of patients was significantly lower than that of controls (37.1±20.4 and 52.2±25.3 ng/ml in patients and controls, respectively; $P=0.00003$; Fig. 1A). The mean serum EGF level was also significantly lower in patients than in controls (395.5±231.7 vs. 560.7±357.1 pg/ml; $P=0.002$; Fig. 1B).

The relation between serum NF levels and age was examined. The age of both patient and control groups ranged from 21 to 59 years. As shown in Fig. 1C (BDNF), Fig. 1D (EGF) and Table 4, there were no significant correlations between serum NF levels and age in either group.

Because both BDNF and EGF were measured simultaneously within the same individuals, the correlation between serum BDNF and EGF was examined in each group. In the controls, a negative correlation between BDNF and EGF levels was found ($r=-0.387$, $P=0.0002$; Fig. 2A). In contrast, there was no significant correlation between the serum BDNF and EGF levels in the patients ($P=0.161$, Fig. 2B).

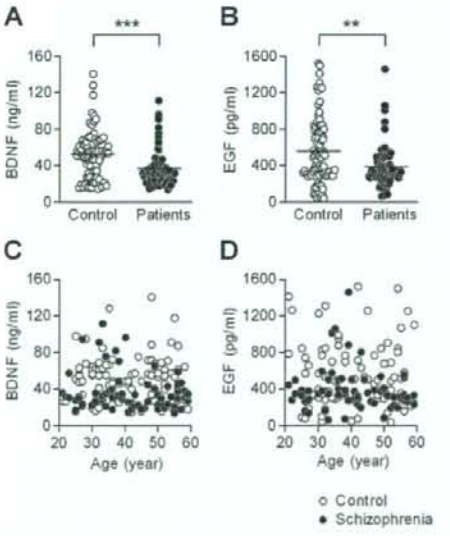


Fig. 1. Serum levels of (A) BDNF and (B) EGF measured by two-site enzyme immunoassay in normal controls ($N=87$) and patients with chronic schizophrenia ($N=74$). Compared with controls, patients exhibited lower serum levels of both neurotrophic factors (BDNF, $^{***}P<0.001$; EGF, $^{**}P<0.01$). Horizontal lines indicate the mean levels. Distributions of serum (C) BDNF and (D) EGF levels in controls (open circles) and patients (filled circles) with age. No significant correlation was observed between NF levels and age (21–59 years) in the two groups. BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor.

Table 4
Correlations between levels of neurotrophic factors and clinical parameters in patients with schizophrenia

Clinical parameters		N	BDNF		EGF	
			r	P	r	P
Age		74	−0.031	0.795	−0.227	0.053
Age at onset		74	0.303	0.009	0.052	0.644
Duration of illness		74	−0.196	0.098	−0.281	0.016
CPZ-EQ (mg/day)		74	0.051	0.520	0.079	0.327
BMI (kg/m^2)		44	0.171	0.267	−0.088	0.569
GAF		33	0.024	0.843	−0.076	0.727
BPRS	Total	33	−0.099	0.588	0.349	0.046
	Positive	33	−0.189	0.303	0.347	0.047
	Negative	33	0.102	0.558	0.127	0.468

CPZ-EQ, Chlorpromazine Equivalents; BMI, Body Mass Index; GAF, Global Assessment of Functioning; BPRS, Brief Psychiatric Rating Scale.

Since the distribution of BDNF in the control group appeared bimodal as shown in Fig. 2A, we examined whether the low-BDNF group (40 ng/ml of BDNF as a tentative threshold for the dichotomy; $N=26$) and high-BDNF group ($N=61$) differed in their biological parameters. Statistical analyses revealed that there were no significant differences in their BMI ($P=0.627$), age ($P=0.959$), sex ratio ($P=0.654$), and smoking habit ($P=0.464$).

3.2. Correlation of serum BDNF and EGF levels with clinical parameters

Overall, clinical parameters did not exhibit robust correlations with the BDNF and EGF levels ($P>0.05/10$ [$=0.005$], corrected for multiple comparisons in Table 4 and Fig. 2B), although age at onset was marginally correlated with the BDNF level ($r=0.303$, $P=0.009$). We also analyzed the effects of BMI and smoking habit on NF levels. There were no significant correlations between serum NF levels and BMI in patients ($P=0.267$ for BDNF, $P=0.569$ for EGF, $N=44$) or in controls ($P=0.687$ for BDNF, $P=0.697$ for EGF, $N=34$). In addition, NF levels were not significantly different between the presence ($N=11$ for patients, $N=16$ for controls) and absence ($N=12$ for patients, $N=18$ for controls) of smoking habit in patients ($P=0.735$ for BDNF, $P=0.132$ for EGF) and in controls ($P=0.569$ for BDNF, $P=0.593$ for EGF).

3.3. Type of antipsychotic drugs and neurotrophic factor levels

Thirteen patients had been taking one or more typical antipsychotic drugs, while thirty-one other patients had been taking only atypical antipsychotic drugs. We found

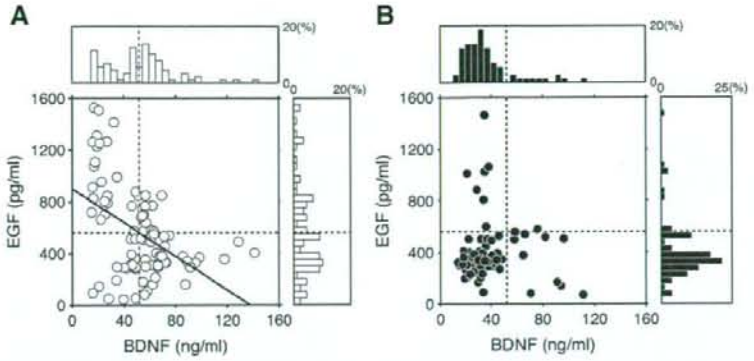


Fig. 2. Relation between the serum levels of BDNF and EGF measured simultaneously in (A) normal controls and (B) chronic schizophrenia patients. For controls, serum levels of the two neurotrophic factors were negatively correlated as shown by the line ($r=-0.387$, $P=0.0002$). The histograms above and on the right of the main plots show the fractions of subjects that fall into particular intervals of serum BDNF (in steps of 5 ng/ml) and EGF (in steps of 50 pg/ml) levels, respectively. In both histograms, dotted lines represent the mean levels of BDNF (52.2 ng/ml) and EGF (560.7 pg/ml) of normal controls, respectively. BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor.

that the levels of both BDNF and EGF did not differ between the patients taking typical and atypical antipsychotic drugs ($P>0.05$, Fig. 3A and B). In addition, there was no significant correlation between the chlorpromazine equivalents of medication and serum NF levels (Fig. 3C and D; Table 4).

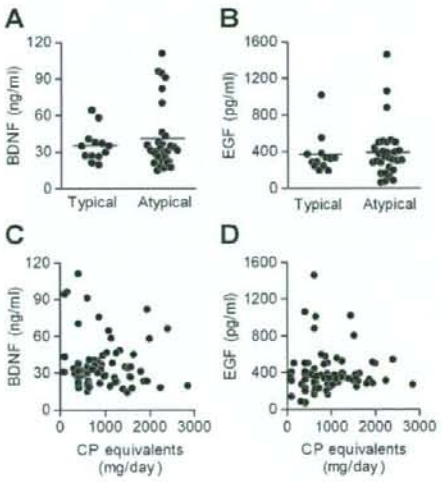


Fig. 3. Effects of antipsychotic drugs on serum (A) BDNF and (B) EGF levels. For both neurotrophic factors, no significant differences were seen between patients taking typical ($N=13$) and atypical ($N=31$) antipsychotic drugs. Horizontal lines indicate the mean levels. Antipsychotic dosages in chlorpromazine equivalents were correlated neither (C) with serum BDNF nor (D) with EGF levels ($N=74$). BDNF, brain-derived neurotrophic factor; EGF, epidermal growth factor; CP, chlorpromazine.

We also analyzed the effects of anticholinergic drugs on the NF levels. Thirty-five patients had been taking anticholinergic drugs including biperiden and trihexyphenidyl in combination with antipsychotic drugs. NF levels were not significantly different between the patients with (BDNF, 37.9±20.1 ng/ml; EGF, 395.8±225.0 pg/ml; $N=35$) and without (BDNF, 36.3±20.9 ng/ml; EGF, 395.3±240.5 pg/ml; $N=39$) anticholinergic drugs ($P=0.626$ for BDNF, $P=0.475$ for EGF).

4. Discussion

4.1. Lower serum BDNF and EGF levels in schizophrenia

As summarized in Tables 1 and 2, previous studies have mostly reported low serum BDNF levels (Grillo et al., 2007; Pirildar et al., 2004; Tan et al., 2005; Toyooka et al., 2002; Zhang et al., 2007), while changes in the serum EGF level have remained a matter of controversy (Futamura et al., 2002; Hashimoto et al., 2005). In the present study, at least, it was clearly shown that most of the chronic schizophrenia patients had lower serum levels of EGF as well as BDNF. Mean serum BDNF values were 37.1 and 52.2 ng/ml in patients and controls, respectively, in the present study. These values were higher than those in several other reports, but, as can be seen in Table 1, BDNF levels varied considerably among the studies reported. Such differences may be due to the antibodies used against neurotrophic factors, the methods of measurement, and the sampling conditions. Actually, the

values in the present study fell into a range similar of values to those in the reports adopting similar methods (Toyooka et al., 2002). In addition, this decrease in NFs was observed in patients regardless of age, ranging from the early 20s to the late 50s. This observation was consistent with previous reports showing no correlation between age and serum BDNF levels (Grillo et al., 2007; Huang and Lee, 2006; Toyooka et al., 2002), lending credence to the hypothesis that schizophrenia is the behavioral outcome of aberration in the neurodevelopmental processes.

In the present work, the simultaneous measurement of NFs revealed a significant negative correlation between serum BDNF and EGF levels in controls (Fig. 2A), whereas there was no correlation between the two NF levels in patients (Fig. 2B), possibly reflecting their low levels of both BDNF and EGF. The fact that no control subjects showed high serum levels of both BDNF and EGF is of particular interest. Neurite outgrowth from EGF-responsive stem cell-derived neurons can be enhanced by treatment with BDNF (Shetty and Turner, 1999), while BDNF reportedly induced the down-regulation of EGF receptors (Huang et al., 1988). In addition, the co-application of transforming growth factor-alpha, a member of the EGF family, with BDNF blocked the BDNF-triggered up-regulation of AMPA receptor expression and currents (Namba et al., 2006). Thus, complementary roles of both factors may underlie the normal development of the nervous system. In other words, chronic schizophrenia may represent a state deficient in NF-regulated neural functions, leading eventually to various mental malfunctions.

The origins of serum BDNF and EGF are not yet completely understood. EGF reportedly enters the brain through the blood-brain barrier (BBB) in mouse (Pan and Kastin, 1999). BDNF is reported to be transported across the BBB in normal mouse (Pan et al., 1998) and rats with cerebral ischemia (Schäbitz et al., 2000), while another report has argued that the transport of BDNF is negligible (Sakane and Pardridge, 1997). EGF and BDNF are produced in various peripheral tissues (Plata-Salamán, 1991; Radka et al., 1996), in addition to the central nervous system as described above. Nevertheless, the serum levels of NFs can be used as clinical markers, since they show different distributions between patients and controls, as shown in previous studies as well as in the present study.

4.2. Clinical parameters and neurotrophic factors

We failed to find any clinical parameters that demonstrated robust correlation with the two NF levels. As shown in Tables 1 and 2, previous reports also examined the correlation between clinical parameters and NF levels: the BDNF level was correlated with the negative symptom subscore of the Positive and Negative Syndrome Scale (Tan et al., 2005); the serum EGF level was significantly correlated with the BPRS score (Hashimoto et al., 2005). Although the reasons for the discrepancy between the previous and present results are unclear, differences in demographic characteristics of the patients (such as age at onset, illness duration, sample size, distribution of BPRS score, and dosage of antipsychotic drugs) might provide at least a partial explanation.

