Table 2
Absolute volumes of temporal lobe structures in control subjects, patients with schizotypal disorder, and patients with schizophrenia

Brain region (mm^3)	Control subjects				Schizotypal patients				Schizophrenia patients				Analysis of covariance[a]		
	Male (N=38)		Female (N=34)		Male (N=24)		Female (N=15)		Male (N=35)		Female (N=30)		Diagnosis effect		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Total fusiform gyrus GM													12.73	2,168	<0.001
Left	9212	1591	8342	1204	8680	1591	7894	1157	7788	1313	7285	1475			
Right	9432	1696	8556	1657	8663	1184	7820	1242	8295	1466	7448	1732			
Anterior fusiform gyrus GM													5.42	2,168	0.005
Left	5287	1156	4796	822	5563	1366	4498	1072	4544	1021	4292	1122			
Right	5352	1017	4879	1111	5202	1043	4365	1114	4750	1049	4384	1188			
Posterior fusiform gyrus GM													12.26	2,168	<0.001
Left	3924	923	3546	865	3317	739	3396	621	3244	837	2993	688			
Right	4080	1020	3677	722	3461	648	3455	660	3544	828	3063	706			
Hippocampus[b]													3.18	2,152	0.045
Left	3212	397	2749	233	2856	322	2735	374	3026	404	2706	392			
Right	3382	345	2983	254	3118	337	2943	418	3184	633	2916	400			
	(N=35)		(N=28)		(N=23)		(N=12)		(N=32)		(N=30)				
Amygdala[b]													18.99	2,152	<0.001
Left	1178	149	1054	103	981	145	984	111	1017	168	947	126			
Right	1186	156	1099	104	981	145	993	118	1108	181	967	120			
	(N=35)		(N=28)		(N=23)		(N=12)		(N=32)		(N=30)				
Parahippocampal gyrus GM													0.32	2,168	0.724
Left	6003	721	5430	649	5988	703	5744	590	5893	775	5474	623			
Right	5918	757	5548	640	5719	551	5470	671	5703	795	5375	607			
Temporal pole GM[c]													3.98	2,168	0.021
Left	13,177	2118	11,950	1854	13,246	2272	13,096	1684	12,977	1783	11,296	2064			
Right	12,134	2175	11,235	1771	12,028	1942	12,530	1513	11,968	1624	10,648	1828			
Superior temporal gyrus GM[c]													51.08	2,168	<0.001
Left	13,279	1631	11,927	1422	10,208	1709	9743	1355	11,053	1928	9866	1600			
Right	11,263	1542	10,530	1288	9557	1242	9197	1463	9672	1638	8982	1245			
Middle temporal gyrus GM													1.44	2,168	0.239
Left	15,360	2223	14,025	1912	16,337	2125	14,432	1512	15,647	2808	14,348	1957			
Right	15,935	1967	14,564	1747	16,249	2282	15,053	1392	15,901	2557	14,475	1995			
Inferior temporal gyrus GM													0.78	2,168	0.459
Left	13,637	1855	11,357	1417	13,408	2411	12,629	1889	13,284	2304	11,783	1957			
Right	12,846	1776	11,434	1243	12,495	1552	11,803	1453	12,232	1858	11,211	1636			

Abbreviation: GM, gray matter.
[a] Age and intracranial volume (ICV) were used as covariates.
[b] Data for the schizophrenia patients and controls (Niu et al., 2004; Suzuki et al., 2005a,b) and for the schizotypal patients (Suzuki et al., 2005b) were partly published elsewhere.
[c] Data for three diagnostic groups were already published elsewhere (Takahashi et al., 2006).

3.1.1. Fusiform gyrus

MANCOVA of the total (anterior and posterior) fusiform gyrus revealed a significant main effect for diagnosis. Post hoc analyses demonstrated that, compared with the controls, the schizophrenia patients had a significantly smaller total fusiform gyrus ($p<0.001$) and the schizotypal patients had a trend towards a significant reduction ($p=0.051$). There was no significant difference in the total fusiform gyrus volume between schizophrenia and schizotypal disorder.

For the anterior fusiform gyrus, MANCOVA revealed a significant main effect for diagnosis, where the schizophrenia patients had a significantly smaller anterior fusiform gyrus than did controls (post hoc test, $p=0.001$). The volume of the anterior fusiform gyrus in the schizotypal disorder patients did not differ significantly from the values in the controls (post hoc test, $p=0.485$) or schizophrenia patients (post hoc test, $p=0.155$).

For the posterior fusiform gyrus, MANCOVA revealed significant main effects for diagnosis and side ($F=4.93$; $df=1,170$; $p=0.028$), where the schizophrenia (post hoc test, $p<0.001$) and schizotypal (post hoc test, $p=0.016$) patients had a significantly smaller posterior fusiform gyrus than did control subjects, and the posterior fusiform gyrus was larger in the right than in

the left hemisphere for all the diagnostic groups (post hoc test, $p=0.022$).

3.1.2. Parahippocampal gyrus

MANCOVA revealed a significant main effect for side ($F=9.97$; $df=1,170$; $p=0.002$) and a significant group-by-side interaction ($F=3.84$; $df=2,170$; $p=0.023$). Post hoc analyses showed the parahippocampal gyrus to be larger in the left than in the right hemisphere ($p=0.001$), but there were no differences in volume among diagnostic groups.

3.1.3. Middle and inferior temporal gyri

MANCOVAs for both the middle ($F=6.08$; $df=1,170$; $p=0.015$) and inferior ($F=22.45$; $df=1,170$; $p<0.001$) temporal gyri revealed a significant main effect for side; the middle temporal gyrus had a right-greater-than-left asymmetry (post hoc test, $p=0.011$) and the inferior temporal gyrus had a left-greater-than-right one (post hoc test, $p<0.001$) for all diagnostic groups. However, the measurements of the middle and inferior temporal gyri did not differ significantly among the diagnostic groups.

3.2. Correlational analyses

For schizophrenia patients, relative volume for the right posterior fusiform gyrus was correlated negatively with the score for affective flattening or blunting of SANS (rho$=-0.324$, $p=0.008$), but the correlation was not significant after correction. For the schizotypal group, there were no significant correlations between the volumetric measurements and the scores for the subscales of the SAPS or SANS.

Spearman's correlational analyses did not reveal any significant correlation between the volumetric measurements of each ROI and daily dosage of neuroleptic medication or duration of medication in either patient group. The volumetric measurements were not significantly correlated with age at onset or duration of illness in schizophrenia patients.

4. Discussion

In this study, we demonstrated that the volume of gray matter in the posterior fusiform gyrus was reduced in both schizophrenia and schizotypal disorder patients compared with healthy controls, whereas a reduction in the volume of gray matter in the anterior fusiform was found only for schizophrenia patients. For the parahippocampal gyrus and the middle and inferior temporal gyri, as predicted, we found no significant reductions in gray matter in either disorder.

This study generally supports previous MRI findings that the gray matter volume of the total fusiform gyrus was reduced bilaterally in schizophrenia patients (Lee et al., 2002; Onitsuka et al., 2003) but not significantly reduced in schizotypal subjects (Dickey et al., 2003b). When the fusiform gyrus was divided into anterior and posterior regions, however, the schizotypal disorder patients showed a significant reduction in volume for the posterior region. Although the functional topography within the fusiform gyrus remains controversial, a particular region within the posterior fusiform gyrus, which is referred to as the "fusiform face area" (Halgren et al., 1999; Kanwisher et al., 1997), is speculated to constitute a core system for the visual analysis of faces along with the posterior superior temporal sulcus region (caudal STG) (Haxby et al., 2000, 2002). It has been shown that first-degree relatives of schizophrenia (Calkins et al., 2005; Conklin et al., 2002; Loughland et al., 2004) or schizotypal individuals (Mikhailova et al., 1996; Poreh et al., 1994) show impairments in face recognition similar to those seen in schizophrenia, suggesting that poor face recognition is associated with the genetic diathesis for schizophrenia. Interestingly, previous MRI studies by our group showed that the volumes of the caudal STG and the amygdala, which play a central role in social cognition associated with face processing (Haxby et al., 2000, 2002), were reduced to the same degree in schizotypal patients as in schizophrenia patients (Suzuki et al., 2005b; Takahashi et al., 2006). Although additional evidence is clearly required to confirm the relationships between regional brain changes and the broad range of neuropsychological deficits in schizophrenia spectrum disorders, it is possible that the observed morphologic changes in regions of the brain involved in the sociality-related neural network especially for face recognition might represent an underlying neurobiological vulnerability to schizophrenia.

On the other hand, we did not find volumetric changes in the anterior fusiform gyrus for schizotypal patients, suggesting that the neuroanatomical abnormalities in this region may be at least in part associated with the development of full-blown schizophrenia. Indeed, Onitsuka et al. (2003) demonstrated that volume reduction of the anterior fusiform gyrus underlie poor delayed memory for faces in schizophrenia, and Hudson and Grace (2000) reported a patient with discrete ischemic lesion in right anterior fusiform gyrus who subsequently developed delusional misidentification syndrome. Although its functional significance is less

well known, the anterior fusiform gyrus might be involved in memory encoding of facial features (George et al., 1999; Kuskowski and Pardo, 1999), which is under the executive control of the prefrontal cortex (Hasegawa et al., 1998; Tomita et al., 1999). As discussed elsewhere (Suzuki et al., 2005b), the schizotypal subjects could be protected from overt psychosis or severe cognitive/social deficits by the increased prefrontal cortical compensatory capacities for the temporal lobe dysfunctions, which presumably constitute a primary abnormality in schizophrenia spectrum (Siever and Davis, 2004). Taken these notions together, the present findings might imply that widespread involvement of the fusiform gyrus including the anterior region could further contribute to the severe cognitive and social deficits in schizophrenia. The possible relevance of the anterior fusiform gyrus abnormalities to the pathophysiology of the schizophrenia spectrum seems worthy of further examination.

