cothliff, R., Sur, C., et al., 2002. Enhanced learning and memory and altered GABAergic synaptic transmission in mice lacking the alpha 5 subunit of the $GABA_A$ receptor. J. Neurosci. 22 (13), 5572–5580.

Crestani, F., Low, K., Keist, R., Mandelli, M., Mohler, H., Rudolph, U., 2001. Molecular targets for the myorelaxant action of diazepam. Mol. Pharmacol. 59 (3), 442–445.

Dean, B., Hussain, T., Hayes, W., Scarr, E., Kitsoulis, S., Hill, C., et al., 1999. Changes in serotonin2A and $GABA_A$ receptors in schizophrenia: studies on the human dorsolateral prefrontal cortex. J. Neurochem. 72 (4), 1593–1599.

Goldman-Rakic, P.S., Selemon, L.D., Schwartz, M.L., 1984. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. Neuroscience 12 (3), 719–743.

Guidotti, A., Auta, J., Davis, J.M., Dong, E., Grayson, D.R., Veldic, M., et al., 2005. GABAergic dysfunction in schizophrenia: new treatment strategies on the horizon. Psychopharmacology (Berl) 180 (2), 191–205.

Halldin, C., Farde, L., Litton, J.E., Hall, H., Sedvall, G., 1992. [^{11}C]Ro 15-4513, a ligand for visualization of benzodiazepine receptor binding. Psychopharmacology 108 (1-2), 16–22.

Impagnatiello, F., Guidotti, A.R., Pesold, C., Dwivedi, Y., Caruncho, H., Pisu, M.G., et al., 1998. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. Proc. Natl. Acad. Sci. U. S. A. 95 (26), 15718–15723.

Inoue, O., Suhara, T., Itoh, T., Kobayashi, K., Suzuki, K., Tateno, Y., 1992. In vivo binding of [^{11}C]Ro15-4513 in human brain measured with PET. Neurosci. Lett. 145 (2), 133–136.

Ishikawa, M., Mizukami, K., Iwakiri, M., Hidaka, S., Asada, T., 2004. Immunohistochemical and immunoblot study of $GABA_A$ alpha1 and beta2/3 subunits in the prefrontal cortex of subjects with schizophrenia and bipolar disorder. Neurosci. Res. 50 (1), 77–84.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Laroche, S., Davis, S., Jay, T.M., 2000. Plasticity at hippocampal to prefrontal cortex synapses: dual roles in working memory and consolidation. Hippocampus 10 (4), 438–446.

Lammertsma, A.A., Hume, S.P., 1996. Simplified reference tissue model for PET receptor studies. NeuroImage 4 (3 Pt 1), 153–158.

Lewis, D.A., Gonzalez-Burgos, G., 2006. Pathophysiologically based treatment interventions in schizophrenia. Nat. Med. 12 (9), 1016–1022.

Lewis, D.A., Pierri, J.N., Volk, D.W., Melchitzky, D.S., Woo, T.U., 1999. Altered GABA neurotransmission and prefrontal cortical dysfunction in schizophrenia. Biol. Psychiatry 46 (5), 616–626.

Lewis, D.A., Volk, D.W., Hashimoto, T., 2004. Selective alterations in prefrontal cortical GABA neurotransmission in schizophrenia: a novel target for the treatment of working memory dysfunction. Psychopharmacology (Berl) 174 (1), 143–150.

Lingford-Hughes, A., Hume, S.P., Feeney, A., Hirani, E., Osman, S., Cunnungham, V.J., et al., 2002. Imaging the GABA-benzodiazepine receptor subtype containing the α5-subunit *in vivo* with [^{11}C]Ro15 4513 positron emission tomography. J. Cereb. Blood Flow Metab. 22 (7), 878–889.

Low, K., Crestani, F., Keist, R., Benke, D., Brunig, I., Benson, J.A., et al., 2000. Molecular and neuronal substrate for the selective attenuation of anxiety. Science 290 (5489), 131–134.

Lüddens, H., Seeburg, P.H., Korpi, E.R., 1994. Impact of beta and gamma variants on ligand-binding properties of gamma-aminobutyric acid type A receptors. Mol. Pharmacol. 45 (5), 810–814.

Lüddens, H., Korpi, E.R., Seeburg, P.H., 1995. $GABA_A$/benzodiazepine receptor heterogeneity: neurological implications. Neuropharmacology 34 (3), 245–254.

Maccotta, L., Buckner, R.L., Gilliam, F.G., Ojemann, J.G., 2007. Changing frontal contributions to memory before and after medial temporal lobectomy. Cereb. Cortex 17 (2), 443–456.

Maeda, J., Suhara, T., Kawabe, K., Okauchi, T., Obayashi, S., Hojo, J., Suzuki, K., 2003. Visualization of alpha5 subunit of $GABA_A$/benzodiazepine receptor by [^{11}C]Ro15-4513 using positron emission tomography. Synapse 47 (3), 200–208.

Mehta, A.K., Ticku, M.K., 1999. An update on $GABA_A$ receptors. Brain Res. Brain Res. Rev. 29, 196–217.

Menzies, L., Ooi, C., Kamath, S., Suckling, J., McKenna, P., Fletcher, P., et al., 2007. Effects of gamma-aminobutyric acid-modulating drugs on working memory and brain function in patients with schizophrenia. Arch. Gen. Psychiatry 64 (2), 156–167.

Mohler, H., Crestani, F., Rudolph, U., 2001. $GABA_A$-receptor subtypes: a new pharmacology. Curr. Opin. Pharmacol. 1 (1), 22–25.

Moss, S.J., Smart, T.G., 2001. Constructing inhibitory synapses. Nat. Rev. Neurosci. 2 (4), 240–250.

Ohnuma, T., Augood, S.J., Arai, H., McKenna, P.J., Emson, P.C., 1999. Measurement of GABAergic parameters in the prefrontal cortex in schizophrenia: focus on GABA content, $GABA_A$ receptor alpha-1 subunit messenger RNA and human GABA transporter-1 (HGAT-1) messenger RNA expression. Neuroscience 93 (2), 441–448.

Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., et al., 1997. Decreased prefrontal dopamine D_1 receptors in schizophrenia revealed by PET. Nature 385 (6617), 634–636.

Pappata, S., Samson, Y., Chavoix, C., Prenant, C., Maziere, M., Baron, J.C., 1988. Regional specific binding of [^{11}C]Ro15 1788 to central type benzodiazepine receptors in human brain: quantitative evaluation by PET. J. Cereb. Blood Flow Metab. 8 (3), 304–313.