Other factors than psychiatric parameters have been reported to affect serum BDNF levels. BMI (Suwa et al., 2006) and age (Ziegenhorn et al., 2007) showed positive and negative correlation with BDNF levels, respectively. Patients with atopic dermatitis have higher levels of serum BDNF in association with the severity of symptoms (Raap et al., 2005; Namura et al., 2007), while smokers have lower values as compared with non-smokers (Kim et al., 2007). We could not completely rule out the possibility that these factors affected the values in the present study, since data could not be obtained from all participants. However, the limited data suggested that neither BMI nor smoking habit affected neurotrophic levels in patients or controls.

4.3. Types of antipsychotic drugs and serum neurotrophic factor levels

In the present study, the NF levels were not correlated with any types or dosages of medications. Although Grillo et al. (2007) found a significant correlation between the BDNF level and clozapine dosage, other investigators found no significant correlation between BDNF (Hori et al., 2007; Shimizu et al., 2003; Tan et al., 2005; Toyooka et al., 2002; Zhang et al., 2007) or EGF level (Futamura et al., 2002) and antipsychotic dosages. In addition, treatment with olanzapine for 8 weeks (Hori et al., 2007) or antipsychotic drugs (risperidone for most patients) for 6 weeks (Pirildar et al., 2004) did not alter BDNF levels in blood. It was recently suggested that the effects of atypical and typical antipsychotic drugs on the BDNF level were different. In animal experiments, haloperidol, a typical antipsychotic drug, decreased the BDNF expression in the hippocampus, whereas atypical antipsychotics did not affect or even up-regulated this expression (Bai et al., 2003; Chlan-Fourney et al., 2002; Parikh et al., 2004). In addition, atypical antipsychotics, but not haloperidol, stimulated neurogenesis in the subventricular zone of the rat brain (Wakade et al., 2002). Clinically, chronic treatment with haloperidol, but not olanzapine, was associated with a significant reduction in gray matter volume in schizophrenia patients with first-

episode psychosis (Lieberman et al., 2005). However, the present study failed to show that the type of drug affects either the BDNF or the EGF serum level. This observation might indicate a limitation concerning the measurement of serum NFs for predicting their function in the brain. Nevertheless, the serum levels of NFs could be used as clinical markers from the viewpoint that they are independent of the type of medication used.

In conclusion, we showed herein that patients with chronic schizophrenia have lower serum levels of both BDNF and EGF across all ages, possibly reflecting pervasive abnormal signaling of NFs underlying the pathophysiology of schizophrenia. A future study should investigate NFs of patients with schizophrenia before pharmacological intervention or those undergoing the first-episode of the disease, thereby addressing whether this overall reduction in NFs is a common characteristic in the symptomatology of schizophrenia.

Role of funding source

Funding for this study was provided by a Grant-in-Aid for Science Research (C) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan, to H. S. (No. 1659028), a Grant-in-Aid for Encouragement of Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS) to N. Y. (No. 18790852) and to Y. I. (No. 17790821). MEXT and JSPS had no further role in the study design, collection, analysis and interpretation of data, writing of the report, and the decision to submit the paper for publication.

Contributors

Y.I. measured the concentrations of BDNF and EGF proteins, analyzed the data and wrote the manuscript. N.Y. undertook the statistical analyses of whole data including neurotrophic factor levels and demographical data, and wrote the manuscript. M.N. developed the two-site enzyme immunoassay for BDNF and EGF and measured the concentrations of BDNF and EGF proteins. I.I, T.T and T.Y recruited the subjects for this project and collected blood samples. Y.O and H.S designed and supervised the whole study and wrote the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgments

We are grateful to all the subjects who participated in the study. We also thank the staff of Asai hospital for their assistance in collecting the demographic data.

References

Alexi, T., Hefti, F., 1993. Trophic actions of transforming growth factor alpha on mesencephalic dopaminergic neurons developing in culture. Neuroscience 55 (4), 903–918.

Bai, O., Chlan-Fourney, J., Bowen, R., Keegan, D., Li, X.M., 2003. Expression of brain-derived neurotrophic factor mRNA in rat hippocampus after treatment with antipsychotic drugs. J. Neurosci. Res. 71 (1), 127–131.

Casper, D., Blum, M., 1995. Epidermal growth factor and basic fibroblast growth factor protect dopaminergic neurons from glutamate toxicity in culture. J. Neurochem. 65 (3), 1016–1026.

Casper, D., Mytilineou, C., Blum, M., 1991. EGF enhances the survival of dopamine neurons in rat embryonic mesencephalon primary cell culture. J. Neurosci. Res. 30 (2), 372–381.

Chen, Z.Y., Jing, D., Bath, K.G., Ieraci, A., Khan, T., Siao, C.J., Herrera, D.G., Toth, M., Yang, C., McEwen, B.S., Hempstead, B.L., Lee, F.S., 2006. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 314 (5796), 140–143.

Chlan-Fourney, J., Ashe, P., Nylen, K., Juorio, A.V., Li, X.M., 2002. Differential regulation of hippocampal BDNF mRNA by typical and atypical antipsychotic administration. Brain Res. 954 (1), 11–20.

Connor, B., Dragunow, M., 1998. The role of neuronal growth factors in neurodegenerative disorders of the human brain. Brain Res. Rev. 27 (1), 1–39.

Durany, N., Michel, T., Zöchling, R., Boissl, K.W., Cruz-Sánchez, F.F., Riederer, P., Thome, J., 2001. Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses. Schizophr. Res. 52 (1–2), 79–86.

Ernfors, P., Ibáñez, C.F., Ebendal, T., Olson, L., Persson, H., 1990. Molecular cloning and neurotrophic activities of a protein with structural similarities to nerve growth factor: developmental and topographical expression in the brain. Proc. Natl. Acad. Sci. U. S. A. 87 (14), 5454–5458.

Futamura, T., Toyooka, K., Iritani, S., Niizato, K., Nakamura, R., Tsuchiya, K., Someya, T., Kakita, A., Takahashi, H., Nawa, H., 2002. Abnormal expression of epidermal growth factor and its receptor in the forebrain and serum of schizophrenic patients. Mol. Psychiatry 7 (7), 673–682.

Futamura, T., Kakita, A., Tohmi, M., Sotoyama, H., Takahashi, H., Nawa, H., 2003. Neonatal perturbation of neurotrophic signaling results in abnormal sensorimotor gating and social interaction in adults: implication for epidermal growth factor in cognitive development. Mol. Psychiatry 8 (1), 19–29.

Grillo, R.W., Ottoni, G.L., Leke, R., Souza, D.O., Portela, L.V., Lara, D.R., 2007. Reduced serum BDNF levels in schizophrenic patients on clozapine or typical antipsychotics. J. Psychiatr. Res. 41 (1–2), 31–35.

Hashimoto, K., Shimizu, E., Komatsu, N., Watanabe, H., Shinoda, N., Nakazato, M., Kumakiri, C., Okada, S., Takei, N., Iyo, M., 2005. No changes in serum epidermal growth factor levels in patients with schizophrenia. Psychiatry Res. 135 (3), 257–260.

Hofer, M., Pagliusi, S.R., Hohn, A., Leibrock, J., Barde, Y.A., 1990. Regional distribution of brain-derived neurotrophic factor mRNA in the adult mouse brain. EMBO J. 9 (8), 2459–2464.

Hori, H., Yoshimura, R., Yamada, Y., Ikenouchi, A., Mitoma, M., Ida, Y., Nakamura, J., 2007. Effects of olanzapine on plasma levels of catecholamine metabolites, cytokines, and brain-derived neurotrophic factor in schizophrenic patients. Int. Clin. Psychopharmacol. 22 (1), 21–27.

Huang, T.L., Lee, C.T., 2006. Associations between serum brain-derived neurotrophic factor levels and clinical phenotypes in schizophrenia patients. J. Psychiatr. Res. 40 (7), 664–668.

Huang, S.S., Lokeshwar, V.B., Huang, J.S., 1988. Modulation of the epidermal growth factor receptor by brain-derived growth factor in Swiss mouse 3T3 cells. J. Cell. Biochem. 36 (3), 209–221.

Ishiyama, J., Saito, H., Abe, K., 1991. Epidermal growth factor and basic fibroblast growth factor promote the generation of long-term potentiation in the dentate gyrus of anaesthetized rats. Neurosci. Res. 12 (3), 403–411.

Karege, F., Schwald, M., Cisse, M., 2002. Postnatal developmental profile of brain-derived neurotrophic factor in rat brain and platelets. Neurosci. Lett. 328 (3), 261–264.

Kim, T.S., Kim, D.J., Lee, H., Kim, Y.K., 2007. Increased plasma brain-derived neurotrophic factor levels in chronic smokers following unaided smoking cessation. Neurosci. Lett. 423 (1), 53–57.

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

Lieberman, J.A., et al., for the HGDH Study Group, 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch. Gen. Psychiatry 62 (4), 361–370.

Mizuno, M., Malta Jr., R.S., Nagano, T., Nawa, H., 2004. Conditioned place preference and locomotor sensitization after repeated administration of cocaine or methamphetamine in rats treated with epidermal growth factor during the neonatal period. Ann. N.Y. Acad. Sci. 1025, 612–618.

Nagano, M., Suzuki, H., 2003. Quantitative analyses of expression of GDNF and neurotrophins during postnatal development in rat skeletal muscles. Neurosci. Res. 45 (4), 391–399.

Namba, H., Nagano, T., Iwakura, Y., Xiong, H., Jourdi, H., Takei, N., Nawa, H., 2006. Transforming growth factor alpha attenuates the functional expression of AMPA receptors in cortical GABAergic neurons. Mol. Cell. Neurosci. 31 (4), 628–641.

Numura, K., Hasegawa, G., Egawa, M., Matsumoto, T., Kobayashi, R., Yano, T., Katoh, N., Kishimoto, S., Ohta, M., Obayashi, H., Ose, H., Fukui, M., Nakamura, N., Yoshikawa, T., 2007. Relationship of serum brain-derived neurotrophic factor level with other markers of disease severity in patients with atopic dermatitis. Clin. Immunol. 122 (2), 181–186.

Nawa, H., Takei, N., 2006. Recent progress in animal modeling of immune inflammatory processes in schizophrenia: implication of specific cytokines. Neurosci. Res. 56 (1), 2–13.

Nawa, H., Takahashi, M., Patterson, P.H., 2000. Cytokine and growth factor involvement in schizophrenia—support for the developmental model. Mol. Psychiatry 5 (6), 594–603.

Pan, W., Kastin, A.J., 1999. Entry of EGF into brain is rapid and saturable. Peptides 20 (9), 1091–1098.

Pan, W., Banks, W.A., Fasold, M.B., Bluth, J., Kastin, A.J., 1998. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37 (12), 1553–1561.

Parikh, V., Khan, M.M., Mahadik, S.P., 2004. Olanzapine counteracts reduction of brain-derived neurotrophic factor and TrkB receptors in rat hippocampus produced by haloperidol. Neurosci. Lett. 356 (2), 135–139.

Pirildar, S., Gönül, A.S., Taneli, F., Akdeniz, F., 2004. Low serum levels of brain-derived neurotrophic factor in patients with schizophrenia do not elevate after antipsychotic treatment. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 28 (4), 709–713.

Plata-Salamán, C.R., 1991. Epidermal growth factor and the nervous system. Peptides 12 (3), 653–663.

Raap, U., Goltz, C., Deneka, N., Bruder, M., Renz, H., Kapp, A., Wedi, B., 2005. Brain-derived neurotrophic factor is increased in atopic dermatitis and modulates eosinophil functions compared with that seen in nonatopic subjects. J. Allergy Clin. Immunol. 115 (6), 1268–1275.

Radka, S.F., Holst, P.A., Fritsche, M., Altar, C.A., 1996. Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. Brain Res. 709 (1), 122–130.