Our findings of the absence of changes in the volume of gray matter in the parahippocampal gyrus, middle temporal gyrus, and the inferior temporal gyrus in either schizophrenia or schizotypal disorder patients suggest that morphologic changes within the temporal lobe gray matter in the schizophrenia spectrum are localized to the STG (Takahashi et al., 2006), amygdala/hippocampus (Suzuki et al., 2005b), and fusiform gyrus. These findings are largely consistent with previous observations using VBM, which is useful for investigating the distribution of multiple structural brain changes, in both schizophrenia (see Honea et al., 2005 for review; Suzuki et al., 2002) and schizotypal disorder (Kawasaki et al., 2004) patients. On the other hand, many but not all volumetric MRI studies have found a volume reduction in the parahippocampal gyrus in schizophrenia (reviewed by Shenton et al., 2001). There has been only a single volumetric MRI study for the middle or inferior temporal gyrus in schizophrenia (Onitsuka et al., 2004), where reductions in the volume of gray matter in the left middle temporal gyrus and bilateral inferior temporal gyrus were found in male chronically medicated patients. However, further studies especially in both male and female patients without sustained neuroleptic treatment or chronic psychosis would be required to generalize their findings. The involvement of the temporal lobe structures in schizotypal subjects has been also controversial. Contrary to the findings of our group, a preserved volume in the hippocampus and amygdala was reported in male neuroleptic-naïve subjects with schizotypal personality disorder (SPD) recruited from the community (Dickey et al., 1999). Decreased STG volume was observed in male but not female SPD subjects (Dickey et al., 1999, 2003a). A study on clinic-based SPD patients showed a smaller temporal lobe but the volume difference was more pronounced in the non-STG region, i.e. the medial temporal lobe and/or the middle and inferior temporal gyri (Downhill et al., 2001). Some of these inconsistencies between reports could be explained by differences in sample characteristics as discussed elsewhere (Takahashi et al., 2005) or in the tracing methodologies. The differences in medication status among the reports might also be an important consideration (Dazzan et al., 2005; Keshavan et al., 1998; Lieberman et al., 2005). Despite these inconsistencies, taking together the present and previous brain morphologic findings and cognitive characteristics in schizotypal subjects (Kurachi, 2003a,b; Siever and Davis, 2004) as well as the morphologic findings in family members of schizophrenia patients (Lawrie et al., 1999; Seidman et al., 2002; Van Erp et al., 2002), the extent of pathology in the medial temporal regions, the STG, and possibly the posterior fusiform gyrus may account for the degree of vulnerability to schizophrenia.

Some limitations of this study should be taken into account. First, the difference in medication status between the schizophrenia and schizotypal patients might have affected the volumetric results. Actually, the significant effect of diagnosis for the anterior fusiform gyrus in this study was reduced to the trend level when covarying for the medication dosage at the time of scanning. However, daily dosage or duration of neuroleptic medication did not correlate with the volumetric measurements for any region. In addition, the effects of medication alone could not explain the localized volume reduction of the fusiform gyrus for its posterior but not anterior region in schizotypal disorder patients. Second, the control subjects in this study were not selected to be educationally equivalent to the patients with both disorders. However, we optimally matched the parental education among the three groups according to the notion that matching on the basis of the educational level of the parents may reduce confounding factors in selection of control groups when brain measures are studied (Andreasen et al., 1990). In addition to these limitations, our cohort may have included schizotypal subjects who were more severely ill than SPD individuals among the general population and the possibility cannot be excluded that some of our schizotypal subjects later develop overt psychosis. Thus, an even longer clinical follow-up would be required.

In summary, the present findings demonstrated that, in conjunction with our previous observations,

morphologic changes of the temporal lobe gray matter in the schizophrenia spectrum are localized to the STG, amygdala/hippocampus, and fusiform gyrus. Our findings also suggest abnormalities in the posterior region of the fusiform gyrus to be a common morphologic substrate for the schizophrenia spectrum, whereas more widespread alterations involving the anterior region might be associated with the development of full-blown schizophrenia.

Acknowledgements

This study was supported in part by a Grant-in-aid for Young Scientists 16790678 from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a Research Grant (11-3) for Nervous and Mental Disorders from the Ministry of Health and Welfare, Japan.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. American Psychiatric Association Press, Washington, DC.

Andreasen, N.C., 1984a. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa, Iowa City, IA.

Andreasen, N.C., 1984b. The Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa, Iowa City, IA.

Andreasen, N.C., Ehrhardt, J.C., Swayze II, V.W., Alliger, R.J., Yuh, W.T., Cohen, G., Ziebell, S., 1990. Magnetic resonance imaging of the brain in schizophrenia: the pathophysiologic significance of structural abnormalities. Archives of General Psychiatry 47, 35–45.

Andreasen, N.C., Flaum, M., Arndt, S., 1992. The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. Archives of General Psychiatry 49, 615–623.

Calkins, M.E., Gur, R.C., Ragland, J.D., Gur, R.E., 2005. Face recognition memory deficits and visual object memory performance in patients with schizophrenia and their relatives. American Journal of Psychiatry 162, 1963–1966.

Conklin, H.M., Calkins, M.E., Anderson, C.W., Dinzeo, T.J., Iacono, W.G., 2002. Recognition memory for faces in schizophrenia patients and their first-degree relatives. Neuropsychologia 40, 2314–2324.

Dazzan, P., Morgan, K.D., Orr, K., Hutchinson, G., Chitnis, X., Suckling, J., Fearon, P., McGuire, P.K., Mallett, R.M., Jones, P.B., Leff, J., Murray, R.M., 2005. Different effects of typical and atypical antipsychotics on grey matter in first episode psychosis: the AESOP study. Neuropsychopharmacology 30, 765–774.

Dickey, C.C., McCarley, R.W., Voglmaier, M.M., Niznikiewicz, M.A., Seidman, L.J., Hirayasu, Y., Fischer, I., Teh, E.K., Van Rhoads, R., Jakab, M., Kikinis, R., Jolesz, F.A., Shenton, M.E., 1999. Schizotypal personality disorder and MRI abnormalities of temporal lobe gray matter. Biological Psychiatry 45, 1393–1402.

Dickey, C.C., McCarley, R.W., Shenton, M.E., 2002. The brain in schizotypal personality disorder: a review of structural MRI and CT findings. Harvard Review of Psychiatry 10, 1–15.

Dickey, C.C., McCarley, R.W., Voglmaier, M.M., Niznikiewicz, M.A., Seidman, L.J., Demeo, S., Frumin, M., Shenton, M.E., 2003a. An MRI study of superior temporal gyrus volume in women with schizotypal personality disorder. American Journal of Psychiatry 160, 2198–2201.

Dickey, C.C., McCarley, R.W., Voglmaier, M.M., Niznikiewicz, M.A., Seidman, L.J., Frumin, M., Toner, S., Demeo, S., Shenton, M.E., 2003b. A MRI study of fusiform gyrus in schizotypal personality disorder. Schizophrenia Research 64, 35–39.

Downhill Jr., J.E., Buchsbaum, M.S., Hazlett, E.A., Barth, S., Lees Roitman, S., Nunn, M., Lekarev, O., Wei, T., Shihabuddin, L., Mitropoulou, V., Silverman, J., Siever, L.J., 2001. Temporal lobe volume determined by magnetic resonance imaging in schizotypal personality disorder and schizophrenia. Schizophrenia Research 48, 187–199.

George, N., Dolan, R.J., Fink, G.R., Baylis, G.C., Russell, C., Driver, J., 1999. Contrast polarity and face recognition in the human fusiform gyrus. Nature Neuroscience 2, 574–580.

Grill-Spector, K., Knouf, N., Kanwisher, N., 2004. The fusiform face area subserves face perception, not generic within-category identification. Nature Neuroscience 7, 555–562.

Halgren, E., Dale, A.M., Sereno, M.I., Tootell, R.B., Marinkovic, K., Rosen, B.R., 1999. Location of human face-selective cortex with respect to retinotopic areas. Human Brain Mapping 7, 29–37.

Hasegawa, I., Fukushima, T., Ihara, T., Miyashita, Y., 1998. Callosal window between prefrontal cortices: cognitive interaction to retrieve long-term memory. Science 281, 814–818.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2000. The distributed human neural system for face perception. Trends in Cognitive Sciences 4, 223–233.

Haxby, J.V., Hoffman, E.A., Gobbini, M.I., 2002. Human neural systems for face recognition and social communication. Biological Psychiatry 51, 59–67.

Hickok, G., Poeppel, D., 2004. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition 92, 67–99.

Honea, R., Crow, T.J., Passingham, D., Mackay, C.E., 2005. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. American Journal of Psychiatry 162, 2233–2245.

Hudson, A.J., Grace, G.M., 2000. Misidentification syndromes related to face specific area in the fusiform gyrus. Journal of Neurology, Neurosurgery and Psychiatry 69, 645–648.

Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. Journal of Neuroscience 17, 4302–4311.

Kawasaki, Y., Suzuki, M., Nohara, S., Hagino, H., Matsui, M., Yamashita, I., Takahashi, T., Chitnis, X., McGuire, P.K., Seto, H., Kurachi, M., 2004. Structural brain differences in patients with schizotypal disorder and schizophrenia demonstrated by voxel-based morphometry. European Archives of Psychiatry and Clinical Neuroscience 254, 406–414.

Keshavan, M.S., Haas, G.L., Kahn, C.E., Aguilar, E., Dick, E.L., Schooler, N.R., Sweeney, J.A., Pettegrew, J.W., 1998. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? Journal of Psychiatric Research 32, 161–167.

Kim, J.J., Crespo-Facorro, B., Andreasen, N.C., O'Leary, D.S., Zhang, B., Harris, G., Magnotta, V.A., 2000. An MRI-based parcellation method for the temporal lobe. Neuroimage 11, 271–288.

Kurachi, M., 2003a. Pathogenesis of schizophrenia: Part I. Symptomatology, cognitive characteristics and brain morphology. Psychiatry and Clinical Neurosciences 57, 3–8.

Kurachi, M., 2003b. Pathogenesis of schizophrenia: Part II. Tempolofrontal two-step hypothesis. Psychiatry and Clinical Neurosciences 57, 9–16.

Kuskowski, M.A., Pardo, J.V., 1999. The role of the fusiform gyrus in successful encoding of face stimuli. Neuroimage 9, 599–610.

Lawrie, S.M., Whalley, H., Kestelman, J.N., Abukmeil, S.S., Byrne, M., Hodges, A., Rimmington, J.E., Best, J.J., Owens, D.G., Johnstone, E.C., 1999. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. Lancet 353, 30–33.

Lee, C.U., Shenton, M.E., Salisbury, D.F., Kasai, K., Onitsuka, T., Dickey, C.C., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2002. Fusiform gyrus volume reduction in first-episode schizophrenia: a magnetic resonance imaging study. Archives of General Psychiatry 59, 775–781.

Lieberman, J.A., Tollefson, G.D., Charles, C., Zipursky, R., Sharma, T., Kahn, R.S., Keefe, R.S., Green, A.I., Gur, R.E., McEvoy, J., Perkins, D., Hamer, R.M., Gu, H., Tohen, M., HGDH Study Group, 2005. Antipsychotic drug effects on brain morphology in first-episode psychosis. Archives of General Psychiatry 62, 361–370.

Loughland, C.M., Williams, L.M., Harris, A.W., 2004. Visual scanpath dysfunction in first-degree relatives of schizophrenia probands: evidence for a vulnerability marker? Schizophrenia Research 67, 11–21.

Martin, F., Baudouin, J.Y., Tiberghien, G., Franck, N., 2005. Processing emotional expression and facial identity in schizophrenia. Psychiatry Research 134, 43–53.

McDonald, B., Highley, J.R., Walker, M.A., Herron, B.M., Cooper, S.J., Esiri, M.M., Crow, T.J., 2000. Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: a postmortem study. American Journal of Psychiatry 157, 40–47.

Mikhailova, E.S., Vladimirova, T.V., Iznak, A.F., Tsusulkovskaya, E.J., Sushko, N.V., 1996. Abnormal recognition of facial expression of emotions in depressed patients with major depression disorder and schizotypal personality disorder. Biological Psychiatry 40, 697–705.

Niu, L., Matsui, M., Zhou, S.-Y., Hagino, H., Takahashi, T., Yoneyama, E., Kawasaki, Y., Suzuki, M., Seto, H., Ono, T., Kurachi, M., 2004. Volume reduction of the amygdala in patients with schizophrenia: a magnetic resonance imaging study. Psychiatry Research. Neuroimaging 132, 41–51 (Erratum in: Psychiatry Research. Neuroimaging 132, 291).

Onitsuka, T., Shenton, M.E., Kasai, K., Nestor, P.G., Toner, S. K., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003. Fusiform gyrus volume reduction and facial recognition in chronic schizophrenia. Archives of General Psychiatry 60, 349–355.

Onitsuka, T., Shenton, M.E., Salisbury, D.F., Dickey, C.C., Kasai, K., Toner, S.K., Frumin, M., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2004. Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. American Journal of Psychiatry 161, 1603–1611.

Poreh, A.M., Whitman, R.D., Weber, M., Ross, T., 1994. Facial recognition in hypothetically schizotypic college students. The role of generalized poor performance. Journal of Nervous and Mental Disease 182, 503–507.

Sachs, G., Steger-Wuchse, D., Kryspin-Exner, I., Gur, R.C., Katschnig, H., 2004. Facial recognition deficits and cognition in schizophrenia. Schizophrenia Research 68, 27–35.

Seidman, L.J., Faraone, S.V., Goldstein, J.M., Kremen, W.S., Horton, N.J., Makris, N., Toomey, R., Kennedy, D., Caviness, V.S., Tsuang, M.T., 2002. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Archives of General Psychiatry 59, 839–849.

Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophrenia Research 49, 1–52.

Siever, L.J., Kalus, O.F., Keefe, R.S.E., 1993. The boundaries of schizophrenia. Psychiatric Clinics of North America 16, 217–244.

Siever, L.J., Davis, K.L., 2004. The pathophysiology of schizophrenia disorders: perspective from the spectrum. American Journal of Psychiatry 161, 398–413.

Suzuki, M., Nohara, S., Hagino, H., Kurokawa, K., Yotsutsuji, T., Kawasaki, Y., Takahashi, T., Matsui, M., Watanabe, N., Seto, H., Kurachi, M., 2002. Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. Schizophrenia Research 55, 41–54.

Suzuki, M., Zhou, S.-Y., Hagino, H., Takahashi, T., Kawasaki, Y., Nohara, S., Yamashita, I., Matsui, M., Seto, H., Kurachi, M., 2004. Volume reduction of the right anterior limb of the internal capsule in patients with schizotypal disorder. Psychiatry Research. Neuroimaging 130, 213–225.

Suzuki, M., Zhou, S.-Y., Hagino, H., Niu, L., Takahashi, T., Kawasaki, Y., Matsui, M., Seto, H., Ono, T., Kurachi, M., 2005a. Morphological brain changes associated with Schneider's first-rank symptoms in schizophrenia: an MRI study. Psychological Medicine 35, 549–560.

Suzuki, M., Zhou, S.-Y., Takahashi, T., Hagino, H., Kawasaki, Y., Niu, L., Matsui, M., Seto, H., Kurachi, M., 2005b. Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. Brain 128, 2109–2122.

Takahashi, T., Kawasaki, Y., Kurokawa, K., Hagino, H., Nohara, S., Yamashita, I., Nakamura, K., Murata, M., Matsui, M., Suzuki, M., Seto, H., Kurachi, M., 2002. Lack of normal structural asymmetry of the anterior cingulate gyrus in female patients with schizophrenia: a volumetric magnetic resonance imaging study. Schizophrenia Research 55, 69–81.

Takahashi, T., Suzuki, M., Zhou, S.-Y., Hagino, H., Tanino, R., Kawasaki, Y., Nohara, S., Yamashita, I., Seto, H., Kurachi, M., 2005. Volumetric MRI study of the short and long insular cortices in schizophrenia spectrum disorders. Psychiatry Research. Neuroimaging 138, 209–220.

Takahashi, T., Suzuki, M., Zhou, S.-Y., Tanino, R., Hagino, H., Kawasaki, Y., Matsui, M., Seto, H., Kurachi, M., 2006. Morphologic alterations of the parcellated superior temporal gyrus in schizophrenia spectrum. Schizophrenia Research 83, 131–143.

Tomita, H., Ohbayashi, M., Nakahara, K., Hasegawa, I., Miyashita, Y., 1999. Top-down signal from prefrontal cortex in executive control of memory retrieval. Nature 401, 699–703.

Toru, M., 2001. Psychotropic Manual, Second edition. IGAKU-SHOIN, Tokyo. (in Japanese).

Van Erp, T.G., Saleh, P.A., Rosso, I.M., Huttunen, M., Lonnqvist, J., Pirkola, T., Salonen, O., Valanne, L., Poutanen, V.P., Standertskjold-Nordenstam, C.G., Cannon, T.D., 2002. Contributions of genetic risk and fetal hypoxia to hippocampal volume in patients with schizophrenia or schizoaffective disorder, their unaffected siblings, and healthy unrelated volunteers. American Journal of Psychiatry 159, 1514–1520.

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

World Health Organization, 1993. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. World Health Organization, Geneva.

Zhou, S.-Y., Suzuki, M., Hagino, H., Takahashi, T., Kawasaki, Y., Nohara, S., Yamashita, I., Seto, H., Kurachi, M., 2003. Decreased volume and increased asymmetry of the anterior limb of the internal capsule in patients with schizophrenia. Biological Psychiatry 54, 427–436.

Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research 143 (2006) 179–187
PSYCHIATRY RESEARCH
www.elsevier.com/locate/psychres

Impairment of event schema in patients with schizophrenia: Examination of script for shopping at supermarket

Mié Matsui [a,b,*], Tomiki Sumiyoshi [a,b], Hiromi Yuuki [a], Kanade Kato [a], Masayoshi Kurachi [a,b]

[a] *Department of Neuropsychology and Neuropsychiatry, School of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama, 930-0194, Japan*
[b] *Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation, Tokyo, Japan*

Received 9 February 2005; received in revised form 31 August 2005; accepted 18 September 2005

Abstract

The purpose of this study was to examine event schema, the conceptualization of past experience based on script theory, in Japanese patients with schizophrenia. Subjects comprised 25 patients meeting DSM-IV criteria for schizophrenia and 31 normal individuals who gave informed consent. This experiment used three script tasks measuring free recall, frequency judgment, and sequencing of events encountered when shopping at a supermarket. Patients with schizophrenia performed significantly worse than did control subjects on all tasks. In particular, patients committed more errors when judging the events that "occasionally happen" in the frequency judgment task. On the other hand, these patients judged "seldom occurring events" relatively well. Patients with schizophrenia made more errors than normal people in the free recall task. Specifically, patients made more intrusion errors and failed to close scripts. There was a negative correlation between scores on the Scale for the Assessment of Positive Symptoms and performance on the free recall task. The results of the present study suggest that event schemas (semantic structure) in patients with schizophrenia are impaired, which may be associated with positive symptoms and frontal lobe dysfunction.

Keywords: Schizophrenia; Semantic memory; Script; Event schema; Positive symptoms; Frontal function

1. Introduction

Neuropsychological functions such as attention, memory, learning, motor, perception, special cognition and language are disturbed in patients with schizophrenia (Saykin et al., 1991; Heinrichs and Zakzanis, 1998; Matsui et al., 2004). Specifically, a number of

* Corresponding author. Department of Neuropsychology and Neuropsychiatry, School of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama, 930-0194, Japan. Tel.: +81 76 434 7448; fax: +81 76 434 5005.
E-mail address: mmatsui@ms.toyama-mpu.ac.jp (M. Matsui).

0165-1781/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2005.09.006

studies have reported memory impairment in patients with schizophrenia (e.g. Saykin et al., 1991; Matsui et al., 2004). While most of these studies have examined episodic memory (Cirillo and Seidman, 2003), others have focused on semantic memory (McKay et al., 1996; Paulsen et al., 1996; Chan et al., 1999; Sumiyoshi et al., 2001). We previously reported that impairment of memory organization is a cardinal feature of memory disturbances in patients with schizophrenia, and indicated its biological basis (Nohara et al., 2000). Accordingly, Sumiyoshi et al. (2001) demonstrated disorganization of semantic structure in subjects with schizophrenia by analyzing data from the category fluency task, a measure of verbal fluency. Chan et al. (1999) showed that semantic organization of events in schizophrenia was impaired using the script task as a measure of semantic knowledge.

Patients with schizophrenia suffer from disabilities in social functioning; however, studies of social cognition have been relatively scarce compared with those of other domains of cognitive functions. Corrigan et al. (1992) and Corrigan and Addis (1995) used the script tasks (they called them "social sequencing tasks") to measure social dysfunction associated with schizophrenia, and found that patients with schizophrenia were significantly less able to temporally sequence component actions of social situations than normal controls. The scripts have been described as a schema-like representation of knowledge composed of a personally or socially relevant/typical sequence of events (Schank and Abelson, 1977). Namely, schemas are knowledge macrostructures that are used by people to understand the causal relations and context of real-world objects and events. Scripts are a simple form of schema, composed of goal-oriented sequences of events that typically occur in a specific order. Hence, scripts may be viewed as templates through which incoming social information is encoded and blueprints by which social behaviors are guided. The absence of the appropriate scripts may result in the selection of inadequate or inappropriate social responses. There have been a few studies using script tasks. Helmes and Bush (2004) examined effects of age and gender on performance on several kinds of script tasks in normal people, and found that effects vary depending on type of scripts. Sirigu et al. (1995, 1996) reported impairments in script information processing in patients with frontal lobe lesions. Specifically, these patients made errors in ordering actions in a correct temporal sequence, and failed to close scripts and remain within the stated boundaries. These observations suggest that the frontal lobe is involved in the processing of some aspects of script knowledge, particularly temporal ordering of events and the ability to discard irrelevant events that do not fit within the internal structure of a script.

The first purpose of this study was to examine how patients with schizophrenia perform on a Japanese version of script tasks. In the present study, we used three tasks, i.e. free recall, frequency judgment, and sequencing. For frequency judgment, script events in the schema of shopping at a supermarket were used. This was a modification of the method of Chan et al. (1999), who used events for dining at restaurants. If disorganization of the structure of semantic knowledge is a prominent feature of schizophrenia, performance on these script tasks would be impaired. By contrast, if patients only showed impairment on the free recall task, which demands effortful retrieval, memory retrieval and/or low motivation would be likely to account for poor performance. According to Chan et al. (1999), the former is predicted in patients with schizophrenia. In addition, patients with schizophrenia are expected to perform worse on middle frequent events, rather than prominent ones, of the frequency judgment based on Chan et al. (1999).

Previous neuropsychological studies (Heinrichs and Zakzanis, 1998) as well as brain-imaging studies (Hill et al., 2004) have provided evidence that patients with schizophrenia demonstrate dysfunction related to the frontal lobes. Therefore, patients with schizophrenia would be expected to commit errors on the script tasks in a manner similar to those of patients with frontal lobe lesions. Sirigu et al. (1995, 1996) showed patients with frontal lobe lesions made more closure errors and more out-of-sequence errors on the script tasks than normal subjects or patients with lesions of the posterior part of the brain. We sought to determine the type of errors on the script tasks according to Sirigu et al. (1995, 1996), which was the second goal of this study.

The third goal of the study was to determine whether deficits in the script tasks are associated with positive and/or negative symptoms of schizophrenia. Liddle et al. (1992) proposed that negative

symptoms, such as psychomotor poverty syndrome, are related to internal generation of words, while the reality distortion syndrome, a component of hallucinations and delusions, is associated with internal monitoring. Semantic knowledge structure may be related to the thinking process or how the world is perceived. Thus, an abnormality of semantic knowledge structure would be expected to be associated with positive symptoms, such as hallucinations and delusions, since these symptoms are supposed to reflect aberrations of thinking or perception.

The above considerations led us to test the following hypotheses: 1) patients with schizophrenia would perform poorly on the script tasks with various levels of difficulty, i.e. free recall, frequency judgment, and sequencing due to impairment of semantic memory structure; 2) patients would commit more errors on judging the events that sometimes happen (middle frequency events) in the frequency judgment task than normal controls; 3) patients would commit more errors in the free recall task, a finding reported in patients with frontal lobe lesions as well; and 4) there would be a correlation between performance on the script tasks and positive symptoms.

2. Methods

2.1. Subjects

Subjects for this study consisted of 25 patients (16 males and 9 females) meeting DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994) and 31 normal controls (20 males and 11 females). The patients were recruited from the outpatient clinic of the Toyama Medical and Pharmaceutical University Hospital. All available clinical information and data were obtained from a structured clinical interview using the Comprehensive Assessment of Symptoms and History (CASH, Andreasen et al., 1992). Subjects were diagnosed by a consensus of at least two experienced psychiatrists based on these data. Whenever possible, the patient's family was interviewed by psychiatrists to provide additional information. The two groups were matched on gender and age. The mean ages of patients with schizophrenia and normal controls were 34.1 years (S.D.=8.3, range=17–56 years) and 31.0 years (S.D.=10.7, range=22–56 years), respectively ($t_{54}=1.19$, $P=0.240$, NS). The patients and normal controls had premorbid estimated IQ of 100.6 (S.D.=14.5) and 105.2 (S.D.=10.6), respectively, as assessed by the Japanese Adult Reading Test (JART). The mean duration of illness of patients was 9.8 years (S.D.=7.4, range=0.1–27 years). Twenty patients were on neuroleptic medication. The mean daily haloperidol-equivalent dose was 3.6 mg (S.D.=4.4, range=0–17.7 mg). Five patients were neuroleptic-naive. Clinical symptoms were rated using the Scale for the Assessment of Positive Symptoms (SAPS, Andreasen, 1984) and the Scale for the Assessment of Negative Symptoms (SANS, Andreasen, 1983). The SAPS includes four symptom factors (hallucinations, delusions, bizarre behavior, and positive formal thought disorder), and the SANS consists of five symptom factors (affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attention). The CASH and the SAPS/SANS were administered by psychiatrists or well-trained clinical psychologists. Interrater reliability was >0.80.

The age- and gender-matched control subjects consisted of 31 healthy volunteers recruited from the hospital staff, university students, and community volunteers. Subjects were excluded if they had a history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, or substance abuse. None of the control subjects were receiving pharmacological treatment for medical illnesses. Candidates were excluded if they had any personal or family history of psychiatric illness. The healthy control group was also screened for a history of psychiatric disorders in their first-degree relatives. All the patients and control subjects were right-handed.

After the purpose and procedures of the study had been fully explained, written informed consent was obtained from the subjects. This study was approved by the Committee on Medical Ethics of Toyama Medical and Pharmaceutical University.

2.2. Procedures

The script test consisted of three tasks. In the free recall task, subjects recalled a typical scenario of shopping at a supermarket. In the frequency judgment task, subjects determined whether the given events happen frequently, occasionally, or rarely in a supermarket based on a previous Japanese source (Kawa-

saki, 1980; Sakane et al., 1981). In the sequencing task, subjects put the randomly presented events in the correct order. The administration of the script tasks was based on the methods for the script of dining at restaurants reported by Chan et al. (1999).