Pinna, G., Agis-Balboa, R.C., Zhubi, A., Matsumoto, K., Grayson, D.R., Costa, E., Guidotti, A., 2006. Imidazenil and diazepam increase locomotor activity in mice exposed to protracted social isolation. Proc. Natl. Acad. Sci. U. S. A. 103 (11), 4275–4280.

Reynolds, G.P., Czudek, C., Andrews, H.B., 1990. Deficit and hemispheric asymmetry of GABA uptake sites in the hippocampus in schizophrenia. Biol. Psychiatry 27 (9), 1038–1044.

Serwanski, D.R., Miralles, C.P., Christie, S.B., Mehta, A.K., Li, X., De Blas, A.L., 2006. Synaptic and nonsynaptic localization of GABAA receptors containing the alpha5 subunit in the rat brain. J. Comp. Neurol. 499 (3), 458–470.

Simpson, M.D., Slater, P., Deakin, J.F., Royston, M.C., Skan, W.J., 1989. Reduced GABA uptake sites in the temporal lobe in schizophrenia. Neurosci. Lett. 107 (1-3), 211–215.

Skilbeck, K.J., O'Reilly, J.N., Johnston, G.A., Hinton, T., 2007. The effects of antipsychotic drugs on $GABA_A$ receptor binding depend on period of drug treatment and binding site examined. Schizophr. Res. 90 (1-3), 76–80.

Suhara, T., Inoue, O., Kobayashi, K., Suzuki, K., Itoh, T., Tateno, Y., 1993. No age-related changes in human benzodiazepine receptor binding measured by PET with [^{11}C]Ro15-4513. Neurosci. Lett. 159 (1-2), 207–210.

Takahashi, H., Kato, M., Hayashi, M., Okubo, Y., Takano, A., Ito, H., Suhara, T., 2007. Memory and frontal lobe functions; possible relations with dopamine D_2 receptors in the hippocampus. NeuroImage 34 (4), 1643–1649.

Tierney, P.L., Degenetais, E., Thierry, A.M., Glowinski, J., Gioanni, Y., 2004. Influence of the hippocampus on interneurons of the rat prefrontal cortex. Eur. J. Neurosci. 20 (2), 514–524.

Tobler, I., Kopp, C., Deboer, T., Rudolph, U., 2001. Diazepam-induced changes in sleep: role of the alpha 1 $GABA_A$ receptor subtype. Proc. Natl. Acad. Sci. U. S. A. 98 (11), 6464–6469.

Verhoeff, N.P., Soares, J.C., D'Souza, C.D., Gil, R., Degen, K., Abi-Dargham, A., et al., 1999. [^{123}I]Iomazenil SPECT benzodiazepine receptor imaging in schizophrenia. Psychiatry Res. 91 (3), 163–173.

Volk, D.W., Pierri, J.N., Fritschy, J.M., Auh, S., Sampson, A.R., Lewis, D.A., 2002. Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. Cereb. Cortex 12 (10), 1063–1070.

Wieland, H.A., Lüddens, H., 1994. Four amino acid exchanges convert a diazepam-insensitive, inverse agonist-preferring $GABA_A$ receptor into a diazepam-preferring $GABA_A$ receptor. J. Med. Chem. 37 (26), 4576–4580.

Epilepsy Research (2008) 78, 201–206

ELSEVIER

journal homepage: www.elsevier.com/locate/epilepsyres

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*

Received 14 March 2007; received in revised form 25 September 2007; accepted 7 December 2007

KEYWORDS
Epilepsy;
Psychosis;
Schizophrenia;
Age of onset;
Sex difference;
Family history

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.
© 2007 Elsevier B.V. All rights reserved.

* 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).

0920-1211/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2007.12.001

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.

References

Adachi, N., 2006. Epilepsy and psychosis. Issues on clinical research in epilepsy psychosis. Seishin Shinkeigaku Zasshi 108, 260–265 (in Japanese).

Adachi, N., Matsuura, M., Okubo, Y., Oana, Y., Takei, N., Kato, M., Hara, T., Onuma, T., 2000. Predictive variables for interictal psychosis in epilepsy. Neurology 55, 1310–1314.

Adachi, N., Matsuura, M., Hara, T., Oana, Y., Okubo, Y., Kato, M., Onuma, T., 2002. Psychoses and epilepsy: are interictal and postictal psychoses distinct clinical entities? Epilepsia 43, 1574–1582.

Adachi, N., Kato, M., Sekimoto, M., Ichikawa, I., Akanuma, N., Uesugi, H., Matsuda, H., Ishida, S., Onuma, T., 2003. Recurrent postictal psychoses after remission of interictal psychosis: further evidence of bimodal psychosis. Epilepsia 44, 1218–1222.

Adachi, N., Ito, M., Kanemoto, K., Akanuma, N., Okazaki, M., Ishida, S., Sekimoto, M., Kato, M., Kawasaki, J., Tadokoro, Y., Oshima, T., Onuma, T., 2007. Duration of postictal psychotic episodes. Epilepsia 48, 1531–1537.

Alda, M., Ahrens, B., Lit, W., Dvorakova, M., Labelle, A., Zvolsky, P., Jones, B., 1996. Age of onset in familial and sporadic schizophrenia. Acta Psychiatr. Scand. 93, 447–450.

Andreasen, N.C., 1994. In: Okazaki, Y., Kitamura, T., Anzai, N., Shima, S., Ohta, T. (Eds.), Comprehensive Assessment of Symptoms and History (CASH). Seiwa Shoten Publishers, Tokyo (Japanese edition translated).

Bredkjaer, S.R., Mortensen, P.B., Parnas, J., 1998. Epilepsy and non-organic non-affective psychosis. Br. J. Psychiatry 172, 235–238.

Bruens, J.H., 1974. Psychoses in epilepsy. In: Vinken, P.J., Bruyn, G.W. (Eds.). Handbook of Clinical Neurology, vol. 15. North-Holland publishing co., North Holland, Amsterdam, pp. 593–610.

Cockerell, O., Moriarty, J., Trimble, M., Sander, J.W.A.S., Shorvon, S.D., 1996. Acute psychological disorders in patients with epilepsy: a nation-wide study. Epilepsy Res. 25, 119–131.

Dana-Haeri, J., Trimble, M.R., 1984. Prolactin and gonadotrophin changes following partial seizures in epileptic patients with and without psychopathology. Biol. Psychiatry 19, 329–336.

Dana-Haeri, J., Trimble, M.R., Oxley, J., 1983. Prolactin and gonadotrophin changes following generalized and partial seizures. J. Neurol. Neurosurg. Psychiatry 46, 331–335.

Gorwood, P., Leboyer, M., Jay, M., Payan, C., Feingold, J., 1995. Gender and age at onset in schizophrenia: impact of family history. Am. J. Psychiatry 152, 208–212.