Rapoport, J.L., Addington, A.M., Frangou, S., Psych, M.R.C., 2005. The neurodevelopmental model of schizophrenia: update 2005. Mol. Psychiatry 10 (5), 434–449.

Ross, C.A., Margolis, R.L., Reading, S.A., Pletnikov, M., Coyle, J.T., 2006. Neurobiology of schizophrenia. Neuron 52 (1), 139–153.

Sakane, T., Pardridge, W.M., 1997. Carboxyl-directed pegylation of brain-derived neurotrophic factor markedly reduces systemic clearance with minimal loss of biologic activity. Pharm. Res. 14 (8), 1085–1091.

Schäbitz, W.R., Sommer, C., Zoder, W., Kiessling, M., Schwaninger, M., Schwab, S., 2000. Intravenous brain-derived neurotrophic factor reduces infarct size and counterregulates Bax and Bcl-2 expression after temporary focal cerebral ischemia. Stroke 31 (9), 2212–2217.

Shetty, A.K., Turner, D.A., 1999. Neurite outgrowth from progeny of epidermal growth factor-responsive hippocampal stem cells is significantly less robust than from fetal hippocampal cells following grafting onto organotypic hippocampal slice cultures: effect of brain-derived neurotrophic factor. J. Neurobiol. 38 (3), 391–413.

Shimizu, E., Hashimoto, K., Watanabe, H., Komatsu, N., Okamura, N., Koike, K., Shinoda, N., Nakazato, M., Kumakiri, C., Okada, S., Iyo, M., 2003. Serum brain-derived neurotrophic factor (BDNF) levels in schizophrenia are indistinguishable from controls. Neurosci. Lett. 351 (2), 111–114.

Stephan, K.E., Baldeweg, T., Friston, K.J., 2006. Synaptic plasticity and dysconnection in schizophrenia. Biol. Psychiatry 59 (10), 929–939.

Suwa, M., Kishimoto, H., Nofuji, Y., Nakano, H., Sasaki, H., Radak, Z., Kumagai, S., 2006. Serum brain-derived neurotrophic factor level is increased and associated with obesity in newly diagnosed female patients with type 2 diabetes mellitus. Metabolism 55 (7), 852–857.

Takahashi, M., Shirakawa, O., Toyooka, K., Kitamura, N., Hashimoto, T., Maeda, K., Koizumi, S., Wakabayashi, K., Takahashi, H., Someya, T., Nawa, H., 2000. Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. Mol. Psychiatry 5 (3), 293–300.

Tan, Y.L., Zhou, D.F., Cao, L.Y., Zou, Y.Z., Zhang, X.Y., 2005. Decreased BDNF in serum of patients with chronic schizophrenia on long-term treatment with antipsychotics. Neurosci. Lett. 382 (1–2), 27–32.

Toyooka, K., Asama, K., Watanabe, Y., Muratake, T., Takahashi, M., Someya, T., Nawa, H., 2002. Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. Psychiatry Res. 110 (3), 249–257.

Ventrella, L.L., 1993. Effect of intracerebroventricular infusion of epidermal growth factor in rats hemitransected in the nigro-striatal pathway. J. Neurosurg. Sci. 37 (1), 1–8.

Wakade, C.G., Mahadik, S.P., Waller, J.L., Chiu, F.C., 2002. Atypical neuroleptics stimulate neurogenesis in adult rat brain. J. Neurosci. Res. 69 (1), 72–79.

Weickert, C.S., Hyde, T.M., Lipska, B.K., Herman, M.M., Weinberger, D.R., Kleinman, J.E., 2003. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. Mol. Psychiatry 8 (6), 592–610.

Wetmore, C., Ernfors, P., Persson, H., Olson, L., 1990. Localization of brain-derived neurotrophic factor mRNA to neurons in the brain by in situ hybridization. Exp. Neurol. 109 (2), 141–152.

Xian, C.J., Zhou, X.F., 1999. Roles of transforming growth factor-alpha and related molecules in the nervous system. Mol. Neurobiol. 20 (2–3), 157–183.

Zhang, X.Y., Tan, Y.L., Zhou, D.F., Cao, L.Y., Wu, G.Y., Xu, Q., Shen, Y., Haile, C.N., Kosten, T.A., Kosten, T.R., 2007. Serum BDNF levels and weight gain in schizophrenic patients on long-term treatment with antipsychotics. J. Psychiatr. Res. 41 (12), 997–1004.

Ziegenhorn, A.A., Schulte-Herbrüggen, O., Danker-Hopfe, H., Malbranc, M., Hartung, H.D., Anders, D., Lang, U.E., Steinhagen-Thiessen, E., Schaub, R.T., Hellweg, R., 2007. Serum neurotrophins—a study on the time course and influencing factors in a large old age sample. Neurobiol. Aging 28 (9), 1436–1445.

Eur Arch Psychiatry Clin Neurosci (2009)

DOI 10.1007/s00406-008-0850-7

ORIGINAL PAPER

Masahiro Suzuki · Sakae Takahashi · Eisuke Matsushima · Masahiko Tsunoda · Masayoshi Kurachi · Takashi Okada · Takuji Hayashi · Yohei Ishii · Kiichiro Morita · Hisao Maeda · Seiji Katayama · Ryuzou Kawahara · Tatsui Otsuka · Yoshio Hirayasu · Mizuho Sekine · Yoshiro Okubo · Mai Motoshita · Katsuya Ohta · Makoto Uchiyama · Takuya Kojima

Exploratory eye movement dysfunction as a discriminator for schizophrenia

A large sample study using a newly developed digital computerized system

Received: 8 November 2007 / Accepted: 28 August 2008 / Published online: 22 January 2009

Abstract In our previous studies, we identified that exploratory eye movement (EEM) dysfunction appears to be specific to schizophrenia. The availability of a biological marker specific to schizophrenia would be useful for clinical diagnosis of schizophrenia. Consequently, we performed the discriminant analysis between schizophrenics and non-schizophrenics on a large sample using the EEM test data and examined an application of the EEM for clinical diagnosis of schizophrenia. EEM performances were recorded in 251 schizophrenics and 389 non-schizophrenics (111 patients with mood disorders, 28 patients with neurotic disorders and 250 normal controls). The patients were recruited from eight university hospitals and three affiliated hospitals. For this study with a large sample, we developed a new digital computerized version of the EEM test, which automatically handled large amounts of data. We measured four parameters: number of eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL) and responsive search score (RSS). These parameters of schizophrenics differed significantly from those of the other three groups.

M. Suzuki · S. Takahashi (✉) · M. Uchiyama · T. Kojima
Dept. of Neuropsychiatry
Nihon University School of Medicine
30-1 Oyaguchi-Kamicho
Itabashi-ku, Tokyo 173-8610, Japan
Tel.: +81-3/3972-8111
Fax: +81-3/3974-2920
E-Mail: sakae@med.nihon-u.ac.jp

E. Matsushima · M. Motoshita · K. Ohta
Section of Liaison Psychiatry and Palliative Medicine
Graduate School of Tokyo Medical and Dental University
1-5-45 Yushima
Bunkyo-ku, Tokyo 113-8519, Japan

M. Tsunoda · M. Kurachi
Dept. of Neuropsychiatry
Graduate School of Medicine and Pharmaceutical Sciences
University of Toyama
2630 Sugitani
Toyama 930-0194, Japan

T. Okada · T. Hayashi
Dept. of Neuropsychiatry
Graduate School of Medicine, Kyoto University
54 Kawahara-cho, Shogoin, Sakyo-ku
Kyoto 606-8507, Japan

Y. Ishii · K. Morita
Cognitive and Molecular Research Institute of Brain Diseases
Kurume University
67 Asahi-machi
Kurume 830-0011, Japan

H. Maeda
Wakahisa Hospital
Wakahisa 5-3-1
Minami-ku, Fukuoka 815-0042, Japan

S. Katayama
Faculty of Medicine, Dept. of Neuropsychiatry
Tottori University
36-1 Nishi-machi
Yonago, Tottori 683-8504, Japan

R. Kawahara
Midorigaoka Mental Clinic
2793-1 Okazaki, Kushira-cho
Kanoya, Kagoshima 893-1603, Japan

T. Otsuka · Y. Hirayasu
Dept. of Psychiatry
Yokohama City University School of Medicine
3-9 Fukuura, Kanazawa-ku
Yokohama 236-0004, Japan

M. Sekine · Y. Okubo
Dept. of Neuropsychiatry
Nippon Medical School
1-1-5 Sendagi
Bunkyo-ku, Tokyo 113-8603, Japan

T. Kojima
Ohmiya-Kosei Hospital
1 Katayanagi, Minuma-ku
Saitama, Saitama 337-0024, Japan

The stepwise regression analysis selected the TESL and the RSS as the valid parameters for discriminating between schizophrenics and non-schizophrenics. In the discriminant analysis using the RSS and TESL as prediction parameters, 184 of the 251 clinically diagnosed schizophrenics were discriminated as having schizophrenia (sensitivity 73.3%); and 308 of the 389 clinically diagnosed non-schizophrenic subjects were discriminated as non-schizophrenics (specificity 79.2%). Based on our findings we believe that the EEM measures may be useful for the clinical diagnosis of schizophrenia.

Key words schizophrenia · exploratory eye movement (EEM) · biological marker · digital computerized system of the EEM test · discriminant analysis

Introduction

Clinical diagnosis of schizophrenia is based on patient interviews and observation of the patient's behavioral patterns. According to the interview and observation, schizophrenia is symptomatically characterized by hallucinations, delusions, disorganized thinking or negative symptoms, etc. These symptoms may be based on a neurobiological brain dysfunction associated specifically with schizophrenia. Therefore, in addition to the interview and observation of the patient, a biological marker related to the brain dysfunction of schizophrenia may also be useful in determining the clinical diagnosis of schizophrenia.

In order to find a biological marker of schizophrenia, many researchers have performed psychophysiological or cognitive neuroscience tests related to the potential brain dysfunction of schizophrenia [5, 40]. Disturbances of event related potentials (ERPs), P300 [4], P50 [35] and mismatch negativity (MMN) [6, 27], prepulse inhibition (PPI) [33, 44], saccadic and smooth pursuit eye movements [8, 11, 21, 37], and working memory [3] have been reported in schizophrenia. Moreover, abnormalities of P50, saccadic and pursuit eye movements, and working memory were utilized for endophenotypes of schizophrenia in genetic studies [1, 2, 7, 28]. Therefore, the above physiological or neuroscience defects may show promise as biological markers of schizophrenia.

We have studied eye movements while subjects freely viewed horizontal S-shaped figures. This method is called the exploratory eye movement (EEM) test. In most previous studies, only schizophrenics have revealed consistent disturbances of the EEM [16–20, 24, 25, 30, 43]. In addition, the parents of schizophrenics showed EEM dysfunctions [41]. Moreover, the EEM showed a significant linkage to chromosome 22q11 [42]. The chromosome 22q11 is one of the most interesting regions in the genetic etiology of schizophrenia [15]. Thus, in addition to the above physiological or neuroscience defects, EEM disturbance may also be a biological marker of schizophrenia.

Based on these findings, we have proposed that the EEM test may be useful as a biological marker for the clinical diagnosis of schizophrenia [19, 26]. Matsushima et al. [26] performed discriminant analysis between 30 schizophrenics and 70 non-schizophrenics using EEM data. They discriminated schizophrenics from non-schizophrenics with a sensitivity of approximately 75% and a specificity of approximately 80%. Kojima et al. [19] also tried to discriminate 145 schizophrenics from 116 depressed patients and 124 healthy controls using EEM data, and obtained a high rate of discrimination with both the sensitivity and specificity being over 80%. These results suggest that EEM may be useful for clinical diagnosis of schizophrenia; however, the sample size of these studies was not very large. Thus, replicated studies with larger samples were needed to confirm these findings. Nevertheless, since our prior method employed an offline analog system, we were not able to handle a large amount of data in our previous studies. For the present study, we developed a new digital computerized version of the EEM test. Using this system, we were able to automatically handle a large amount of data. Consequently, to confirm our previous findings [19, 26], we used a larger sample in the discriminant analysis between schizophrenics and non-schizophrenics using the EEM test data. According to results of the discriminant analysis, we examined an application of the EEM for the clinical diagnosis of schizophrenia in this study.