Each subject was tested in a quiet room. The tasks were administered in a fixed order. The free recall task was administered first. Subjects were given 10 min to generate a detailed list of the things that typically happen, in the right order, when shopping in a supermarket. Subjects were also instructed that the script's starting point was "Enter the supermarket" and the ending point was "Left the supermarket". The responses of the subject were tape-recorded for transcription and were analyzed at a later time.

After the free recall task, the frequency judgment task was administered. In this task, the subjects were shown the following 16 events written on a sheet.

High frequency: Enter the supermarket, Hold the basket, Put items in the basket, Stay in line at a checkout counter, Pay the bill, Put the items in a bag, Return the basket, Leave the supermarket.
Middle frequency: Meet a neighbor, Taste on the suggestion by a salesman, Clerk takes a wrong register, Drop an item on the floor.
Low frequency: Turn off the light, Do her washing, Drive a car, Change her clothes.

The first eight items, according to the data reported by Kawasaki (1980) and Sakane et al. (1981), represent the events that usually or always happen when an individual goes to a supermarket (high frequency items). The 9th to 16th items represent unusual events with four infrequent (middle frequency items) and four improbable events (low frequency items). The events were presented in a fixed random order, and subjects were told to judge whether each event happens always, occasionally, or rarely when they shop at a supermarket. A letter size card with the instructions and the three choices of answers was placed in front of subjects. No feedback was given during the task. The total number of times subjects correctly judged the frequency of the events was counted at the end of the task.

In the sequencing task, the eight typical events mentioned above were presented again. Examiners put the cards on the table in a fixed random order, and the subjects were asked to put the cards in the right order. The response of the subject was recorded without giving any feedback. A subject gained one point for correctly putting a pair of adjacent events together, for a possible total score of seven.

2.3. Data analysis

The following parameters of performance were scored under three levels of the script tasks. Parameters (1) to (3) represent the basic measures for each task. Parameters (4) to (6) describe the rate of correct response at each frequency level in the frequency judgment task. Parameters (7) to (9) were for error analysis on the free recall task, based on Sirigu et al. (1995).

(1) For the number of high frequency events generated in the free recall task, each correct high frequency item receives a score of 1, for a total maximum score of 8.
(2) For rate of correct answers in the frequency judgment task, each correct response receives a score of 1, for a total maximum score of 16.
(3) For rate of correct sequencing in the sequencing task, each correctly sequenced pair receives a score of 1, for a total maximum score of 7.
(4) For rate of correct answers of the high frequency items in the frequency judgment task, each correct response receives a score of 1, for a total maximum score of 8.
(5) For rate of correct answers of the middle frequency items in the frequency judgment task, each correct response receives a score of 1, for a total maximum score of 4.
(6) For rate of correct answers of the low frequency items in the frequency judgment task, each correct response receives a score of 1, for a total maximum score of 4.
(7) Total number of closures: it included violations of script rules.
Early closure: script stops short of the stated end point.
Late closure: script extends beyond the stated end point.
(8) Total number of intrusions; the number of generated events that does not belong to the script.
(9) Total number of out-of-sequence events; the number of out-of-sequence events in free recall.

2.4. Statistical analysis

(1) Script performance was analyzed using repeated measures analysis of variance (ANOVA), with Group (patients, controls) as the between-subject factor, and Task (Free recall, Frequency judgment, Sequencing) as the within-subject factor. Post-hoc Tukey's tests were conducted to follow up the significant main effects or interactions.
(2) Performance on the frequency judgment task was analyzed using repeated measures ANOVA, with Group (patients, controls) as the between-subject factor, and Level of Frequency (high frequency, middle frequency, low frequency) as the within-subject factor. Post-hoc Tukey's tests were conducted to follow up the significant main effects or interactions.
(3) For parameters (7) to (9), Fisher's exact test was used to compare the frequency of error patterns in the free recall task between patients and controls. Because most subjects did not commit errors for these parameters, it was appropriate to dichotomize the subjects according to the presence or absence of errors.
(4) Correlations between psychopathology measures and script performance were determined using the Spearman rank correlation test. For each script task, significance was considered at the $P<0.006$ level in the total patient cohort, so that findings would remain significant if they were judged against a Bonferroni adjustment of $P<0.05$ for multiple correlations. Patients were divided into two groups according to whether they committed errors or not, and psychopathology scores were compared using two-tailed t-tests. To determine the effect of age, duration of illness, drug dose, or IQ on script performance, Spearman rank correlation coefficients were used for patients with schizophrenia.

3. Results

3.1. Effect of task

Patients with schizophrenia performed significantly worse than control subjects on the script tasks (main effect of Group: $F_{1,\ 54}=33.65$, $P<0.0001$). There was also a main effect of Task ($F_{2,\ 108}=21.50$, $P<0.0001$). Thus, the rates of correct answers were in the order of Sequencing>Frequency>Free recall, irrespective of Group (patients, controls). There was no significant interaction between Group and Task ($F_{2,\ 108}=0.84$, $P=0.43$).

3.2. Effect of frequency level

The results of ANOVA on the frequency judgment task showed a significant main effect of Group ($F_{1,\ 54}=35.59$, $P<0.0001$). There was no significant main effect of level of frequency ($F_{2,\ 108}=0.82$, $P=0.45$). Post-hoc Tukey's tests showed that performance of patients with schizophrenia was significantly worse than that of control subjects in the high ($P=0.007$) and middle ($P=0.0002$) frequency judgments, but not the low frequency judgment ($P=0.43$).

3.3. Frequency of error pattern in the free recall task

Eight out of 25 patients (32%) committed closure errors, while one of 31 normal controls (3.2%) did (Fisher's exact test, $P<0.005$).

Thirteen out of 25 patients (52%) and 1 of 31 controls (3.2%) made intrusion errors. A signifi-

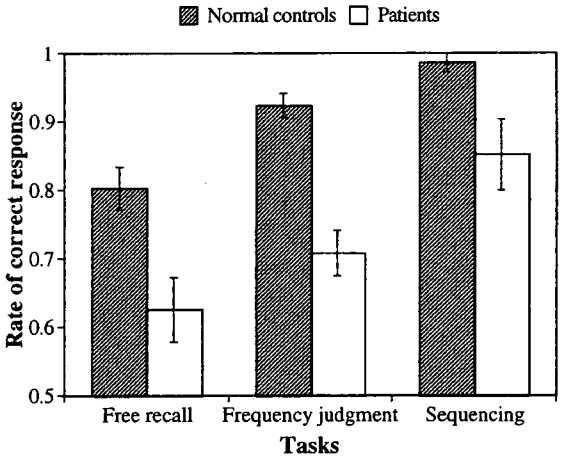

Fig. 1. Rate of correct response in the script tasks. Two-factor ANOVA revealed a significant main effect of Group ($F_{1,\ 54}=33.65$, $P<0.0001$; schizophrenia<normal controls) and a significant main effect of Task ($F_{2,\ 108}=21.50$, $P<0.0001$; Sequencing>Frequency>Free recall), but no significant Group by Task interaction ($F_{2,\ 108}=0.84$, $P=0.43$).

cant difference was found between patients and controls for the intrusion errors (Fisher's exact test, $P<0.0001$).

Three out of 25 patients (12%) made out-of-sequence errors, while no such error was observed in normal controls; the difference did not reach statistical significance.

3.4. Relationship between clinical symptoms and script performance

Significant negative correlations were found between performance on the free recall task and the SAPS total score ($\rho=-.55$, $P<0.006$), but not the SANS total score ($\rho=-32$, $P=0.119$). Specifically, there were significant negative correlations between free recall performance vs. Hallucinations ($\rho=-.60$, $P<0.006$) and Delusions ($\rho=-.59$, $P<0.006$) subscale scores. There was no significant correlation between free recall performance and any other subscale scores (Bizarre Behavior $\rho=-0.19$, $P=0.352$; Positive Formal Thought Disorder $\rho=-0.26$, $P=0.210$; Affective Flattening $\rho=-0.23$, $P=0.265$; Alogia $\rho=-0.10$, $P=0.629$; Avolition-Apathy $\rho=-0.36$, $P=0.073$; Anhedonia-Asociality $\rho=-0.19$, $P=0.354$; Attention $\rho=-0.39$, $P=0.057$). Neither performance on the frequency judgment task (SAPS $\rho=0.03$, $P=0.877$; SANS $\rho=0.03$, $P=0.889$) nor that on the sequencing task (SAPS $\rho=-0.16$, $P=0.439$; SANS $\rho=-0.13$, $P=0.525$) was significantly correlated with any of the psychopathology measures.