Hafner, H., Hambrecht, M., Loffler, P., Munk-Jorgensen, P., Riecher-Rossler, A.I., 1998. Is schizophrenia a disorder of all ages? A comparison of first episodes and early course across the lifecycle. Psychol. Med. 28, 351–365.

ILAE, 1989. Commission on classification and terminology of the international league against epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 30, 389–399.

Jablensky, A., Sartorius, N., Ernberg, G., Anker, M., Korten, A., Cooper, J.E., Day, R., Bertelsen, A., 1992. Schizophrenia: Mani-

festations, Incidence and Course in Different Cultures: A World Health Organization 10-Country Study. Psychol Med Monograph (Suppl. 20). Cambridge University Press, Cambridge.

Kanemoto, K., Kawasaki, J., Kawai, I., 1996. Postictal psychosis: a comparison with acute interictal and chronic psychoses. Epilepsia 37, 551–556.

Kendler, K.S., Karkowski-Shuman, L., Walsh, D., 1996. Age at onset in schizophrenia and risk of illness in relatives. Results from the Roscommon Family Study. Br. J. Psychiatry 169, 213–218.

Kitamura, T., Shima, S., Sekino, E., Kato, M., 1984. Reliability study on Family History-Research Diagnostic Criteria (FH-RDC) by using case vignettes. Jpn. J. Soc. Psychiatry 7, 308–312 (in Japanese).

Klein, D.N., Schatzberg, A.F., McCullough, J.P., Dowling, F., Goodman, D., Howland, R.H., Markowitz, J.C., Smith, C., Thase, M.E., Rush, A.J., LaVange, L., Harrison, W.M., Keller, M.B., 1999. Age of onset in chronic major depression: relation to demographic and clinical variables, familiy history and treatment response. J. Affect. Disord. 55, 149–157.

Kristensen, O., Sindrup, E.H., 1978. Psychomotor epilepsy and psychosis. I. Physical aspects. Acta Neurol. Scand. 57, 361–369.

Leiderman, D.B., Csernansky, J.G., Moses Jr., J.A., 1990. Neuroendocrinology and limbic epilepsy: relationships to psychopathology, seizure variables, and neuropsychological function. Epilepsia 31, 270–274.

Logsdail, S.J., Toone, B.K., 1988. Post-ictal psychoses. A clinical and phenomenological description. Br. J. Psychiatry 152, 246–252.

Maier, M., Mellers, J., Toone, B., Trimble, M., Ron, M.A., 2000. Schizophrenia, temporal lobe epilepsy and psychosis: an *in vivo* magnetic resonance spectroscopy and imaging study of the hippocampus/amygdale complex. Psychol. Med. 30, 571–581.

Mellers, J.D.C., Adachi, N., Takei, N., Cluckie, A., Toone, B.K., Lishman, W.A., 1998. SPET study of verbal fluency in schizophrenia and epilepsy. Br. J. Psychiatry 173, 69–74.

Mendez, M.F., Grau, R., Doss, R.C., Taylor, J.L., 1993. Schizophrenia in epilepsy: seizure and psychosis variables. Neurology 43, 1073–1077.

Onuma, T., Adachi, N., Hisano, T., Uesugi, S., 1992. 10-year follow-up study of epilepsy with psychosis. Jpn. J. Psychiatry Neurol. 45, 360–361.

Pond, D.A., 1957. Psychiatric aspects of epilepsy. J. Ind. Med. Prof. 3, 1421–1451.

Qin, P., Xu, H., Laursen, T.M., Vestergaard, M., Moriensen, P.B., 2005. Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: population based cohort study. Br. Med. J. 331, 23–25.

Rayport, M., Ferguson, S.M., 2001. Psychosis of epilepsy. An integrated approach. In: Ettinger, A.B., Kanner, A.M. (Eds.), Psychiatric Issues in Epilepsy. A Practical Guide to Diagnosis and Treatment. Lippincott Williams & Wilkins, Philadelphia, pp. 73–94.

Ridley, R.M., Baker, H.F., Crow, T.J., 1986. Transmissible and transmissible neurodegenerative disease: similarities in age of onset and genetics in relation of aetiology. Psychol. Med. 16, 199–207.

Sachdev, P., 1998. Schizophrenia-like psychosis and epilepsy: the status of the association. Am. J. Psychiatry 155, 325–336.

Slater, E., Beard, A.W., Glithero, E., 1963. The schizophrenia-like psychoses of epilepsy. Br. J. Psychiatry 109, 95–150.

Tarulli, A., Devinsky, O., Alper, K., 2001. Progression of postictal to interictal psychosis. Epilepsia 42, 1468–1471.

Trimble, M.R., 1991. The Psychoses of Epilepsy. Raven Press, New York.

Weinbergar, D.R., 1987. Implications of normal brain development for pathogenesis of schizophrenia. Arch. Gen. Psychiatry 44, 660–667.

Weissman, M.M., Merikangas, K.R., Wickramaratne, P., Kidd, K.K., Prusoff, B.A., Leckman, J.F., Pauls, D.L., 1986. Understanding the clinical heterogeneity of major depression using family data. Arch. Gen. Psychiatry 43, 430–434.

World Health Organization, 1992. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. World Health Organization, Geneva.

Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research 158 (2008) 287–296
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Gaze-triggered orienting is reduced in chronic schizophrenia

Tomoko Akiyama [a,*], Motoichiro Kato [b], Taro Muramatsu [b], Takaki Maeda [b], Tsunekatsu Hara [a], Haruo Kashima [b]

[a] *Department of Psychiatry, Komagino Hospital, 273 Uratakao-cho, Hachioji City, Tokyo, 193-8505, Japan*
[b] *Department of Neuropsychiatry, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan*

Received 26 April 2006; received in revised form 31 July 2006; accepted 6 December 2006

Abstract

Patients with schizophrenia have been reported to demonstrate subtle impairment in gaze processing, which in some cases indicates hypersensitivity to gaze, while in others, hyposensitivity. The neural correlate of gaze processing is situated in the superior temporal sulcus (STS), a major portion of which is constituted by the superior temporal gyrus (STG), and may be the underlying dysfunctional neural basis to the abnormal gaze sensitivity in schizophrenia. To identify the characteristics of gaze behavior in patients with chronic schizophrenia, in whom the STG has been reported to be smaller in volume, we tested 22 patients (mean duration of illness 29 years) in a spatial cueing paradigm using two central pictorial gaze cues, both of which effectively triggered attentional orienting in 22 age-matched normal controls. Arrow cues were also employed to determine whether any compromise in schizophrenia, if present, was gaze-specific. Results demonstrated that schizophrenic subjects benefit significantly less from congruent cues than normal subjects, which was evident for gaze cues but not for arrow cues. This finding is suggestive of a relatively gaze-specific hyposensitivity in patients with chronic schizophrenia, a finding that is in line with their clinical symptomatology and that may be associated with a hypoactive STS.
© 2006 Elsevier Ireland Ltd. All rights reserved.