Methods

Subjects

We studied 251 schizophrenic patients, 111 patients with mood disorders, 28 patients with neurotic and stress related disorders and 250 normal controls. The patients were in/outpatients recruited from eight university hospitals and three affiliated hospitals. Diagnoses were made by experienced psychiatrists according to the ICD-10 criteria for research [45]. The control subjects were also recruited from the eight university hospitals and three affiliated hospitals. Most controls were employees of these hospitals. Table 1 shows the demographic characteristics of the subjects. There were significant differences between the groups in age, gender and duration of illness. Psychiatric patients who had a history of alcohol abuse or illicit substance abuse, or head injury were excluded from the study; also excluded were those with convulsive, neurologic or ophthalmologic disorders. Detailed subtypes of the patients are described in Table 2.

The clinical symptoms of the schizophrenic patients were assessed by the brief psychiatric rating scale (BPRS) [32], which yielded an average score of 41.5 ± 13.3. The clinical symptoms of the patients with mood disorders were assessed using the Hamilton depression rating scale (HAM-D) [10], for an average score of 12.1 ± 8.59. Of the 251 patients with schizophrenia, 249 received neuroleptic medication. The average daily dosage was expressed as a haloperidol equivalent [13] of 13.9 ± 10.7 mg. Of the 111 patients with mood disorders, 100 were taking antidepressant medication and an average daily dosage was expressed as an imipramine equivalent [13] of 107.7 ± 81.3 mg.

Table 1 Clinical and demographic characteristics of the subjects

Diagnosis	Schizophrenia	Mood disorder	Neurotic disorder	Controls
Subjects (*n*)	251	111	28	250
Age (years, mean ± SD)[a]	37.9 ± 11.3	44.3 ± 12.8	32.7 ± 10.3	37.1 ± 11.3
Gender (M/F)[b]	157/94	49/62	9/19	112/138
Duration of illness (years, mean ± SD)[c]	14.5 ± 13.1	5.9 ± 6.78	6.1 ± 6.6	

[a]ANOVA; F (3, 636) = 12.0, $P < 0.01$
[b]Chi-square test; Chi-square = 23.3, $df = 3$, $P < 0.01$
[c]ANOVA; F(2, 387) = 25.6, $P < 0.01$

Table 2 Subtypes of each patient group

ICD-10 diagnosis	*n* (%)
Schizophrenia	
Paranoid type	164 (65.3)
Hebephrenic type	40 (15.9)
Catatonic type	3 (1.2)
Undifferentiated types	13 (5.2)
Residual type	24 (9.6)
Simple type	4 (1.6)
Unspecified type	3 (1.2)
Mood disorder	
Bipolar disorder	13 (11.7)
Depressive disorder	97 (87.4)
Dysthymia	1 (0.9)
Neurotic and stress related disorder	
Panic disorder	13 (46.4)
Adjustment disorder	8 (28.6)
Others	7 (25.0)

The normal controls were healthy volunteers without physical, ophthalmologic, neurological or psychiatric disorders, and there was no family history of psychiatric disorders as distant as third degree relatives. This study was approved by the Ethics Committees of the eight universities. Written informed consent was obtained from all participants, after the procedures and possible risks of the study were fully explained.

Procedure

For this study, we developed a new digital eye-mark recording system (nac Image Technology, EMR-NS, Tokyo, Japan) (Fig. 1). In the white box, there was an eye camera that detected corneal reflection of infrared light to identify eye movements, and a 15-in. LCD monitor (1,024 × 768 pixels) to display target figures for the EEM tasks. This system automatically recorded the subjects' eye movements while he/she was viewing the figures on the LCD monitor.

The subject sat on a chair and a pair of goggles with a flexible band was fixed on his/her face. The face was positioned 425 mm from the LCD panel on which the target figures appeared. Three horizontal S-shaped figures (an original target figure and two figures slightly different from the original target figure) were individually displayed on the LCD monitor (Fig. 2). The figures were 845 pixels wide and 724 pixels high at a sight angle of 33°.

A standard test of EEM was performed. The method is briefly shown as follows:

1. Retention task

The subject was instructed to carefully view the figure for the purpose of drawing it later. The subject was then shown the original target figure (Fig. 2a) for 15 s. (the subject drew the original figure from memory at the end of the test).

Fig. 1 Digital eye-mark recording system (nac Image Technology, EMR-NS)

2. Comparison task

(a) The subject was instructed to compare a new figure with the original figure (Fig. 2a) and was then shown a figure slightly different from the original one, which had one bump in a different position (Fig. 2b), for 15 s.
(b) After 15 s had elapsed and with the figure still in view, the subject was asked whether it differed from the original figure and, if it did, how it differed.
(c) After the subject had replied and while the figure was still displayed, he/she was asked "Are there any other differences?".

#. The above 2a–2c were repeated with a figure without bumps (Fig. 2c).

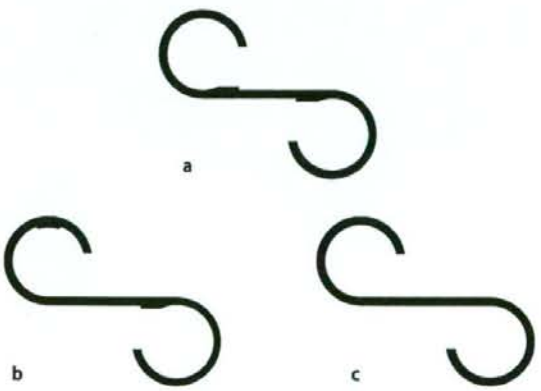


Fig. 2 The original target figure (**a**) and two figures slightly different from the target (**b**, **c**)

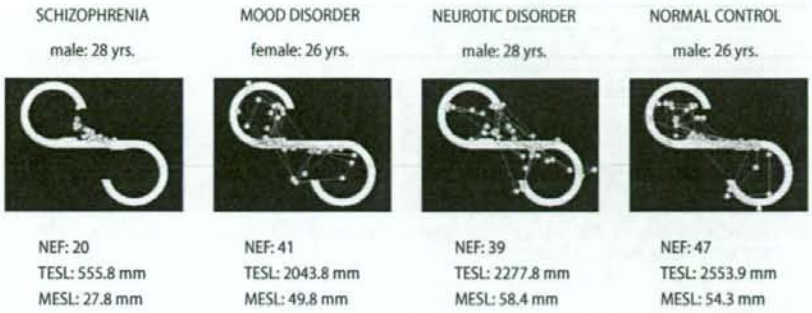


Fig. 3 The retention task, NEF, TESL and MESL in a schizophrenic patient, a mood disorder patient, a neurotic patient and a normal control

Table 3 Results of the ANCOVA [*F* (*df*) and *P*]

	Diagnosis	Gender	Diagnosis × gender	Age
Parameters of retention task				
NEF	34.61 (3, 631), $P < 0.0001$	1.56 (1, 631), $P = 0.21$	0.25 (3, 631), $P = 0.85$	0.45 (1, 631), $P = 0.49$
TESL	42.27 (3, 631), $P < 0.0001$	0.44 (1, 631), $P = 0.50$	0.19 (3, 631), $P = 0.89$	0.00 (1, 631), $P = 0.97$
MESL	22.64 (3, 631), $P < 0.0001$	0.19 (1, 631), $P = 0.65$	0.35 (3, 631), $P = 0.78$	1.52 (1, 631), $P = 0.21$
Parameter of comparison task				
RSS	60.77 (3, 631), $P < 0.0001$	0.33 (1, 631), $P = 0.56$	1.33 (3, 631), $P = 0.26$	0.30 (1, 631), $P = 0.58$

NEF number of eye fixations, *TESL* total eye scanning length, *MESL* mean scanning length, *RSS* responsive search scores

In the digital eye-mark recording system, the detected eye movements were automatically analyzed by a digital computerized EEM analyzer. As a result, four parameters emerged: number of eye fixations (NEF), total eye scanning length (TESL), mean eye scanning length (MESL) and responsive search score (RSS). The NEF, TESL and MESL were based on data of eye movements that occurred during 15 s of the retention task. In the comparison task, the RSS was based on data of eye movements that occurred for 5 s immediately after the question: "Are there any other differences?". More detailed descriptions of the EEM test methods have been presented in our previous studies [16, 19].

Statistical analysis

As mentioned above, there were significant differences between the groups in the demographic data (age, gender and duration of illness; see Table 1). Thus, differences for each parameter (NEF, TESL, MESL or RSS) were tested by a two-way (diagnosis × gender) analysis covariance (ANCOVA) with age as a covariate. The duration of illness was not adopted as a covariate; this was based on the hypothesis that the duration of illness for different diseases was not essential for the group comparisons. For pairwise multiple comparisons, Bonferroni adjustment was used (SPSS manual). In order to discriminate between schizophrenics and non-schizophrenics, we performed the discriminant analysis between schizophrenics and non-schizophrenics with stepwise variable selection method using the above four parameters. Statistical significance was set at $P < 0.01$. All statistical analyses were performed using SPSS for Windows version 14.0.

Results

Group comparisons of the EEM test parameters

Parameters in the retention task

Figure 3 shows the representative examples of the eye scanning tracks of a schizophrenic patient, a mood disorder patient, a neurotic disorder patient and a healthy control for the retention task. The eye fixation points were less frequent, and the length of eye scanning was shorter in the schizophrenic patients than in other groups.

Table 3 shows the results of the ANCOVA. There was a significant main effect for diagnosis but not for gender or the interaction between diagnosis and gender (diagnosis × gender) on each retention task parameter (NEF, TESL or MESL). Age as the covariate was also not significant for any parameter. In the multiple comparisons, the NEF, TESL and MESL were significantly lower in the schizophrenic patients than in the other three groups. None of the parameters in the retention task showed statistically significant differences between the other three groups (Table 4, Fig. 4).