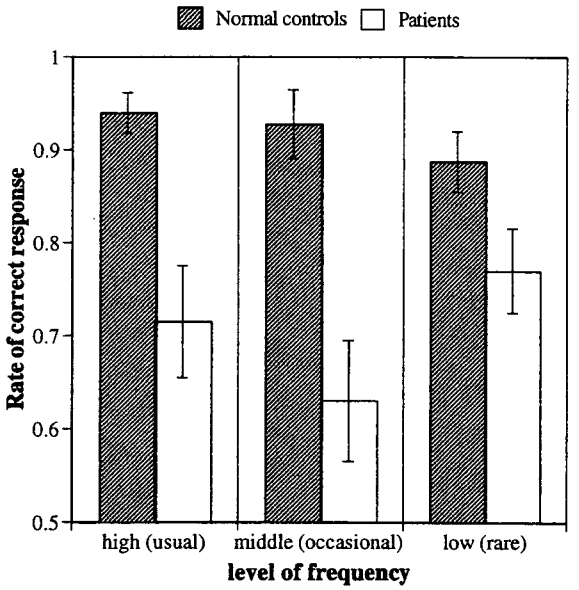

Fig. 2. Rate of correct response in the judgment of frequency task. Two-factor ANOVA revealed a significant main effect of Group (patients, controls; $F_{1,\ 54}=35.59$, $P<0.0001$), but no significant main effect of level of frequency (high frequency, middle frequency, low frequency; $F_{2,\ 108}=0.82$, $P=0.45$). Post-hoc Tukey's tests indicated patients with schizophrenia performed significantly worse than controls in the high ($P=0.007$) and middle ($P=0.0002$) frequency judgments, but not the low frequency judgment ($P=0.43$).

Patients who exhibited closure errors had significantly higher SAPS Delusions subscale scores than patients without closure errors ($t_{23}=2.43$, $P<0.02$). No such difference was noted for other psychopathology measures. There was also no significant difference in any of the SAPS or SANS subscale scores between patients with intrusion errors and those without. There was no significant difference in any of the SAPS or SANS subscale scores between patients with out-of-sequence errors and those without. There were no significant correlations between the rate of correct response vs. premorbid estimated IQ, age, duration of illness, or neuroleptic dose for any of the script tasks (Figs. 1 and, 2).

4. Discussion

The results of the present study suggest that event schema, as measured by script tasks show impairment, in patients with schizophrenia compared with healthy normal people. Further, we observed that the impairment is dependent on the difficulty of the tasks. These results confirm and extend the finding from previous studies on script tasks in patients with schizophrenia (Chan et al., 1999; Corrigan et al., 1992; Corrigan and Addis, 1995). Furthermore, there was an association between free recall performance and positive symptoms.

This study, using shopping scripts to measure semantic structure, yielded results similar to those reported by Chan et al. (1999), who administered the script of having a meal at a restaurant. On the other hand, Helmes and Bush (2004) used three sorts of scripts, i.e. "Bake a cake", "Change a tire", and "Shop for groceries" in normal people, and reported effects of age and sex on the first two scripts. They

suggested the effects of stereotypic familiarity in these scripts. The results of the present study are in agreement with those of Helmes and Bush (2004), who reported no sex difference for the shopping script.

The total number of out-of-sequence events in the free recall task did not differ between patients and control subjects, indicating a minimum semantic structure (event schema) is relatively preserved in patients with schizophrenia. On the other hand, patients with schizophrenia demonstrated intrusions and incoherent organization as assessed by the free recall task. This is consistent with Chan et al. (1999), who suggested a bottom-up impairment in semantic knowledge, with the overall, general event schema intact (as represented here by relatively good performance on the sequencing task and normal out-of-sequence scores), but impairments in the more specific components of the event schema (e.g. poverty of free recall, intrusions, and closures). These observations indicate poor performance on the free recall tasks most likely represents impairment of an aspect of the event schema rather than an inability to access the intact schematic structure. Evidence in support of this notion also comes from performance on the frequency judgment and sequencing tasks. These tasks require a less effortful retrieval ability compared with the free recall task. Patients with schizophrenia also performed poorly on judging the frequency of the items and putting the items in a correct sequence. Therefore, although patients with schizophrenia generated inadequate information shopping at a supermarket, their retrieval deficits cannot totally account for the impairment in the description of an event schema. Furthermore, patients made more errors on judging middle frequency events in the frequency judgment task than did normal controls, while their judgment of low frequency events was not significantly disturbed. These observations suggest that part of the semantic structure in schizophrenia patients is disorganized compared with that of normal people.

Sirigu et al. (1995, 1996) reported that patients with lesions in the prefrontal cortical regions made intrusion errors frequently, and failed to close scripts and remain within the stated boundaries. These results are similar to our data, reported here, in patients with schizophrenia, suggesting that the impaired event schema in schizophrenia may be attributable to dysfunction of the prefrontal cortex. Crozier et al. (1999) found that the frontal area in the brain was activated during performance on the script task using functional magnetic resonance imaging (fMRI) in normal subjects. They argued that action planning and temporal ordering, which are related to long-term memory, probably require a neural network within the prefrontal areas. Thus, the prefrontal cortex may play a critical role in storing and retrieving certain critical features of script-based knowledge including the sequential and hierarchical organization of events. Grafman (1995) has proposed that various components of script knowledge are stored as basic units of managerial knowledge in the frontal lobes. Also, Grafman (1995) and Shallice (1988) hypothesized that the generation of adaptive behaviors results from an adequate mental representation of activities, and that the prefrontal cortex plays a major role in the processing of large conceptual units of knowledge. These considerations lead to the concept that impairment of frontal lobe functioning contributes to the disturbances in planning, initiation, and regulation of goal-directed behaviors in subjects with schizophrenia.

The relationship between the SAPS score and performance on the free recall task in patients with schizophrenia suggests that impairment of semantic structure is associated with positive symptoms, e.g. hallucinations and delusions. Simpson and Done (2002) reported that deluded subjects retained their schema boundaries in the recall of script items relevant to their own delusions, but were less able to adhere to a script framework in the recall of materials unrelated to their delusions. Magaro (1980) argued that the deluded individual's cognition is dominated by one or several schemas of delusions that determine or influence the interpretation of incoming stimuli. These previous observations may explain why delusions are associated with confabulations in the recall tasks, such as the Hopkins Verbal Learning Test, as reported by Mahurin et al. (1998). The relationship between delusions, or reality distortion, and impaired memory performance is consistent with findings from neuroimaging studies demonstrating the role of both frontal and temporal lobes in the storage and retrieval of new verbal materials (Squire, 1992; Stuss and Alexander, 2000). Frith and Done (1988, 1989) have proposed a model of neuroanatomical disconnection between the medial temporal

cortex and the prefrontal cortex that is responsible for disordered internal monitoring, resulting in the alien quality of hallucinations and delusions. The results of the present study are consistent with these previously proposed concepts.

The present findings should be considered in light of the limitations of the study. The sample size was relatively small and application of the present findings requires caution. Second, this study found no significant correlation between performance on the script tasks and dose of antipsychotic drugs that are dopamine-D_2 antagonists. On the other hand, Sumiyoshi et al. (2001) reported adjunctive treatment with 5-HT_{1A} agonists improves an aspect of memory organization in patients with schizophrenia. Further study is warranted to develop pharmacological agents to treat impairment of event schema in schizophrenia.

In summary, the results of this study suggest that event schemas (semantic structure) in patients with schizophrenia are disorganized compared with those of healthy normal people. A relationship between impairment of semantic structure and positive symptoms of schizophrenia also emerged. Future research should clarify neural mechanisms underlying disturbed performance on the script tasks in patients with schizophrenia.

Acknowledgments

This study was supported by Grant-in-Aid for Scientific Research (C) (2), 16530445 and 16591126 from the Japan Society for the Promotion of Science (JSPS). The authors thank Ms. Kuniko Tanaka and Ms. Rie Abe for help in data collection.

References

American Psychiatric Association, 1994. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. 4th Rev. ed. American Psychiatric Press, Washington, DC.

Andreasen, N.C., 1983. The Scale for the Assessment of Negative Symptoms (SANS). The University of Iowa, Iowa.

Andreasen, N.C., 1984. The Scale for the Assessment of Positive Symptoms (SAPS). The University of Iowa, Iowa.

Andreasen, N.C., Flaum, M., Arndt, S., 1992. The Comprehensive Assessment of Symptoms and History (CASH). An instrument for assessing diagnosis and psychopathology. Archives of General Psychiatry 49, 615–623.

Chan, A.S., Chiu, H., Lam, L., Pang, A., Chow, L.Y., 1999. A breakdown of event schemas in patients with schizophrenia: an examination of their script for dining at restaurants. Psychiatry Research 87, 169–181.

Cirillo, M.A., Seidman, L.J., 2003. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. Neuropsychology Review 13, 43–77.

Corrigan, P.W., Addis, I.B., 1995. The effects of cognitive complexity on a social sequencing task in schizophrenia. Schizophrenia Research 16, 137–144.

Corrigan, P.W., Wallace, C.J., Green, M.F., 1992. Deficits in social schemata in schizophrenia. Schizophrenia Research 8, 129–135.

Crozier, S., Sirigu, A., Lehericy, S., van de Moortele, P.F., Pillon, B., Grafman, J., Agid, Y., Dubois, B., LeBihan, D., 1999. Distinct prefrontal activations in processing sequence at the sentence and script level: an fMRI study. Neuropsychologia 37, 1469–1476.

Frith, C.D., Done, D.J., 1988. Towards a neuropsychology of schizophrenia. British Journal of Psychiatry 153, 437–443.

Frith, C.D., Done, D.J., 1989. Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. Psychological Medicine 19, 359–363.

Grafman, J., 1995. Similarities and distinctions among current models of prefrontal cortical functions. Annals of the New York Academy of Sciences 769, 337–368.

Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia; a quantitative review of the evidence. Neuropsychology 12, 426–445.

Helmes, E., Bush, J.D., 2004. Script analysis and verbal working memory in early and late adulthood. Brain Impairment 5 (Supplement), 41. (Abstract).