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

1. Introduction

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

* Corresponding author. Tel.: +81 426 63 2222; fax: +81 426 63 3286.
E-mail address: tee-i@mxv.mesh.ne.jp (T. Akiyama).

0165-1781/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2006.12.004

gaze and head direction (Langdon et al., 2006). The neural correlate of such gaze processing is located in the superior temporal sulcus (STS) region, through animal studies (Campbell et al., 1990; Perrett et al., 1992), human activation studies (Puce et al., 1998; Wicker et al., 1998; Hoffman and Haxby, 2000; Hooker et al., 2003; Pelphrey et al., 2003; Kingstone et al., 2004), and a recent neuropsychological case (Akiyama et al., 2006a). Here, gaze cognition is considered one component in a wider range of biological motion understanding, which is essential in social interaction (Allison et al., 2000). It coincides that the schizophrenic brain has been reported repeatedly to show significantly smaller superior temporal gyrus (STG) volume (Rajarethinam et al., 2000, 2004; Onitsuka et al., 2004), which constitutes the upper bank of the STS. There is a possibility that the hyper/hyposensitivity to gaze in schizophrenic subjects might actually have a brain-based origin, for example, in a dysfunctional STS.

One way of testing behavior toward gaze is a gaze-cued target detection test. Friesen and Kingstone (1998) have applied Posner's spatial cueing paradigm (1980), using centrally presented pictorial gaze direction as a cue in detecting peripheral targets. Normal subjects demonstrated significantly faster target detection when cued by gaze direction congruent to the target location, compared with incongruently cued targets, in a non-predictive condition. Subsequently, a number of studies have confirmed the nature of gaze to strongly orient the viewer's attention in its direction (Driver et al., 1999; Zorzi et al., 2003). The congenital, or peri-natal patient group of autism, in which the STG has also been reported to be dysfunctional (Ohnishi et al., 2000; Zilbovicius et al., 2000; Boddaert et al., 2004; Pelphrey et al., 2005), and whose cardinal symptom is a deficit in reciprocal gaze interaction, has been studied recently with this spatial cueing paradigm. This patient group has demonstrated an absence of gaze-triggered orienting in a non-predictive condition (Ristic et al., 2005). Schizophrenia also has some common fundamental features, and as is the case for autism, its pathogenesis is far from elucidated. Investigation of the performance of schizophrenic subjects in such a paradigm would offer insight into the generation of the hyper/hyposensitivity toward gaze, as well as have some implications concerning the neural basis of such symptoms.

In this report, we have investigated the behavior toward gaze in a group of relatively uniform, long-term, unremitted schizophrenic subjects (mean duration of illness 29 years), using three different stimuli as directional cues. Given the well-documented concreteness in schizophrenic visual processing (Silverstein et al., 2000; Vianin et al., 2002; Uhlhaas et al., 2005), two gaze stimuli (ambiguous rectangular eyes, concrete elliptical eyes) were employed so as not to let very subtle compromise go unnoticed, if present. Arrow signs, which like gaze, have distinct directional property but no biological significance, have also been extensively studied in spatial cueing paradigms in normal (Tipples, 2002; Friesen et al., 2004), autistic (Senju et al., 2004), and schizophrenic subjects (Bustillo et al., 1997), and were used in this experiment as well for comparison with gaze cues. This comparison of behavior toward gaze versus arrows would give us an opportunity to determine whether any detected compromise in schizophrenia was specific to gaze, or represented a more generalized deficit. As hypo-arousal to gaze has been the clinical impression in chronic schizophrenia, we hypothesized that this patient group would demonstrate a distinct behavior pattern attributable to gaze hyposensitivity. Additionally, in relation to the documented schizophrenic volume decrease of the STG, which has been implicated in biological motion processing, we expected that such hyposensitivity would be specific to gaze in comparison to arrows.

2. Experiment 1

2.1. Methods for Experiment 1

2.1.1. Subjects

Twenty-two clinical participants were recruited from a psychiatric hospital in the suburbs of Tokyo. The inclusion criteria were a DSM-IVdiagnosis of schizophrenia (American Psychiatric Association, 1994), a duration of illness longer than 10 years, a history of multiple hospitalizations for acute psychosis, and currently undergoing treatment with neuroleptics. The exclusion criteria were an acute relapse within a year, mental retardation, and a neurological deficit. Twenty-

Table 1
Demographic data

	Schizophrenia (N=22)	Normal controls (N=22)
Age	51.2±7.2	51.2±11.3
Gender	M 17, F 5	M 12, F 10
Handedness	R 21, L 1	R 20, L 2
Education (years)	12.5±1.7	14.5±2.8
Duration of illness (years)	28.9±9.3	
Neuroleptic dosage (HP-mg)	12.8±6.5	
Inpatient/outpatient	15/7	
PANSS score		
Positive symptoms	20.2±5.5	
Negative symptoms	21.0±3.6	
Total	82.3±12.5	

HP-mg; haloperidol-equivalent milligram.

two normal volunteers also participated as controls. The exclusion criteria were a psychiatric history and a neurological history. All participants had normal or corrected-to-normal vision. Demographic information, including the neuroleptic dosage and psychiatric status as indicated by the Positive and Negative Syndrome Scale score (PANSS; Kay et al., 1987), appear in Table 1. The two groups were matched for age, but patients had significantly fewer years of education.

This study was approved by the ethical committee at our institutions, and all subjects gave their informed consent prior to participation.

2.1.2. Stimuli

The experiment was controlled by Superlab software, and the stimuli were presented on a 14-inch computer monitor. There were three blocks to the experiment, each with a different stimulus for the cue. The cues were black line drawings representing rectangular eyes for the first block, arrows for the second, and elliptical eyes for the third block, as illustrated in Fig. 1.

In the first, Rectangle block, a fixation display was composed of one central circle subtending 0.4°, and two rectangles, each 1.8° wide and 0.9° high, the center of which was 1.0° above, and 1.4° to the left and right of the circle. The central circle was used as the fixation point, and was displayed for 675 ms, followed by the cue display. In the cue display, a black square subtending 0.9° appeared within each rectangle, positioned either centrally (straight 'gaze'), or 11% off the rectangle center to the right or left (right/left 'gaze'). The cue was presented for 100, 300 or 700 ms randomly (stimulus onset asynchrony; SOA), after which a target, X, subtending 0.6°, appeared either to the right or left of the cue, 7.1° from the central circle.