Responsive search score in the comparison task

The representative examples of the RSSs for a schizophrenic patient, a mood disorder patient, a neurotic disorder patient and a healthy control are shown in Fig. 5b. Figures that were slightly different from the original target figure were shown to the subjects. The top figures have a bump in the left upper part of the circles, but no bump on the left horizontal plane. The bottom figures have no bump. In the comparison task, the subjects explore the figure again and attempt to search for differences after the question, "Are there any other differences?" The normal control subject looked at six sections in the top figure and six sections in the bottom figure. Consequently,

Table 4 Comparison of eye movement parameters among groups

	Schizophrenia	Mood disorder	Neurotic disorder	Controls
Parameters of retention task				
NEF (mean ± SD)	26.49 ± 8.69	32.72 ± 7.85*	33.36 ± 7.70*	33.15 ± 6.99*
TESL (mm, mean ± SD)	1097.85 ± 533.54	1490.46 ± 492.86*	1599.90 ± 377.76*	1619.22 ± 546.64*
MESL (mm, mean ± SD)	40.39 ± 11.45	45.21 ± 10.55*	49.00 ± 9.17*	48.12 ± 9.72*
Parameter of comparison task				
RSS (mean ± SD)	6.36 ± 2.37	8.43 ± 2.23*	8.86 ± 2.32*	8.87 ± 1.95*

NEF number of eye fixations, *TESL* total eye scanning length, *MESL* mean scanning length, *RSS* responsive search scores
*$P < 0.01$ versus schizophrenia of Bonferroni

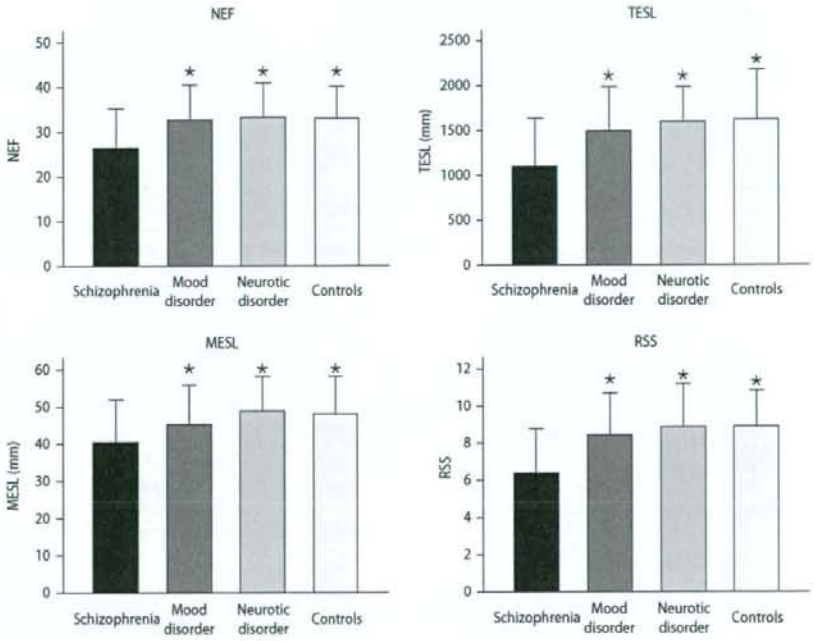


Fig. 4 The results of each parameter for schizophrenic patients, mood disorder patients, neurotic patients and normal controls
NEF number of eye fixations, *TESL* total eye scanning length, *MESL* mean scanning length, *RSS* responsive search scores
*$P < 0.01$ versus schizophrenia of Bonferroni

the RSS of the normal control was 12. Results for the mood disorder patient and the neurotic disorder patient were similar to the normal control. On the other hand, the schizophrenic patient looked at three sections of the top figure and three of the bottom. Thus, the RSS of the schizophrenic patient was six. The schizophrenic patient showed lower RSS than all other subjects.

There was a significant main effect for diagnosis but not for gender or the interaction between diagnosis and gender on the RSS by ANCOVA. Age as the covariate was also not significant (Table 3). In the multiple comparisons, the schizophrenic group had significantly lower RSS than all other groups. There were no significant differences between the patients with mood disorders, patients with neurotic disorders and healthy controls (Table 4, Fig. 4).

As shown in Table 1, there were significant differences between the groups for gender and age in the sample of this study. However, the two-way ANCOVA neither demonstrated significant main effects of gender as another factor of diagnosis nor gender by diagnosis interactions on all EEM test parameters. Moreover, group comparisons for all EEM parameters controlling for age as the covariate were significant. Therefore, this indicates that gender and age did not influence the group comparisons of the EEM parameters.

The EEM test and duration of illness

In our previous studies, we have not investigated the relationship between the EEM test and duration of illness in detail. Hence, we examined it in this study. We divided schizophrenic patients into three groups based on illness history (duration of illness: 1–5, 5–10 and >10 years), and compared the EEM parameters

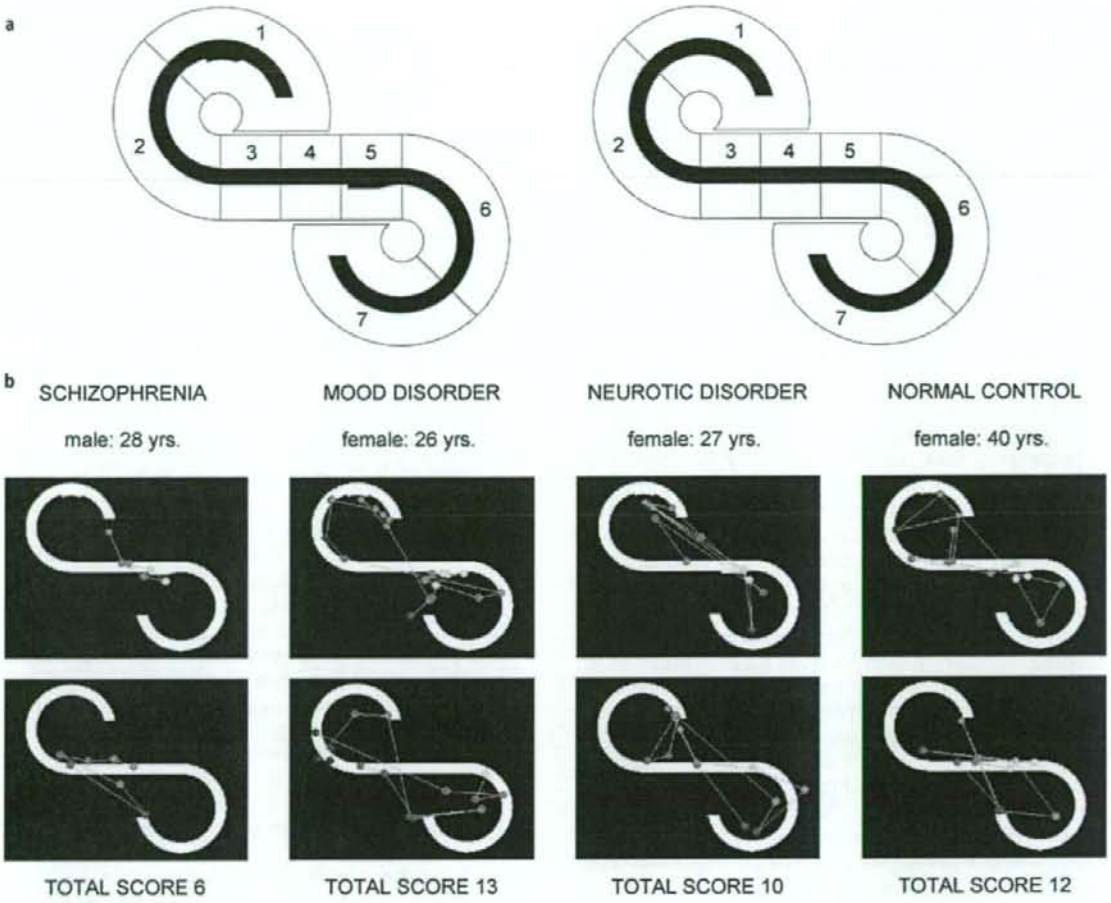


Fig. 5 **a** Seven sections for scoring the RSS. **b** The comparison task, RSS in a schizophrenic patient, a mood disorder patient, a neurotic patient and a normal control. When the RSS was scored, each horizontal S-shaped figure was divided into seven sections. If the eyes fixed on a section, the fixation points were highlighted by *unique colors*. For example, when the eyes fixed in fourth section, the fixation points were highlighted by green (see fourth section in **a** and *green* fixation points of schizophrenia in **b**). Fixation points highlighted by *gray* are out of the scoring area

between the three groups. As a result, ANOVA showed no significant main effect in any parameter (NEF: $P = 0.71$, TESL: $P = 0.65$, MESL: $P = 0.12$ and RSS: $P = 0.96$).

Discriminant analysis

In the discriminant analysis, TESL and RSS were selected as the valid parameters for discriminating between schizophrenics and non-schizophrenics. Using these as predictive parameters, we performed a discriminant analysis between schizophrenics and non-schizophrenics. As a result, we obtained the following discriminant formula: $D = 4.100 - (0.001 \times \text{TESL} + 0.332 \times \text{RSS})$. Utilizing this formula, we discriminated between 251 schizophrenics and 389 non-schizophrenics (111 patients with mood disorders, 28 patients with neurotic disorders and 250 normal controls). Consequently, 184 of the 251 clinically diagnosed schizophrenics were discriminated as having schizophrenia (sensitivity 73.3%); and 308 of the 389 clinically diagnosed non-schizophrenic subjects were discriminated as non-schizophrenics (specificity 79.2%) in the discriminant analysis (Table 5).

Discussion

In most previous studies, there were no normal individuals or patients with non-schizophrenic psychiosis in whom the parameters of the EEM test were similar to those of schizophrenic patients. Only schizophrenic

Table 5 Results of discriminant analysis for each group

	Schizophrenic	Non-schizophrenic
Schizophrenics	184/251 (73.3%)	67/251 (26.7%)
Non-schizophrenics		
Patients with mood disorders	33/111 (29.7%)	78/111 (70.3%)
Patients with neurotic disorders	5/28 (17.9%)	23/28 (82.1%)
Healthy controls	43/250 (17.2%)	207/250 (82.8%)
Total non-schizophrenics	81/389 (20.8%)	308/389 (79.2%)

Schizophrenics were discriminated from non-schizophrenics with a sensitivity of 73.3% and a specificity of 79.2%

patients have consistently shown disturbances of the EEM [16–20, 24, 25, 30, 43]. Moreover, we discriminated schizophrenics from non-schizophrenics with a high probability using EEM data [19, 26]. Therefore, we hypothesized that the EEM test may be specific to schizophrenia. However, the samples used in our previous studies were not very large. Thus, the findings of those studies required cautious interpretation and additional studies with larger samples were needed to confirm our findings. In our previous studies, one of the most important reasons that we initially used smaller samples was based on the prevailing method and existing technology. The previous method relied on an offline analog system, thus we devoted a substantial amount of time to performing the test and analyzing the data. Furthermore, the data analysis method was not completely standardized; it was also not automatic. In the present study, the authors developed a digital computerized version of the EEM test. This newly developed system handles the online detection of eye fixation points during the EEM task. Using this system, we yielded the following benefits: (1) automatic detection of eye movement data, (2) automatic standardized data analyzing system, and (3) accordingly, the time required to perform the test and analyze the data was drastically reduced. Consequently, we did the first large sample study to confirm our previous findings.

Parameters of the EEM test

The NEF, TESL and MESL, parameters of the retention task, were significantly lower in schizophrenic patients than in the other three groups. None of the retention task parameters showed statistically significant differences between the patients with mood disorders, patients with neurotic disorders and healthy controls. These results indicate that eye movements were less frequent and two-dimensional spatial distributions of the eye movements were much more limited in schizophrenics than in other groups.

The RSS, parameter of comparison task, was significantly lower for the patients with schizophrenia than for the other three groups and no significant differences were found between the other three groups. Nemoto et al. [29] investigated brain activation during a visual exploration task that was similar to the comparison task using the functional MRI in schizophrenics and normal controls. The normal control subjects showed activations at the bilateral thalamus and the left anterior medial frontal cortex. In contrast, the schizophrenic subjects had activations at the right anterior cingulate gyrus, but no activations at the thalamus and the left anterior medial frontal cortex. These findings indicate that the RSS abnormality of schizophrenia may be associated with the dysfunctions of the thalamus, frontal cortex or cingulate gyrus. In all of our studies, only schizophrenic patients have shown the RSS abnormalities [16–20, 24, 25, 30, 43]. Therefore, the dysfunction of neuronal networks involving the thalamus, frontal cortex or cingulate gyrus may be associated with schizophrenia.

The medication effect for the EEM test

Almost all patients with schizophrenia were taking neuroleptic medication. Consequently, the effect of these drugs on the EEM test should be discussed. Kojima et al. [20] investigated the effect of neuroleptics on the EEM test in schizophrenics. They contrasted a neuroleptic-medicated performance with a non-medicated performance for the EEM test in the same subjects. They found that the EEM performances were not influenced by the use of neuroleptics.

Eye movement research of schizophrenia

As eye movement research of schizophrenia, saccadic or smooth pursuit eye movement has been conducted in many laboratories on a worldwide basis [8, 11, 21, 37]. However, abnormalities of saccadic or smooth pursuit eye movement were shown in non-schizophrenic patients [9, 12, 14, 22, 39]. However, as mentioned above, the EEM abnormalities may be specific to schizophrenia, and not influenced by medication. Therefore, we used the EEM parameters for discriminating schizophrenics from non-schizophrenics.