Hill, K., Mann, L., Laws, K.R., Stephenson, C.M., Nimmo-Smith, I., McKenna, P.J., 2004. Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. Acta Psychiatrica Scandinavica 110, 243–256.

Kawasaki, E., 1980. Memory knowledge structure and sentence recognition task. Abstract of 44th Annual Meeting of Japanese Psychological Association 44, 330.

Liddle, P.F., Friston, K.J., Frith, C.D., Frackowiak, R.S., 1992. Cerebral blood flow and mental processes in schizophrenia. Journal of Royal Social Medicine 85, 224–227.

Mahurin, R.K., Velligan, D.I., Miller, A.L., 1998. Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. Psychiatry Research 79, 139–149.

Magaro, P.A., 1980. Cognition in Schizophrenia and Paranoia: The Integration of Cognitive Processes. Lawrence Erlbaum Associates, Hillsdale, NJ.

Matsui, M., Sumiyoshi, T., Kato, K., Yoneyama, E., Kurachi, M., 2004. Neuropsychological profile in patients with schizotypal personality disorder or schizophrenia. Psychological Reports 94, 387–397.

McKay, A.P., McKenna, P.J., Bentham, P., Mortimer, A.M., Holbery, A., Hodges, J.R., 1996. Semantic memory is impaired in schizophrenia. Biological Psychiatry 39, 929–937.

Nohara, S., Suzuki, M., Kurachi, M., Yamashita, I., Matsui, M., Seto, H., Saitoh, O., 2000. Neural correlates of memory organization deficits in schizophrenia—a single photon emission computed tomography study with 99 m Tc-ECD during a verbal learning task. Schizophrenia Research 42, 209–222.

Paulsen, J.S., Romero, R., Chan, A., Davis, A.V., Heaton, R.K., Jeste, D.V., 1996. Impairment of the semantic network in schizophrenia. Psychiatry Research 63, 109–121.

Sakane, M., Kuwabara, N., Nomura, Y., 1981. Factor and relationship in knowledge structure: structure and evaluation value of 16 scripts. Educational Science Seminary 13, 39–55.

Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, B., Stafiniak, P., 1991. Neuropsychological function in schizophrenia; selective impairment in memory and learning. Archives of General Psychiatry 48, 618–624.

Schank, R.C., Abelson, R.P., 1977. Script, Plans, Goals and Understanding: An Inquiry Into Human Knowledge Structures. Lawrence Erlbaum Associates, Hillsdale, NJ.

Shallice, T., 1988. From Neuropsychology to Mental Structure. Cambridge University Press, Cambridge.

Simpson, J., Done, D.J., 2002. Elasticity and confabulation in schizophrenic delusions. Psychological Medicine 32, 451–458.

Sirigu, A., Zalla, T., Pillon, B., Grafman, J., Agid, Y., Dubois, B., 1995. Selective impairments in managerial knowledge following pre-frontal cortex damage. Cortex 31, 301–316.

Sirigu, A., Zalla, T., Pillon, B., Grafman, J., Agid, Y., Dubois, B., 1996. Encoding of sequence and boundaries of scripts following prefrontal lesions. Cortex 32, 297–310.

Squire, L.R., 1992. Memory and hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychological Review 9, 195–231.

Stuss, D.T., Alexander, M.P., 2000. Executive functions and the frontal lobes: a conceptual view. Psychological Research 63, 289–298.

Sumiyoshi, C., Matsui, M., Sumiyoshi, T., Yamashita, I., Sumiyoshi, S., Kurachi, M., 2001. Semantic structure in schizophrenia as assessed by the category fluency test; effect of verbal intelligence and age of onset. Psychiatry Research 105, 187–199.

Sumiyoshi, T., Matsui, M., Yamashita, I., Nohara, S., Uehara, T., Kurachi, M., Sumiyoshi, S., Sumiyoshi, C., Meltzer, H.Y., 2001. The effect of tandospirone, a serotonin 1A agonist, on memory function in schizophrenia. Biological Psychiatry 49, 861–868.

Available online at www.sciencedirect.com
ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 30 (2006) 1299–1303
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Electrical brain activity and response to olanzapine in schizophrenia: A study with LORETA images of P300

Tomiki Sumiyoshi [a,b,*], Yuko Higuchi [a], Yasuhiro Kawasaki [a,b], Mie Matsui [b,c], Kanade Kato [c], Hiromi Yuuki [c], Hirofumi Arai [b,c], Masayoshi Kurachi [a,b]

[a] *Department of Neuropsychiatry, University of Toyama School of Medicine, Toyama, Japan*
[b] *Core Research for Evolutional Science and Technology, Japan Science and Technology Corporation, Tokyo, Japan*
[c] *Department of Psychology, University of Toyama School of Medicine, Toyama, Japan*

Received 6 January 2006; received in revised form 20 March 2006; accepted 17 April 2006
Available online 12 June 2006

Abstract

The aim of this study was to evaluate the change in the distribution for the P300 generator, as demonstrated by Low Resolution Electromagnetic Tomography (LORETA) images, in patients with schizophrenia during treatment with olanzapine. Data were obtained from five right-handed patients treated with olanzapine for 6 months. Five right-handed normal volunteers also participated in the study. LORETA images of P300 in response to the odd-ball auditory discrimination task revealed a left dominant lateralized high current source density in the temporal lobes in all control subjects. Although this pattern of brain activation was not evident in patients at baseline, 6-month treatment with olanzapine recovered the left dominant pattern of the electrical density in the temporal regions, such as the Heschl gyrus, and improved performance on a test of verbal learning and memory. Scores of the Brief Psychiatric Rating Scale and the Global Assessment of Functioning Scale also improved during treatment. These results provide the first suggestion that enhancement of verbal memory and the functional status by treatment with some antipsychotic drugs may be associated with modulations of the anatomical configuration of electrical brain activity in patients with schizophrenia.

Keywords: Antipsychotic drugs; Event-related potentials; LORETA; Schizophrenia; Second generation; Temporal lobes; Verbal learning and memory

1. Introduction

There is accumulated evidence for the ability of the second generation antipsychotic drugs, or atypical antipsychotic drugs (AAPDs), such as clozapine, olanzapine, risperidone, quetiapine, melperone, and ziprasidone, to ameliorate cognitive impairment and enhance functional outcomes in patients with schizophrenia (Meltzer and Sumiyoshi, 2003; Sumiyoshi et al., 2003). A limited number of studies has attempted to clarify neural mechanisms underlying cognitive benefits of AAPDs by measuring electrical activity in the brain (e.g. Umbricht et al., 1998; Niznikiewicz et al., 2005). For this purpose, event-related potentials (ERPs) provide a tool to assess effects of medications on underlying brain activity with superior time resolution. Particularly, P300 has been suggested to provide an electrophysiological measure of attention-dependent information processing (Kawasaki et al., 1997). Its amplitude, thought to reflect activation of immediate memory, is reduced in subjects with schizophrenia (Kawasaki et al., 1997; Nieman et al., 2002; Umbricht et al., 1998).

Umbricht et al. (1998) reported that treatment with clozapine but not haloperidol for 9–16 weeks increased the P300 amplitude without affecting deficits in mismatch negativity and N200, other measures of ERP, in patients with schizophrenia. More recently, Niznikiewicz et al. (2005) observed an increase in the P300 amplitude at left temporal electrodes during treatment with clozapine. The results from these previous studies indicate a region-specific P300 response to treatment

Abbreviations: AAPDs, atypical antipsychotic drugs; AVLT, Auditory Verbal Learning Test; BPRS, Brief Psychiatric Rating Scale; GAF, Global Assessment of Functioning Scale; LORETA, Low Resolution Electromagnetic Tomography.

* Corresponding author. Department of Neuropsychiatry, University of Toyama School of Medicine, 2630 Sugitani, Toyama 930-0194 Japan. Tel.: +81 76 434 7323; fax: +81 76 434 5030.
E-mail address: sumiyo@med.u-toyama.ac.jp (T. Sumiyoshi).

0278-5846/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2006.04.028

with some AAPDs. However, limited spatial resolution with traditional ERP methods has hampered localization of the electrical generator of the P300 potential.

Low Resolution Electromagnetic Tomography (LORETA) provides three-dimensional images of brain electrical activity (Pascual-Marqui, 1999). For example, localization of the P300 generator with LORETA revealed high cortical current density areas in the left temporal cortex and surrounding structures in normal subjects (Mulert et al., 2004).

The aim of this preliminary study was to determine the change in the anatomical configuration of the P300 generator in patients with schizophrenia treated with olanzapine. We herein report LORETA images of P300 in patients who exhibited improvement in verbal learning and memory as well as the functional status during treatment with olanzapine. The a priori hypothesis was that these subjects would show recovery of electrical activity in the left temporal regions, such as the primary auditory receptive cortex (area 41) and auditory integration region (area 42), i.e., the transverse temporal gyrus of Heschl.

2. Methods

2.1. Subjects

Data were obtained from five outpatients (male/female=4/1) meeting DSM-IV criteria for schizophrenia (APA, 1994) who underwent treatment with olanzapine for 6 months. All subjects were right-handed, and were treated at Toyama University Hospital. Diagnosis was made based on the Structured Clinical Interview for DSM-IV (SCID). A psychiatric and treatment history was obtained from the subjects, informants, and medical records. Subjects with current history of substance abuse or dependence, seizure or head injury were excluded from the study. Eligible patients had a complete physical examination. Standard laboratory testing was normal. Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in research. If the mental status of a subject was impaired to the point where s/he could not understand the nature of the study, its risks and benefits, or the option not to participate, the subject was not approached to be in research. This protocol was approved by the Committee on Medical Ethics of University of Toyama. After complete description of the study to the subjects, written informed consent was obtained. At baseline, the patients had been receiving the following antipsychotic drugs for at least 3 months: haloperidol (2), risperidone (1), or risperidone+perospirone (1). One subject was neuroleptic-free. The demographic data of the subjects is shown in Table 1.