In the second, Arrow block, a cross subtending 3.9° horizontally and 1.9° vertically appeared in the center, of which the intersection served as the fixation point. For the cue, arrowheads or vertical bars appeared at each horizontal end of the cross. Arrowheads (1.3°×0.6°) at both ends pointed in the same direction, cueing either to the right or left. The vertical bars (1.3°) served as the neutral cue, similar to straight gaze in other blocks. All other specifications were identical to the first block.

The third, Ellipse block was identical to the first block, except ellipses and circles were now used in place of rectangles and squares.

2.1.3. Design

There were three cue types (Rectangles, Arrows, Ellipses), each in three separate blocks. The order of the blocks remained fixed among subjects. Within each block, cue-target SOA (100, 300, 700 ms), cue-target relation (congruent, incongruent, neutral), cue direction (right, left, straight) and target location (right, left) were randomly selected with equal probability to make up a non-predictive, spatially cued, target detection test. Ten catch trials in which no target followed the cue were randomly dispersed within each block.

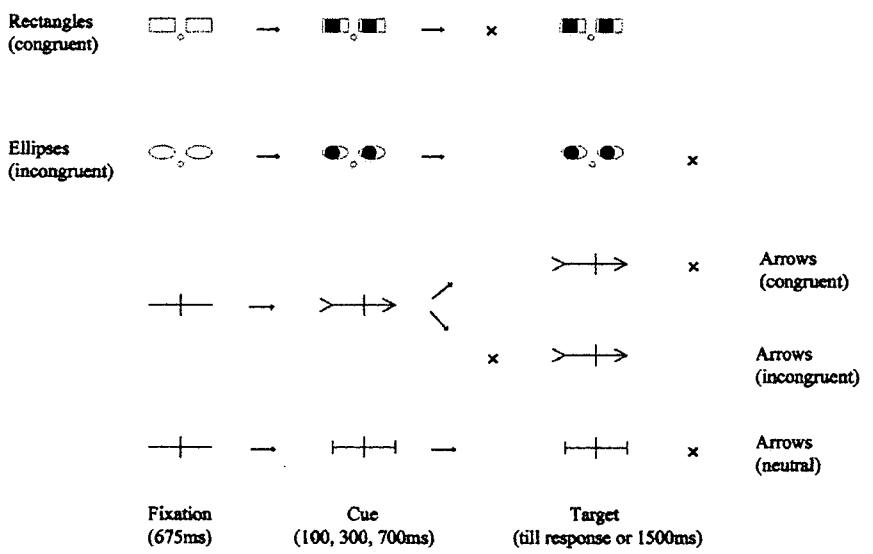

Fig. 1. Illustration of the trial sequence in the experiment. A fixation display was presented for 675 ms, followed by a cue display, which was either gaze or arrow direction. The cue was displayed for 100, 300, or 700 ms; then a target was presented, either to the right or left of the cue, and irrespective of cue direction.

Table 2
Results of the experiment

Cue type	Schizophrenia			Normal controls		
	RT	S.D.	%*E*	RT	S.D.	%*E*
Arrows	462	124	2.3	372	82	0.7
Rectangles	450	125	1.6	359	74	0.5
Ellipses	446	127	1.4	358	72	0.5
Overall	453	125	1.7	363	76	0.6

RT; reaction time (in ms), S.D.; standard deviation, %*E*; error rate.

2.1.4. Procedure

Participants sat 45 cm from the monitor. Subjects were instructed to maintain fixation throughout each trial, and upon target detection, to press the spacebar on the keyboard with their dominant index finger. The nature of the cue stimuli (e.g., their resemblance to eyes or arrows) was never mentioned, nor was the probability in relation to cue-target congruency. Fifteen practice trials were given before each block. The reaction time (RT) from the onset of the target to the pressing of the key was recorded. Time out was set at 1500 ms, with an inter-stimulus interval of 3000 ms. A total of 190 trials constituted one block, which took approximately 15 min to complete. Subjects were given a minimum of 10 min between blocks to rest. The patients were monitored for any change in their psychiatric state throughout this period, but all patients remained stable. There was no change in medication for any of the patients during this period. Eye movements were not monitored for the control subjects, for it has been confirmed in a number of studies that normal subjects reliably do not move their eyes in similar experiments (Posner, 1980; Friesen and Kingstone, 2003; Friesen et al., 2004). Patients with schizophrenia were monitored for eye movements by direct viewing of the experimenter. One patient had difficulty maintaining fixation and was therefore removed from the patient group. All 22 patients who were included in this study were able to maintain fixation almost all of the time.

3. Results for Experiment 1

Errors, defined as anticipations (RTs < 100 ms), RTs longer than 1000 ms, time-outs (no response), and incorrect responses (pressing a key other than the correct spacebar), were first discarded from further analysis, which eliminated less than 2% of both schizophrenic and normal data. The mean RTs, standard deviations, and error rates for each block are presented for both groups in Table 2. The mean RTs as a function of congruency and SOA for each cue type for each group are illustrated in Fig. 2. ANOVA was then conducted, with a between-subject variable of group (schizophrenia, normal), and within-subject variables of cue-type (Arrows, Rectangles, Ellipses), cue-target congruency (congruent, incongruent, neutral) and SOA (100, 300, 700 ms). There was a significant main effect of group (slower RTs in schizophrenia) [$F(1,42)=4529.05$, $P<0.001$], cue-type (slowest for arrows) [$F(2,42)=48.68$, $P<0.001$], congruency (fastest in congruent conditions) [$F(2,42)=37.32$, $P<0.001$], and SOA (from the slowest to the fastest at SOA 100, 700, 300 ms) [$F(2,42)=176.16$, $P<0.001$]. The significant interactions were group × congruency [$F(2,42)=3.46$,