Discriminant analysis

By using the TESL and RSS as the valid variables, we discriminated schizophrenics from non-schizophrenics with a sensitivity of 73.3% and with a specificity of 79.2%. This result was essentially consistent with our previous study [19, 26]; however, the sample size of the previous study was not very large. In this study, we replicated our previous findings with higher probability in a larger sample.

To date, there have been several studies that attempted to discriminate between schizophrenics and non-schizophrenics using psychophysiological or

neurophysiological measures. Shagass et al. [38] quantified a basic EEG activity in unmedicated patients with schizophrenia, depression, mania, neuroses and personality disorders, and performed the discriminant analyses between schizophrenics and non-schizophrenics using quantified EEG data. They discriminated schizophrenic patients from non-schizophrenic patients with a sensitivity over 50% and a specificity from 68.0 to 86.2%. Ogura et al. [31] recorded ERP, N200 and P300, to discriminate between 37 schizophrenics and 29 normal controls. They discriminated schizophrenics from normal controls with a sensitivity of 88.2% and a specificity of 85.2%. Pfefferbaum et al. [34] tried to diagnose schizophrenia, depression and dementia using P300 measures but was unsuccessful. Mather et al. [23] investigated the pursuit eye movements in 24 schizophrenics, 10 patients with unipolar depression and 16 normal controls. They correctly classified schizophrenics in 84% of cases. Price et al. [36] recorded MMN, P50, P300, and antisaccade in 60 schizophrenics and 44 normal controls; and they investigated association between the multivariate endophenotype and diagnostic groups with logistic regression. In a logistic regression using all four features, the diagnostic grouping had a sensitivity of 81.7% and a specificity of 72.7% in predicting group membership.

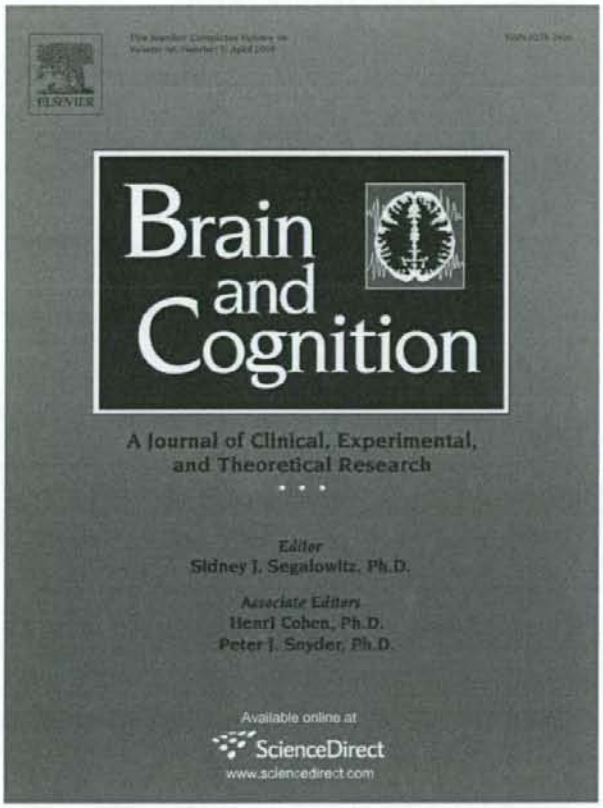
Discrimination between schizophrenics and non-schizophrenics using the EEM data demonstrated the following characteristics: (1) both sensitivity and specificity were higher than 70%, (2) schizophrenia was compared with other psychiatric disorders, and (3) the sample was large enough to confirm the results. Based on our findings and other studies, no other study using a physiological measure for discrimination meets all of the above criteria. Therefore, we believe that the EEM may be useful for discriminating between schizophrenics and non-schizophrenics. Thus, the EEM measures may show promise as a biological marker for the clinical diagnosis of schizophrenia. However, in order to apply the EEM to the clinical diagnosis of schizophrenia, higher sensitivity and specificity values are needed. Hence, we need a more detailed contrivance for the application of the EEM for the diagnosis of schizophrenia. Moreover, when discriminant analysis is used in this type of study, the following approach is recommended: (1) the discriminant analysis should be performed among subjects, and a discriminant function with excellent sensitivity and specificity should be obtained; and (2) to test the external validity of the discriminant function, it should be applied to a group that is separate from the study group. However, we did not use the above recommended approach because we were eager to have a prominent function by using a large sample in this study. The findings of this study can be applied to other samples in the future.

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

References

1. Arolt V, Lencer R, Nolte A, Muller-Myhsok B, Purmann S, Schurmann M, Leutelt J, Pinnow M, Schwinger E (1996) Eye tracking dysfunction is a putative phenotypic susceptibility marker of schizophrenia and maps to a locus on chromosome 6p in families with multiple occurrence of the disease. Am J Med Genet 67:564–579
2. Arolt V, Lencer R, Purmann S, Schurmann M, Muller-Myhsok B, Krecker K, Schwinger E (1999) Testing for linkage of eye tracking dysfunction and schizophrenia to markers on chromosomes 6, 8, 9, 20, and 22 in families multiply affected with schizophrenia. Am J Med Genet 88:603–606
3. Barrantes-Vidal N, Aguilera M, Campanera S, Fatjo-Vilas M, Guitart M, Miret S, Valero S, Fananas L (2007) Working memory in siblings of schizophrenia patients. Schizophr Res 95:70–75
4. Bharath S, Gangadhar BN, Janakiramaiah N (2000) P300 in family studies of schizophrenia: review and critique. Int J Psychophysiol 38:43–54
5. Braff DL (1993) Information processing and attention dysfunctions in schizophrenia. Schizophr Bull 19:233–259
6. Devrim-Ucok M, Keskin-Ergen HY, Ucok A (2007) Mismatch negativity at acute and post-acute phases of first-episode schizophrenia. Eur Arch Psychiatry Clin Neurosci 258:179–185
7. Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, Polymeropoulos M, Holik J, Hopkins J, Hoff M, Rosenthal J, Waldo MC, Reimherr F, Wender P, Yaw J, Young DA, Breese CR, Adams C, Patterson D, Adler LE, Kruglyak L, Leonard S, Byerley W (1997) Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci USA 94:587–592
8. Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M (1988) Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. Biol psychiatry 23:670–677
9. Gooding DC, Tallent KA (2001) The association between antisaccade task and working memory task performance in schizophrenia and bipolar disorder. J Nerv Ment Dis 189:8–16
10. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
11. Haraldsson HM, Ettinger U, Magnusdottir BB, Sigmundsson T, Sigurdsson E, Petursson H (2008) Eye movement deficits in schizophrenia: investigation of a genetically homogenous Icelandic sample. Eur Arch Psychiatry Clin Neurosci 258:373–383
12. Holzman PS, O'Brian C, Waternaux C (1991) Effects of lithium treatment on eye movements. Biol Psychiatry 29:1001–1015
13. Inagaki A, Inada T (2006) Dose equivalence of psychotropic drugs. Part 18: dose equivalence of psychotropic drugs: 2006-version. Jpn J Clin Psychopharmacol 9:1443–1447 (in Japanese)
14. Katsanis J, Kortenkamp S, Iacono WG, Grove WM (1997) Antisaccade performance in patients with schizophrenia and affective disorder. J Abnorm Psychol 106:468–472
15. Kirov G, O'Donovan MC, Owen MJ (2005) Finding schizophrenia genes. J Clin Invest 115:1440–1448
16. Kojima T, Matsushima E, Ando K, Ando H, Sakurada M, Ohta K, Moriya H, Shimazono Y (1992) Exploratory eye movements and neuropsychological tests in schizophrenic patients. Schizophr Bull 18:85–94
17. Kojima T, Matsushima E, Iwama H, Ando H, Moriya H, Ando K, Takahashi R, Shimazono Y (1986) Visual perception process in amphetamine psychosis and schizophrenia. Psychopharmacol Bull 22:768–773

18. Kojima T, Matsushima E, Nakajima K, Shiraishi H, Ando K, Ando H, Shimazono Y (1990) Eye movements in acute, chronic, and remitted schizophrenics. Biol Psychiatry 27:975–989
19. Kojima T, Matsushima E, Ohta K, Toru M, Han YH, Shen YC, Moussaoui D, David I, Sato K, Yamashita I, Kathmann N, Hippius H, Thavundayil JX, Lal S, Vasavan Nair NP, Potkin SG, Prilipko L (2001) Stability of exploratory eye movements as a marker of schizophrenia—a WHO multi-center study. Schizophr Res 52:203–213
20. Kojima T, Potkin SG, Kharazmi M, Matsushima E, Herrera J, Shimazono Y (1989) Limited eye movement patterns in chronic schizophrenic patients. Psychiatry Res 28:307–314
21. Levy DL, Holzman PS, Matthysse S, Mendell NR (1994) Eye tracking and schizophrenia: a selective review. Schizophr Bull 20:47–62
22. Malaspina D, Amador XF, Coleman EA, Mayr TL, Friedman JH, Sackeim HA (1994) Smooth pursuit eye movement abnormality in severe major depression: effects of ECT and clinical recovery. J Neuropsychiatry Clin Neurosci 6:36–42
23. Mather JA, Neufeld RW, Merskey H, Russell NC (1992) Disruption of saccade production during oculomotor tracking in schizophrenia and the use of its changes across target velocity as a discriminator of the disorder. Psychiatry Res 43:93–109
24. Matsukawa Y, Takahashi S, Aoki M, Yamakami K, Nishinarita S, Horie T, Fukura Y, Tanabe E, Yara K, Matsuura M, Kojima T (2002) Patients with systemic lupus erythematosus show a normal responsive search score in exploratory eye movement analysis: comparison with schizophrenia. Ann Rheum Dis 61:748–750
25. Matsushima E, Kojima T, Ohbayashi S, Ando H, Ando K, Shimazono Y (1992) Exploratory eye movements in schizophrenic patients and patients with frontal lobe lesions. Eur Arch Psychiatry Clin Neurosci 241:210–214
26. Matsushima E, Kojima T, Ohta K, Obayashi S, Nakajima K, Kakuma T, Ando H, Ando K, Toru M (1998) Exploratory eye movement dysfunctions in patients with schizophrenia: possibility as a discriminator for schizophrenia. J Psychiatr Res 32:289–295
27. Michie PT (2001) What has MMN revealed about the auditory system in schizophrenia? Int J Psychophysiol 42:177–194
28. Myles-Worsley M, Coon H, McDowell J, Brenner C, Hoff M, Lind B, Bennett P, Freedman R, Clementz B, Byerley W (1999) Linkage of a composite inhibitory phenotype to a chromosome 22q locus in eight Utah families. Am J Med Genet 88:544–550
29. Nemoto Y, Matsuda T, Matsuura M, Motoshita M, Ohkubo T, Ohkubo H, Suzuki M, Kanaka N, Matsushima E, Kojima T (2004) Neural circuits of eye movements during performance of visual exploration task, which is similar to responsive search score task, in schizophrenia patients and normal subjects. J Nihon Univ Med Ass 63:352–359 (in Japanese)
30. Obayashi S, Matsushima E, Okubo Y, Ohkura T, Kojima T, Kakuma T (2001) Relationship between exploratory eye movements and clinical course in schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 251:211–216
31. Ogura C, Nageishi Y, Matsubayashi M, Omura F, Kobayashi T, Shimokochi M (1985) Event-related potentials in patients with schizophrenia and depression, and their application to clinical diagnosis. Psychiatr Neurol Jpn 87:944–951 (in Japanese)
32. Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812
33. Parwani A, Duncan EJ, Bartlett E, Madonick SH, Efferen TR, Rajan R, Sanfilipo M, Chappell PB, Chakravorty S, Gonzenbach S, Ko GN, Rotrosen JP (2000) Impaired prepulse inhibition of acoustic startle in schizophrenia. Biol Psychiatry 47:662–669
34. Pfefferbaum A, Wenegrat BG, Ford JM, Roth WT, Kopell BS (1984) Clinical application of the P3 component of event-related potentials. II. Dementia, depression and schizophrenia. Electroencephalogr Clin Neurophysiol 59:104–124
35. Potter D, Summerfelt A, Gold J, Buchanan RW (2006) Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. Schizophr Bull 32:692–700
36. Price GW, Michie PT, Johnston J, Innes-Brown H, Kent A, Clissa P, Jablensky AV (2006) A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia. Biol Psychiatry 60:1–10
37. Sereno AB, Holzman PS (1995) Antisaccades and smooth pursuit eye movements in schizophrenia. Biol Psychiatry 37:394–401
38. Shagass C, Roemer RA, Straumanis JJ, Josiassen RC (1984) Psychiatric diagnostic discriminations with combinations of quantitative EEG variables. Br J Psychiatry 144:581–592
39. Sweeney JA, Strojwas MH, Mann JJ, Thase ME (1998) Prefrontal and cerebellar abnormalities in major depression: evidence from oculomotor studies. Biol Psychiatry 43:584–594
40. Szymanski S, Kane JM, Lieberman JA (1991) A selective review of biological markers in schizophrenia. Schizophr Bull 17:99–111
41. Takahashi S, Matsushima E, Kojima T, Tanabe E, Yara K, Hagiwara M (2000) Study of the families and twins of schizophrenics. In: Kojima T, Matsushima E, Ando K (eds) Eyes and the mind. Karger, Basel, pp 75–79
42. Takahashi S, Ohtsuki T, Yu SY, Tanabe E, Yara K, Kamioka M, Matsushima E, Matsuura M, Ishikawa K, Minowa Y, Noguchi E, Nakayama J, Yamakawa-Kobayashi K, Arinami T, Kojima T (2003) Significant linkage to chromosome 22q for exploratory eye movement dysfunction in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 123:27–32
43. Tonoya Y, Matsui M, Kurachi M, Kurokawa K, Sumiyoshi T (2002) Exploratory eye movements in schizophrenia: effects of figure size and the instruction on visual search. Eur Arch Psychiatry Clin Neurosci 252:255–261
44. Weike AI, Bauer U, Hamm AO (2000) Effective neuroleptic medication removes prepulse inhibition deficits in schizophrenia patients. Biol Psychiatry 47:61–70
45. World Health Organization (1993) The international classification of mental and behavioural disorders: diagnostic criteria for research. WHO, Geneva