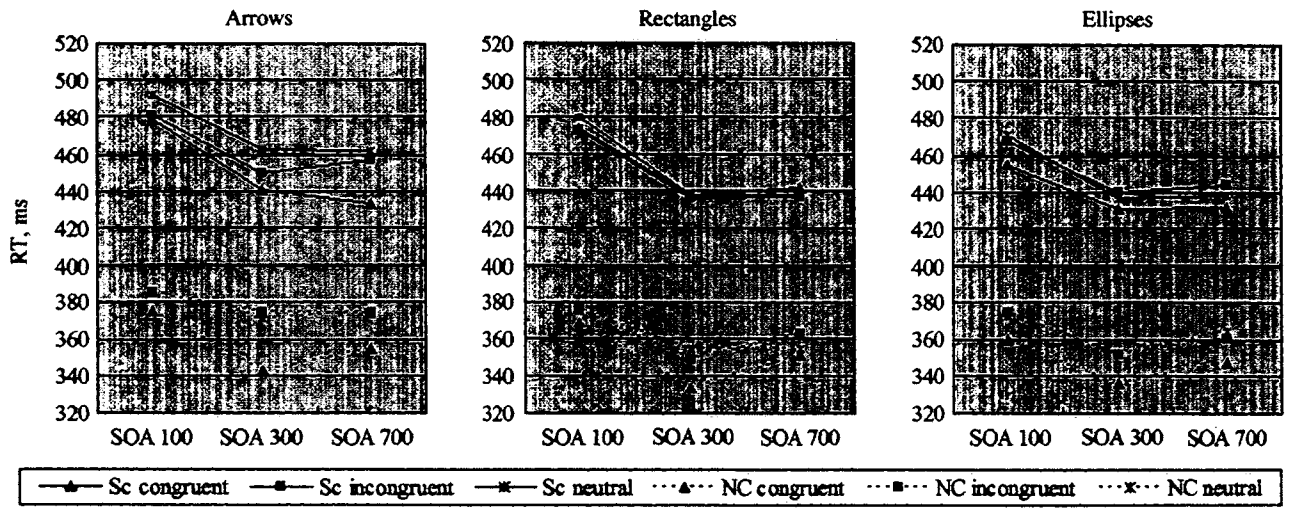

Fig. 2. Results of Experiment 1. The mean RTs of the schizophrenic group (Sc; lines) and normal controls (NC; dotted lines) for each cue type, as a function of cue-target congruency and SOA length.

$P=0.031$], group × SOA [$F(2,42)=13.01$, $P<0.001$], and cue-type × congruency [$F(4,42)=4.89$, $P=0.001$]. The significant interactions are further analyzed and detailed below.

To explore the critical interaction of congruency by group, separate ANOVAs were conducted for each group with congruency as the variable, which revealed a significant main effect of congruency for both schizophrenia [$F(2,21)=6.85$, $P=0.001$] and normal subjects [$F(2,21)=55.49$, $P<0.001$]. The group difference of congruency was further analyzed using Tukey's HSD within groups. The two groups demonstrated a similar pattern of congruency effect, in that RTs for congruent conditions were faster than both incongruent [schizophrenia; $P=0.046$, normal; $P<0.001$] and neutral [schizophrenia; $P=0.001$, normal; $P<0.001$] conditions. Thus, the magnitude of the benefit from congruent cues appears to be crucially different between the two groups. To quantify this difference, the benefit of congruent cues, defined as RTneutral–RTcongruent (positive values indicate benefits), and the cost of incongruent cues, defined as RTneutral–RTincongruent (negative values indicate costs), were calculated for each individual in both groups, using the mean RTs collapsed according to congruency (i.e., across SOAs) within each cue type. The averaged benefits and costs for both groups are illustrated in Fig. 3. Two-tailed t-tests comparing benefits between groups demonstrated no significant difference for Arrows [$t(42)=0.20$, $P=0.844$], a significant difference for Rectangles, [$t(42)=2.10$, $P=0.042$], and a trend for a difference for Ellipses [$t(42)=1.76$, $P=0.085$], reflecting smaller benefits of congruent gaze cues in schizophrenia. None of the cost differences were significant [Arrows: $t(42)=1.09$, $P=0.286$; Rectangles: $t(42)=1.38$, $P=0.176$; Ellipses: $t(42)=0.672$, $P=0.505$]. The interaction of congruency by group identified in ANOVA can thus be attributed to the reduction of congruency benefit in schizophrenia, which was evident for gaze cues (Rectangles, and to a lesser degree, Ellipses), but not for Arrows.

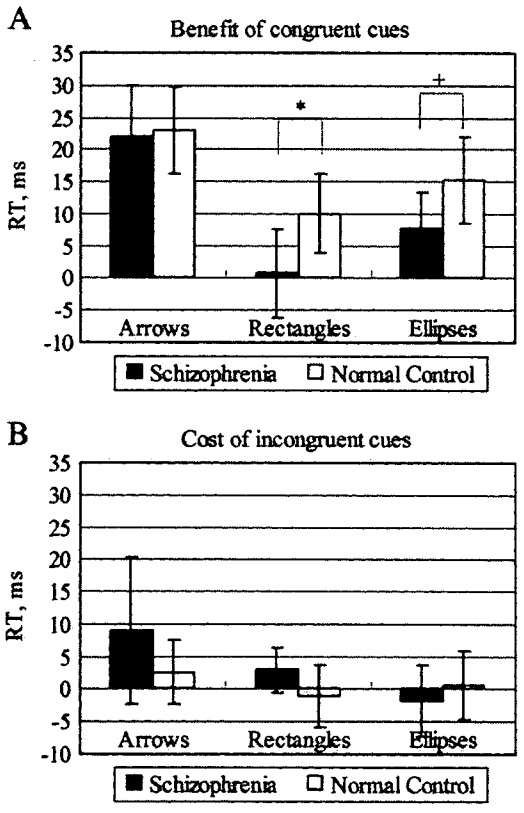

Fig. 3. Benefit of congruent cues and cost of incongruent cues. (A) The averaged benefit of congruent cues, calculated as RTneutral–RTcongruent, and (B) the averaged cost of incongruent cues, calculated as RTneutral–RTincongruent, are shown according to cue type and subject group. Positive (negative) values indicate benefits (costs). Error bars indicate the 95% confidence interval. *$P<0.05$, +$P=0.085$.

The interaction of congruency by cue-type was broken down by conducting separate ANOVAs for each cue-type with congruency as the variable. Arrows and Ellipses demonstrated significant effects of congruency [Arrows: $F(2,42)=25.57$, $P<0.001$; Ellipses: $F(2,42)=11.23$, $P<0.001$], while Rectangles did not [$F(2,42)=1.68$, $P=0.187$]. Although the interaction of group × cue-type × congruency did not reach significance, there appeared to be a group difference in the congruency effect for Rectangles (see Fig. 2). We therefore conducted a series of ANOVAs for each cue-type, with group and congruency as the variables. The interaction of group × congruency was not significant in any of the blocks, but approached significance for Rectangles [$F(2,42)=2.87$, $P=0.057$]. An additional series of ANOVAs for each cue-type and group was conducted, which revealed that the congruency effect for normal subjects was highly significant across cue-types [Arrows: $F(2,21)=30.70$, $P<0.001$; Rectangles: $F(2,21)=8.97$, $P<0.001$; Ellipses: $F(2,21)=18.80$, $P<0.001$], in contrast to schizophrenic subjects, who demonstrated a significant congruency effect only for Arrows [$F(2,21)=9.40$, $P<0.001$], with Ellipses approaching significance [$F(2,21)=2.93$, $P=0.053$], and no congruency effect whatsoever for Rectangles [$F(2,21)=0.207$, $P=0.813$]. The overall lack of a congruency effect for Rectangles can thus be attributed to a deficit in the schizophrenia group.

The interaction of SOA by group was also broken down by conducting separate ANOVAs for each group with SOA as the variable. Both groups demonstrated highly significant effects of SOA [schizophrenia: $F(2,21)=90.12$,

Table 3
Results of Experiment 2

Cue type	RT	S.D.	%E
Rectangles *	456	120	1.1
Rectangle-as-eyes	465	140	1.2

RT; reaction time (in ms), S.D.; standard deviation, %E; error rate.
* The results of the four patients who dropped out after Experiment 1 are eliminated; the same 18 participants as in Rectangle-as-eyes are evaluated.

$P<0.001$] [normal: $F(2,21)=102.81$, $P<0.001$]. Further analysis using Tukey's HSD revealed group differences in the SOA effect, such that schizophrenia demonstrated the slowest RTs for SOA of 100 ms, while RTs for SOA or 300 and 700 ms were essentially the same, whereas controls demonstrated RTs which were, from the slowest to the fastest, at SOA 100, 700, and 300 ms. The performance peak in schizophrenia appears to be at a longer SOA than the control subjects, indicating that this patient group might benefit from longer cue-target intervals than the controls.

Finally, the benefit differences and cost differences for each cue-type were tested for any correlation with the PANSS scores (positive, negative, and general psychopathology subscales, and total score), but none proved significant.

4. Discussion for Experiment 1

In a spatial cueing experiment using central gaze/arrow direction as cues, we have demonstrated that a relatively uniform population of chronic, medicated patients with schizophrenia differs from normal controls in terms of reduced benefit from congruently directed cues in detecting peripheral targets. Moreover, this benefit reduction in schizophrenia appears to be evident for gaze cues, but not for arrow cues. In other words, patients with chronic schizophrenia are compromised in orienting attention toward gaze direction, in the face of a relatively normal orienting for arrows. However, there is one major caveat to this experiment that needs to be addressed; the reduced congruency benefit in schizophrenia was mainly driven by the ambiguous rectangular eyes. The complete lack of congruency benefit seen in schizophrenia for the rectangles might just be reflecting the fact that schizophrenic subjects, as concrete perceivers simply do not perceive the rectangles as eyes; thus, such a cue cannot be considered a 'gaze' cue for schizophrenia in the first place. To overcome this caveat, we made further investigations in Experiment 2.

5. Experiment 2

5.1. Methods for Experiment 2

In this experiment, we tested the same patients who had completed Experiment 1, in an additional block of Rectangles. The only difference from the Rectangles in Experiment 1 were the instructions given before the trial. Subjects were first asked what they perceived of the rectangles. When they were unable to spontaneously perceive the rectangles as eyes, they were explicitly instructed to perceive them as such throughout the block. Such instructions should eliminate the possibility of a failure in schizophrenic subjects to perceive the rectangles as eyes. Additionally, this block would give us an opportunity to directly compare the performance for rectangles whose resemblance to gaze was not explicitly mentioned with the performance for rectangles that were explicitly instructed to be perceived as eyes. The interest lies in whether such explicit instructions are effective in normalizing behavior in chronic schizophrenia, such that a top-down regulation now allows them to infer the biological directional information from the rectangles.

5.2. Subjects

Of the 22 schizophrenic patients in Experiment 1, 18 patients participated in this experiment. One patient

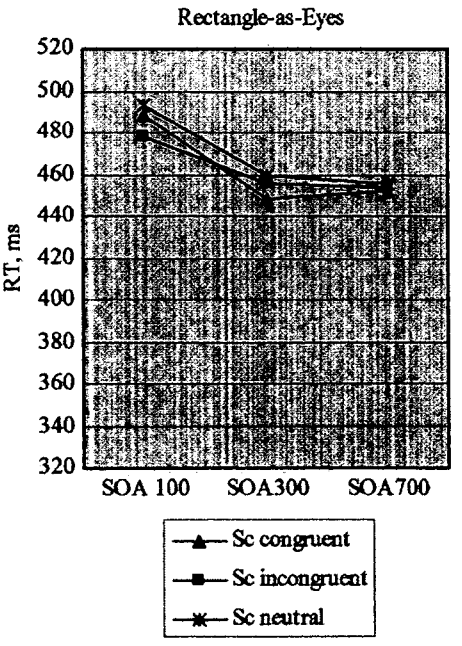

Fig. 4. Results of Experiment 2. The mean RTs for the schizophrenic group are shown as a function of cue-target congruency and SOA length.

dropped out due to an exacerbation of psychosis, two inpatients had returned home after Experiment 1, and one patient refused to participate.

5.3. Stimuli

Exactly the same stimuli were used as the Rectangles in Experiment 1.

5.4. Procedure

The procedure was essentially the same as the Rectangles in Experiment 1, except this time, the subjects were asked, during the practice trials, what the rectangles looked like. When they were unable to spontaneously perceive the rectangles as eyes, they were encouraged to perceive them as such, and were asked if they were successful. Finally, they were explicitly instructed to perceive the rectangles as eyes throughout the block. Therefore, practice trials were not limited to 15, but were continued until the patients fully understood the instructions.

6. Results for Experiment 2

Of the 18 participants, two patients were unable to spontaneously perceive the rectangles as eyes. The two reported the stimulus concretely as 'a black square within a white rectangle'. When encouraged to perceive them as eyes, both subjects immediately reported that they were able to.

The mean RTs, standard deviations, and error rates of all participants in Experiment 2, and of the same 18 participants in the Rectangles of Experiment 1, are presented in Table 3. An ANOVA was conducted with condition (with or without explicit instruction), cue-target congruency (congruent, incongruent, neutral), and SOA (100, 300, 700 ms) as the variables. There was a significant main effect of condition (slower RTs with instruction) [$F(1,17)=8.05$, $P<0.005$] and SOA (slowest at SOA 100 ms) [$F(2,17)=50.54$, $P<0.001$], but the effect of congruency was non-existent [$F(2,17)=0.86$, $P=0.421$]. None of the interactions were significant. Further analysis confirmed that there was no congruency effect even when the conditions were evaluated separately, or when evaluated separately for each SOA. Fig. 4 illustrates the mean RTs in Experiment 2, as a function of congruency and SOA.

To ensure that the confounding factor of perceptive failure had been eliminated, an ANOVA was conducted with only the 16 participants who were successful in spontaneously perceiving the rectangles as eyes. There was a significant main effect of SOA (slowest at SOA 100 ms) [$F(2,15)=45.29$, $P<0.001$]. The congruency effect was again non-existent [$F(2,15)=0.83$, $P=0.434$]. None of the interactions were significant. Further analysis confirmed that there was no congruency effect even when the conditions were evaluated separately, or when evaluated separately for each SOA.