Available online at www.sciencedirect.com
ScienceDirect
Brain and Cognition 66 (2008) 306–310
Brain and Cognition
www.elsevier.com/locate/b&c

Brief Communication

Superior fluid intelligence in children with Asperger's disorder

Mika Hayashi [a,*], Motoichiro Kato [a], Kazue Igarashi [b], Haruo Kashima [a]

[a] *Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan*
[b] *Department of Child Culture, Shirayuri College, 1-25 Midorigaoka, Choufu-shi, Tokyo 182-8525, Japan*

Accepted 25 September 2007
Available online 5 November 2007

Abstract

Asperger's disorder is one of autistic spectrum disorders; sharing clinical features with autism, but without developmental delay in language acquisition. There have been some studies of intellectual functioning in autism so far, but very few in Asperger's disorder. In the present study, we investigated abstract reasoning ability, whose form of intelligence has been labeled fluid intelligence in the theory of Cattell [Cattell, R. B. (1963). Theory of fluid and crystallized intelligence: A critical experiment. *Journal of Educational Psychology, 54*, 1–22.], in children with Asperger's disorder. A test of fluid intelligence, the Raven's Standard Progressive Matrices Test, was administered to 17 children with Asperger's disorder and 17 age-, gender-, and FIQ-matched normal children. The results showed that children with Asperger's disorder outperformed on the test of fluid reasoning than typically developing children. We suggest that individuals with Asperger's disorder have higher fluid reasoning ability than normal individuals, highlighting superior fluid intelligence.

Keywords: General fluid intelligence; Raven's progressive matrices test; Abstract reasoning ability

1. Introduction

Asperger's disorder is a pervasive developmental disorder characterized by impairments in social interaction, with restricted and repetitive patterns of behaviors and interests. This disorder is a subgroup on the autistic spectrum, sharing many clinical features with Autistic Disorder (American Psychiatric Association., 1994), but without clinically significant developmental delays in language acquisition. In Asperger's disorder, basic language skills are intact, although there are delays in nonverbal communication skills and pragmatics (Stein et al., 2004). There has been a report that individuals with Asperger's disorder often have a distinct profile on standard tests of intelligence such as the Wechsler Adult Intelligence Scale (WAIS) and Wechsler Intelligence Scale for Children (WISC), characterized by high verbal IQ and relatively low performance IQ (Klin, Volkmer, Sparrow, Cichetti, & Rourke, 1995).

Some studies have indicated that children with Asperger's disorder have high performances on the Vocabulary and Comprehension verbal subtests of the WISC, while their performances on nonverbal subtests, including Block Design and Object Assembly, are impaired (Ehlers et al., 1997). These findings at first sight suggest that individuals with Asperger's disorder have superior verbal crystallized intelligence, rather than nonverbal fluid intelligence. However, Wechsler-type intelligence scale is not considered as a test of fluid intelligence but rather an example of tests that typically measure skills and knowledge, crystallized intelligence (Gray & Thompson, 2004). General fluid intelligence (gF) is a major dimension of individual differences and refers to reasoning and novel problem-solving ability (Cattell, 1963; Gray & Thompson, 2004). Empirically, fluid intelligence is strongly associated with frontal executive function (Duncan, Burgess, & Emslie, 1995), attentional control and working memory (Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Gray, Chabris, & Braver, 2003; Kane & Engle, 2002), and the core function of fluid intelligence is the abstract reasoning ability, which has been a component of most formal theories of intelligence (Stern-

* Corresponding author. Fax: +81 3 5379 0187.
E-mail address: di055010@sc.itc.keio.ac.jp (M. Hayashi).

0278-2626/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.bandc.2007.09.008

berg, 1985; Thurstone, 1938). On the other hand, general crystallized intelligence is distinct from gF, referring to overlearned skills and static knowledge such as vocabulary, and there is empirical evidence for a distinction between the psychological processes and the neural substrates that subserve fluid reasoning and crystallized knowledge (Cattell, 1963; Duncan et al., 1995). As a test of fluid intelligence, the Raven Progressive Matrices test (Raven, Raven, & Court, 1993) is regarded as one of the best measurements, because it provides an optimal domain-independent measure of the abstract reasoning processes relevant to the management of novel problem-solving goals in working memory (Carpenter, Just, & Shell, 1990; Duncan et al., 2000; Gray & Thompson, 2004; Gray et al., 2003).

In cognitive research with autism, IQ is the most frequent matching variable in use, and Wechsler scales, British Picture Vocabulary Scale (BPVS) and the Raven's Coloured Progressive Matrices test (RCPM) are the frequently used instruments to determine IQ. Mottron (2004) claimed that there is a high probability of overestimating the level of intelligence in percentile vales of BPVS and RCPM score as compared to those of Wechsler scale, recommending a replacement to Wechsler scale as a basis of IQ matching.

Thus, the RCPM is frequently used to assess intelligence in individual with pervasive developmental disorders. However, the RCPM was developed to assess young children (5 to 101/2 years), whereas the Raven's Standard Progressive Matrices (RSPM) was developed for use with older children and adults (Raven et al., 1993). The colored backgrounds on which the problems are printed attract attention and make the test spontaneously interesting (Raven et al., 1993), and so the way to solve the problems on the RCPM is closely tied to the perceptual and analytical processes. By contrast, most of the problems on the RSPM are not as closely tied to the perceptual format and require a more abstract characterization in terms of dimensions and attributes (Carpenter et al., 1990). Therefore, the RSPM is widely accepted as a measure of high level analytical reasoning and of fluid intelligence (Carpenter et al., 1990; Dawson, Soulieres, Gernsbacher, & Mottron, 2007).

It is possible to assume that individuals with Asperger's disorder would show low fluid intelligence, as in the case of autistics who showed poor fluid reasoning (Blair, 2006; Pennington & Ozonoff, 1996) and poor performance on the tests of high-level integration or abstraction (Courchesne & Pierce, 2005; Just, Cherkassky, Keller, & Minshew, 2004). However, a recent study by Dawson and colleagues (2007) provided us with empirical evidence that autistic children showed high scores on the test of fluid intelligence using the RSPM. Such an empirical study has never been documented in Asperger's disorder or high-functioning autism. Here, we aimed to examine fluid intelligence in children with Asperger's disorder, using the Raven's Standard Progressive Matrices test (RSPM).

2. Methods

2.1. Participants

Seventeen participants with Asperger's disorder (10 boys and 7 girls, ages 6 to 12 years) were recruited from the outpatient's clinic of one children's hospital and took part in this study. These participants all were found to meet DSM-IV (American Psychiatric Association, 1994) criteria for a diagnosis of Asperger's disorder and were screened for psychiatric disorders through an in-depth clinical investigation performed by two of us (M.K., a psychiatrist and K.I., a child neuropsychologist) at the time of passing a standardized diagnostic instrument. Exclusion criteria included epileptic disorder, severe head trauma, the other neurological illness, or serious medical problems. In particular, those who had attention deficit/hyperactivity disorder, learning disability and developmental dyslexia were excluded from this study. None of them were on medication or showed signs of gross neurological abnormalities at the time of testing.

Although all participants with Asperger's disorder showed clinical symptoms including abnormal social interaction, and restricted and repetitive patterns of behaviors, they could use single words by the age of two years and communicative phrases by the age of three, and had no echolalia, pronoun reversal, nor stereotyped language.

Participants with Asperger's disorder showed a mean full-scale IQ of 96.7 (SD = 15.3) as measured with the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), and their mean verbal IQ (VIQ) (101.7 ± 13.7) was higher than their mean performance IQ (PIQ) (91.5 ± 19.3) [$t(16) = 2.29$, $p < .05$].

Seventeen typically developing children (10 boys and 7 girls) participated in this study as age- and sex matched controls (NC). They were recruited from public primary schools in Tokyo. All participants were initially screened by teachers and were evaluated further by a structured psychiatric interview of two independent child psychiatrists and medical assessment. The exclusion criteria were a history of DSM-IV psychiatric disorders including attention deficit / hyperactivity disorder, learning disability and evidence of any other organic diseases. These control children had a mean FIQ of 99.8 (SD = 9.8) as measured with WISC-III, and their mean verbal IQ (VIQ) (101.3 ± 9.2) did not differ from their mean performance IQ (PIQ) (99.1 ± 10.2) [$t(16) = .96$, $p > .05$]. There were no significant differences on the mean of age and FIQ score between the participants with Asperger's disorder and the control participants ($p > .05$, Table 1.). The parents of each group were mostly from upper middle-class social status. Written informed consent was obtained from all participants and their parents.

2.2. Measures

The Raven's Standard Progressive Matrices test (RSPM) (Raven, Court, & Raven, 1992) was administered

Table 1
Descriptive characteristics of participants in control (NC) and Asperger's disorder (AD) groups

	Groups	
	NC	AD
N (boys/girls)	17 (10/7)	17 (10/7)
Age (years)	9.5 (2.5)	9.2 (1.9)
WISC-III		
FIQ	99.8 (9.8)	96.7 (15.3)
VIQ	101.3 (9.2)	101.7 (13.7)
PIQ	99.1 (10.2)	91.5 (19.3)*

Data are expressed as group mean and standard deviation in parentheses. WISC-III, Wechsler Intelligence Scale for Children-Third Edition.
* The mean PIQ score was significantly lower than the mean VIQ in AD group ($p < .05$).

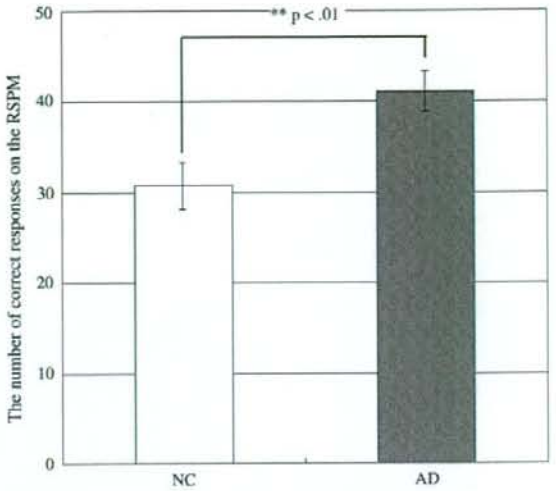


Fig. 1. Mean numbers of correct responses on the RSPM for control (NC) and Asperger's disorder (AD) groups. Open (left) and filled (right) columns represent numbers of correct responses in NC and AD groups, respectively. Vertical bars represent the standard error of the mean.

to the participants. The RSPM comprises 60 problems, divided into five sets (A–E) of increasing difficulty, and the each set begins with easy problems and ends with difficult ones. Each item contains a matrix of geometric design with one cell of the matrix removed, and there are six or eight alternatives given to insert in place of the missing cell, one of which fits correctly.

All participants were tested individually, and the RSPM was administered without time limit.

3. Results

Mean numbers of correct responses on the RSPM in the Asperger's disorder (AD) and normal controls (NC) groups are shown in Fig. 1. The number of matrices correctly solved in both groups were analyzed as a dependent variable, and two-tailed t tests revealed that the AD group (41.1 ± 9.3) made significantly more correct responses than the NC group (30.7 ± 10.3) [$t(32) = -3.08$, $p < .01$, Cohen's $ds = 1.05$].

Furthermore, a two-way ANOVA with groups and gender as variables, revealed significant main effects of groups [$F(1,30) = 8.69$, $p < .01$] and group × gender interaction [$F(1,30) = 17.37$, $p < .01$]. Regarding the boys, the AD group (46.0 ± 2.6) outperformed the NC group (26.0 ± 2.6) [$ds = 2.48$]. On the other hand, the girls in the AD group (34.0 ± 3.0) showed the equivalent number of correct responses to the girls in the NC group (37.4 ± 3.0) [$ds = 0.42$].

There was no significant correlation between the number of correct responses on the RSPM, and FIQ ($r = .24$, $p > .05$), VIQ ($r = .27$, $p > .05$) and PIQ ($r = .16$, $p > .05$) on the WISC-III for all children combined.

4. Discussion

The present study demonstrates that participants with Asperger's disorder made more correct responses on the RSPM than did normal controls. The results of this study suggest that Asperger's disorder involves superior abstract reasoning ability or higher general fluid intelligence. A theoretical account in the literature regarding the processing of the Raven test (Carpenter et al., 1990) proposes that the RSPM involves abstraction and goal management processes. In order to solve the problems on the RSPM, it is necessary to induce rules from the relationship between elements in matrices, and to generate and maintain goals in working memory until a target satisfies a theorem as a whole. As compared to normally developing children, the performance on the RSPM in children with Asperger's disorder was critically different and was significantly better, implying the superiority in fluid intelligence in Asperger's disorder.

Moreover, from clinical case records of children with Asperger's disorder diagnosed by Hans Asperger and his team, it was revealed that some individuals with Asperger's disorder had a special gift for abstract thinking and logical reasoning (Hippler & Klicpera, 2003). Hans Asperger contended, in his original paper, that the traits of this disorder were in fact necessary for high achievement in the arts and sciences (Wing, 2005). Logical reasoning ability is a premise for conducting scientific research, and in fact there have been some outstanding scientists who were the cases of Asperger's disorder (Asperger, 1944; Frith, 2004). Such clinical characteristics could be in correspondence to the superior performance on abstract reasoning problems of the RSPM in the present study.

Recently, an interesting study of autistic intelligence has been published (Dawson et al., 2007). In this study, autistic children showed high scores on the RSPM. However, the percentile score on the RSPM were higher than the percentile scores on the Wechsler scales of intelligence in autistic

children, while typically developing children did not show such discrepancy. The results of this study suggested that intelligence has been underestimated in autistics. Although this study was conducted to children with autism, and some autistics included IQ score below the average, indicating 'low-functioning' autism (i.e., in the range of mental retardation), our participants included children with Asperger's disorder who had average or high IQ scores. Nevertheless, the results of our study were in line with those of the study by Dawson and colleagues (2007), since Asperger's disorder shares the same clinical features to autism in poor social communication and is considered as one of autistic spectrum disorders (Wing, 1981).

Recent cognitive neuroscience studies showed that analytic reasoning activates the left frontal cortex (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997; Wharton et al., 2000). Moreover, general fluid intelligence reflects the function of a specific neural system, including the lateral frontal cortex as one major part (Duncan et al., 2000; Gray et al., 2003). Thus, the left lateral frontal function may play an important role for fluid reasoning, and our results of superior fluid intelligence in Asperger's disorder may imply the unique involvement in the left frontal lobe functioning. Future research should explore the neural substrates for fluid intelligence in Asperger's disorder.

Although we demonstrated new cognitive characteristics in Asperger's disorder, there are some limitations in our study. The major one is the small number of participants with Asperger's disorder. The results of this study suggested that boys with Asperger's disorder particularly performed better on the RSPM. It might be because that males are better at 'systemizing', that is, 'to predict and to respond to the behavior of nonagentive deterministic systems by analyzing rules that govern such systems' (Baron-Cohen, 2002). Hans Asperger himself even noted that autistic mind is an extreme variant of male intelligence (Asperger, 1944; Frith, 2004; Wing, 2005). However, unfortunately, it would be too early to reason from such a small number of participants. The comparison of boys versus girls in Asperger's disorder with more cases would be of importance and should be carefully examined. Another limitation is the lack of multiple measures of general fluid intelligence in this study. Although we suppose that the RSPM would be a good and convincing enough measure, it would be hard to clearly articulate the types of cognitive processes that the RSPM taps into. Future study is expected to investigate general fluid intelligence with some other cognitive tests in Asperger's disorder. Thirdly, the children participated in this study were diagnosed as Asperger's disorder. This diagnosis was made only for autistic children without relevant delay or deficits in language development. It would be interesting and necessary to compare the performance on the tests of fluid intelligence in Asperger's disorder with high-functioning autism. Finally, what is the most puzzling for us is why persons with Asperger's disorder have such a special abstract reasoning ability? We should explore what cognitive factors associated with Asperger's disorder would contribute to high fluid intelligence in future research.

In conclusion, we demonstrated that individuals with Asperger's disorder are able to perform better on the RSPM than normally developing individuals, and highlights superior abstract reasoning ability and high general fluid intelligence in this disorder. This study provides new insight into the cognitive strengths associated with Asperger's disorder.

References

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*. Washington, DC: American Psychiatric Association.

Asperger, H. (1944). Die "Autistischen Psychopathen" im Kindersalter. *Archiv fur Psychiatrie und Nervenkrankheiten, 117*, 76–136.

Baron-Cohen, S. (2002). The extreme male brain theory of autism. *Trends in Cognitive Sciences, 6*, 248–254.

Blair, C. (2006). How similar are fluid cognition and general intelligence? A developmental neuroscience perspective on fluid cognition as an aspect of human cognitive ability. *Behavioral and Brain Sciences, 29*, 109–125.

Carpenter, P. A., Just, M. A., & Shell, P. (1990). What one intelligence test measures: Atheoretical account of the processing in the Raven Progressive Matrices Test. *Psychological Review, 97*, 404–431.

Cattell, R. B. (1963). Theory of fluid and crystallized intelligence: A critical experiment. *Journal of Educational Psychology, 54*, 1–22.

Conway, A. R. A., Cowan, N., Bunting, M. F., Therriault, D. J., & Minkoff, S. R. B. (2002). A latent variable analysis of working memory capacity, short term memory capacity, processing speed and general fluid intelligence. *Intelligence, 30*, 163–183.

Courchesne, A., & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: Long over-connectivity but long-distance disconnection. *Current Opinion in Neurobiology, 15*, 225–230.

Dawson, M., Soulieres, I., Gernsbacher, M. A., & Mottron, L. (2007). The level and nature of autistic intelligence. *Psychological Science, 18*, 657–662.

Duncan, J., Burgess, P., & Emslie, H. (1995). Fluid intelligence after frontal lobe lesions. *Neuropsychologia, 33*, 261–268.

Duncan, J., Seitz, R. J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., et al. (2000). A neural basis for general intelligence. *Science, 289*, 457–460.

Ehlers, S., Nyden, A., Gillberg, C., Sandberg, A. D., Dahlgren, S., Hjelmquist, E., et al. (1997). Asperger syndrome, autism and attention disorders: A comparative study of the cognitive profiles of 120 children. *Journal of Child Psychology and Psychiatry, 38*, 207–217.

Frith, U. (2004). Emanuel Miller lecture: Confusion and controversies about Asperger syndrome. *Journal of Child Psychology and Psychiatry, 45*, 672–686.

Gray, J. R., Chabris, C. F., & Braver, T. S. (2003). Neural mechanisms of general fluid intelligence. *Nature Neuroscience, 6*, 316–322.

Gray, J. R., & Thompson, P. M. (2004). Neurobiology of intelligence: Science and ethics. *Nature Reviews Neuroscience, 5*, 471–482.

Hippler, K., & Klicpera, C. (2003). A retrospective analysis of the clinical case records of 'autistic psychopaths' diagnosed by Hans Asperger and his team at the University Children's Hospital, Vienna. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 358*, 291–301.

Just, M. A., Cherkassky, V. L., Keller, T. A., & Minshew, N. J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain, 127*, 1811–1821.

Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention and general fluid intelligence: an individual-differences perspective. *Psychonomic Bulletin & Review, 9*, 637–671.

Klin, A., Volkmer, F. R., Sparrow, S. S., Cichetti, D. V., & Rourke, B. P. (1995). Validity and neurospsychological characterization of Asperger syndrome. *Journal of Child Psychology and Psychiatry, 36*, 1127–1140.

Mottron, L. (2004). Matching strategies in cognitive research with individuals with high-functioning autism: Current practices, instrument biases and recommendations. *Journal of Autism Developmental Disorders, 34*, 19–27.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 37*, 51–87.

Prabhakaran, V., Smith, J. A. L., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. E. (1997). Neural substrates of fluid reasoning: an fMRI study of neocortical activation during performance of the Raven's Progressive Matrices Test. *Cognitive Psychology, 33*, 43–63.

Raven, J. C., Court, J. H., & Raven, J. (1992). *Raven manual: Section 3. The standard progressive matrices*. Oxford, England: Oxford Psychologists Press.

Raven, J., Raven, J. C., & Court, J. H. (1993). *Raven manual: Section 1. General overview*. Oxford, England: Oxford Psychologists Press.

Stein, M. T., Klin, A., Miler, K., Goulden, K., Coolman, R., & Coolman, D. M. (2004). When Asperger's syndrome and a nonverbal learning disability look alike. *Journal of Developmental and Behavioral Pediatrics, 25*, 190–195.

Sternberg, R. J. (1985). *Beyond IQ: A triarchic theory of human intelligence*. Cambridge: Cambridge University Press.

Thurstone, L. L. (1938). *Primary mental abilities*. Chicago: University of Chicago Press.

Wharton, C. M., Grafman, J., Flitman, S. S., Hansen, E. K., Braumer, J., Marks, A., et al. (2000). Toward neuroanatomical models of analogy: A positron emission tomography study of analogical mapping. *Cognitive Psychology, 40*, 173–197.

Wing, L. (1981). "Asperger's syndrome: A clinical account". *Psychological Medicine, 11*, 115–129.

Wing, L. (2005). Reflections on opening Pandora's box. *Journal of Autism Developmental Disorders, 35*, 197–203.