7. Discussion for Experiment 2

Even when the schizophrenic subjects were certainly successful in organizing the intended percept from the rectangles, as evidenced by spontaneous reporting, rectangles failed to elicit a congruency benefit. Thus, the benefit decrease from congruent rectangular eyes in schizophrenia cannot be attributed to perceptive deficits. Rather, patients with schizophrenia can actually perceive gaze-like stimuli as eyes, but fail to utilize the biological information in orienting their attention. In sum, Rectangles failed to elicit a congruency benefit despite practice, explicit instructions, and even successful perception in subjects with chronic schizophrenia.

8. General discussion

In the present two experiments, we have demonstrated that congruency benefit is reduced in long-term schizophrenia in a spatial cueing paradigm using central directional cues. This reduction of congruency benefit was most prominent for the ambiguous gaze cues, tentatively present for the concrete gaze cues, but non-existent for the non-biological arrow cues. The prominent benefit reduction for the ambiguous gaze cues was not attributable to a perceptive failure, but more likely attributable to a failure in extracting the critical information from the perceived eyes. This finding, though subtle, is indicative of a gaze-specific hyposensitivity in chronic schizophrenia.

In a recent report, Langdon et al. (2006) have made similar investigations with a group of diverse schizophrenic subjects, and have shown that they might be hypersensitive to gaze cues, in terms of a very early facilitatory effect of gaze observed in their patients compared with controls. This effect was not replicated in our experiment. Two major differences between their experiments and ours are most likely to be responsible for the discordant results: 1. The nature of the stimulus used was different. Langdon et al.'s stimuli employed photographs with two directional components (head and gaze), as opposed to the stimuli used in our study which were pictorial and strictly specific to gaze. 2. The profile of the patients was different. The range of the duration

of illness in Langdon et al.'s patients was 1–26 years, relative to 13–45 years in our study. As has been mentioned, most schizophrenic symptoms, including that of gaze, are surprisingly state-dependent. In the extreme case such as the sensitivity to gaze, the symptom might completely reverse itself from the acute to the chronic state. The necessity of demarcating its state when investigating schizophrenia has been demonstrated in identical spatial cueing experiments using peripheral cues; the behavior pattern in the acutely ill stage of schizophrenia differed from all other schizophrenic states (Posner et al., 1988; Carter et al., 1992; Maruff et al., 1995; Wigal et al., 1997).With regard to the subjects who participated in Langdon et al.'s experiments, they were quite diverse as to the duration of illness. Patients both acutely sensitive to gaze, and bluntly unresponsive to gaze, might have been mingled in such a group. It is quite conceivable that Langdon et al. might have captured a more acute state of the symptoms than we have. On the other hand, we believe we have extracted a behavior pattern strictly specific to gaze, and also specific to chronic schizophrenia.

However, some non-significant but intriguing consistency with Langdon et al.'s study is also present. The contrast between the schizophrenic performance of Arrows and Ellipses might be of relevance. Our schizophrenic group demonstrated a trend for a congruency effect for the Ellipses, which appears to be equally present from SOA 100 ms throughout 700 ms (note that this is also the case for the normal controls in our study, contrary to that of Langdon et al.). On the other hand, the significant congruency effect for Arrows in schizophrenia appears to grow from SOA 100 ms to 700 ms (note, however, that this congruency × SOA interaction was not significant). Such a contrast in the time-course of the congruency effect might indicate an early orienting of attention to gaze cues relative to arrow cues in schizophrenia, and might dovetail with the results of Langdon et al.'s study.

Taken together repeated findings of smaller volume STG in schizophrenia (Rajarethinam et al., 2000, 2004; Onitsuka et al., 2004), the gaze-specific hyposensitivity that we have demonstrated in this study might be reflective of STS dysfunction in schizophrenia. Indeed, we have previously demonstrated, in a selective right STG damaged case, a deficit in gaze-triggered orienting despite a sparing of arrow-triggered orienting (Akiyama et al., 2006b), a pattern similar to that of chronic schizophrenia in the present study. The possible transition from an early hypersensitivity to a later hyposensitivity toward gaze in schizophrenia is consistent with the clinical picture of the disorder, and might be indicative of the nature and the time-course of brain dysfunction associated with it. Several studies of the brain of childhood-onset schizophrenia, a severe variant of schizophrenia, have demonstrated normal (Thompson et al., 2001) or even relatively increased STG volume (Jacobsen et al., 1996; Taylor et al., 2005) at the onset of the disease, which then progressively decreases (Jacobsen et al., 1998) to a subnormal degree within a course of 5 years (Thompson et al., 2001). Since childhood-onset schizophrenia is considered an ideal patient group in revealing the neurodevelopmental disturbance which underlies the later-onset counterpart of schizophrenia, such a finding in the time-course of the STG volume might be helpful in interpreting the hyper/hyposensitivity to gaze seen in later-onset schizophrenia. For example, in the acute phase, when there is yet no gross STG volume loss, the earliest disintegration might begin, resulting in a heightened aberrant activity in the STS, and manifesting as a hypersensitivity to gaze. STG volume might then decrease in the patient's course into chronicity, dulling STS activity and resulting in a hyposensitivity to gaze. Correlating STG volume and behavioral results such as Langdon et al.'s and our experiments in future studies might offer fruitful insight into the time-course of schizophrenia.

The group differences in the effect of SOA on performance seen in this study, such that schizophrenic performance peaks at a longer SOA than the performance of normal subjects, might be reflective of some basic compromise in schizophrenia. Slower visual processing, motor slowing, and restricted attentional resources due to psychomotor retardation inherent to the disorder, and/or as an effect of neuroleptic medication, might be some of the factors that demand longer cue-target intervals for optimal performance in schizophrenia.

The effect of stimulus ambiguity on performance, although not the main focus of this study, is nonetheless an interesting issue. The difference between Rectangles and Ellipses used in this experiment can be defined as the ambiguity of their resemblance to eyes. Both schizophrenic and normal groups demonstrated a weaker congruency effect for the more ambiguous (or less ecological) rectangular eyes, indicating some effect of stimulus ambiguity on performance. However, the congruency effect was still highly significant for both Rectangles and Ellipses in the normal group, whereas no such congruency effect was present for Rectangles in schizophrenia. Stimulus ambiguity might have a stronger impact on patients with schizophrenia, perhaps reflecting their concreteness in perception. On the other hand, the absence of a congruency effect for Rectangles in schizophrenia was replicated even when the subjects were able to spontaneously perceive them as eyes, ruling out the possibility of a