Five age and gender-matched right-handed healthy volunteers [male/female=4/1; mean (SD) age=40.2 (8.1) years; education=16.8 (1.1) years] participated in the study as the control subjects.

2.2. Clinical assessment

The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and the Global Assessment of Functioning Scale (GAF) (APA, 1994) were assessed by an experienced psychiatrist who was not informed of medication status. The Auditory Verbal Learning Test (AVLT) (Nohara et al., 2000; Matsui et al., in press) – Random List was administered by Master's level psychologists, who were not informed of other clinical data or medication status. Different versions of the same test were used at baseline and 6-month evaluation.

Table 1
Demographic and clinical data of patients

	Baseline	6 months
Age, years	39.2(10.8)	–
Education, years	13.6 (2.2)	–
Duration of illness	14.6 (7.5)	–
Neuroleptic dose at baseline*	3.6 (2.9)	–
BPRS score	14.6 (13.6)	6.6 (7.2)[a]
AVLT score	19.8 (10.5)	25.6 (9.9)[b]
GAF score	55.0 (6.1)	66.0 (8.2)[c]

Values represent mean (SD).
BPRS, Brief Psychiatric Rating Scale.
AVLT, Auditory Verbal Learning Test.
GAF, Global Assessment of Functioning Scale.
*Haloperidol equivalent dose (mg/day).
[a,b,c] $p<0.05$, significantly different from baseline values.

Immediately after the baseline assessment, antipsychotic medications were switched stepwise to olanzapine during the initial 6 weeks. The treating psychiatrists adjusted the dose to optimize improvement in psychopathology, while attempting to keep the side effects of the drug tolerable.

2.3. ERP recording

The ERPs were recorded at the time of clinical assessment using an auditory odd-ball paradigm, based on a previous report (Kawasaki et al., 1997) with modifications. Electroencephalograms (EEGs) were recorded with a 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kohden Corp., Tokyo, Japan) and an acquisition software (EEGFOCUS version 2.0, MEGIS, Munich, Germany). Recordings were performed using an electro cap (Electrocap Inc., Eaton, OH) in a sound-attenuated room. Auditory stimuli were delivered binaurally through headphones with variable inter-stimulus intervals ranging from 1.5 to 2.5 s. Target tones of 2000 Hz were randomly presented in a series of standard tones of 1000 Hz, with the presentation probability of 0.2 for the target tones. All tones were 100 ms in duration with a rise–fall time of 10 ms. The subjects were requested to press a button promptly and accurately in response to the infrequent target tones. EEG was recorded with 19 electrodes located at FP1, FP2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6, Fz, Cz, and Pz, according to the international 10–20 system. All electrodes were referred to the average amplitude of the ear electrodes (bandwidth=0.16–100 Hz, 60 Hz notch filter). Eye movement artifacts (blinks and eye movements) were rejected off-line. Electrode impedance was less than 10 kΩ. The recording epoch was 700 ms, including a 100-ms pre-stimulus baseline. Data were collected with a sampling rate of 500 Hz. A total of more than twenty EEG responses

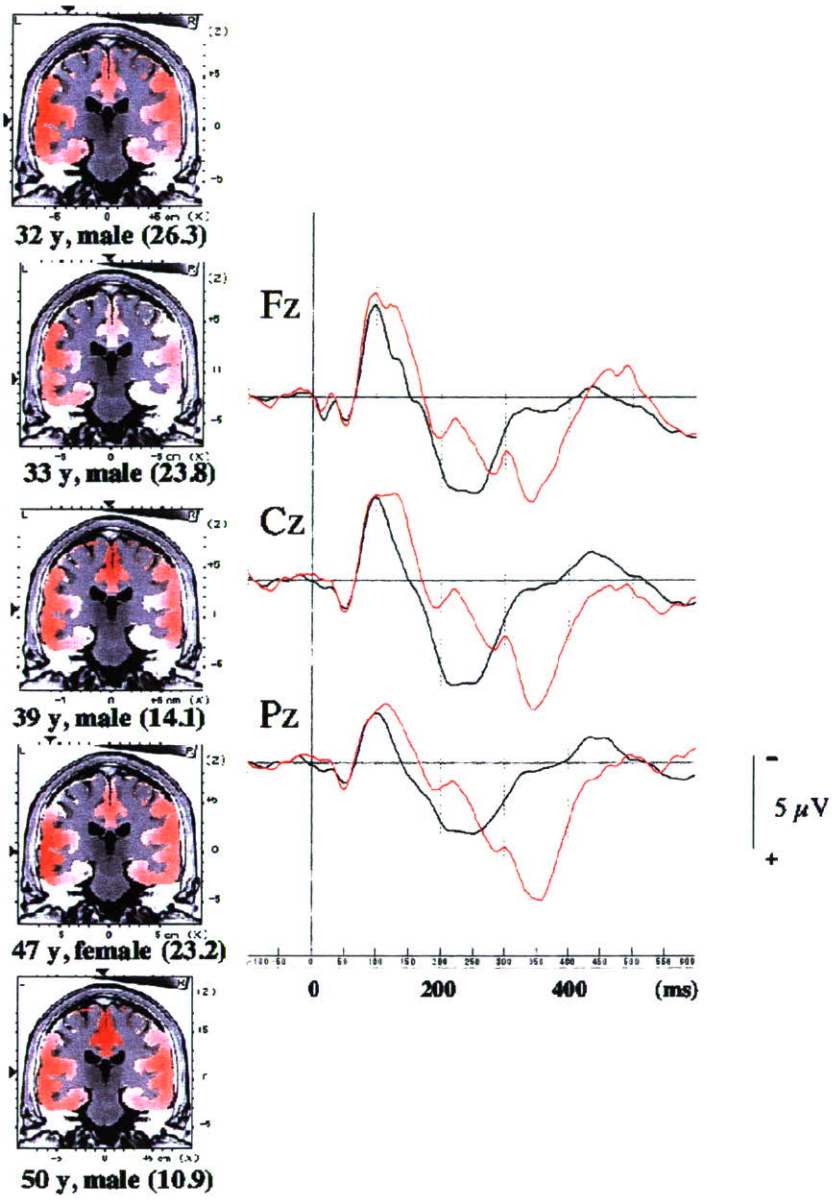

Fig. 1. Grand average of the ERPs (black and red lines represent the responses to non-target and target stimuli, respectively) and the LORETA images of P300 in response to the odd-ball auditory discrimination task in control subjects. Values in the parentheses represent the Laterality Index (see text).

(mean=36.9) to target tones were averaged off-line. Averaging of ERP waves and related procedures were performed using EPLYZER II software (Kissei Comtec, Co. Ltd. Nagano, Japan).

2.4. LORETA analysis

LORETA images were obtained by estimating the current source density distribution for epochs of brain electric activity on a dense grid of 2394 voxels at 7-mm spatial resolution applied to the digitized Talairach human atlas (Talairach and Tournoux, 1988), based on the established method (Pascual-Marqui, 1999). LORETA made use of the three-shell spherical head model registered to the Talairach atlas available as a digitized MRI from the Brain Imaging Centre, Montreal Neurologic Institute. Registration between spherical and realistic head geometry used EEG electrode coordinates reported by Towle et al. (1993). The solution space was restricted to cortical gray matter and hippocampus, as determined by the corresponding digitized Probability Atlas also available from the Brain Imaging Centre. A voxel was labeled as gray matter if it met the following three conditions: its probability of being gray matter was higher than that of being white matter, its probability of being gray matter was higher than that of being cerebrospinal fluid, and its probability of being gray matter was higher than 33% (Pascual-Marqui, 1999). We calculated LORETA images for each ERP in the time frame 250–500 ms post-stimulus.

The Laterality Index (L.I.) was defined by using the LORETA values in the temporal lobes (area 41, 42), as follows:

$$\text{L.I.} = (\text{Lt}-\text{Rt})/(\text{Lt}+\text{Rt});$$

where Lt and Rt represent the LORETA values from areas (41+42) in the left and right hemispheres, respectively.

2.5. Data analysis

Statistical comparisons were performed using Wilcoxon's signed rank test. Significance was considered when the p-value was less than 0.05.

3. Results

The mean (SD) dose of olanzapine at 6 months was 7.5 (4.3) mg/day. No patient experienced noticeable side effects. Only one subject was receiving bromazepam 4 mg/day as a concomitant medication. Scores of the AVLT ($z=-2.0$, $p<0.05$), BPRS ($z=-2.0$, $p<0.05$), and GAF ($z=-2.0$, $p<0.05$) significantly improved during treatment with olanzapine (Table 1).

Besides a high current source density area in the mid-parietal region, the temporal regions were also activated with the left dominant laterality in all control subjects [mean (SD) L.I. = 19.7 (6.7)] (Fig. 1). On the other hand, this activation pattern was not evident in the patients at baseline [L.I. = −10.8 (27.8)] (Fig. 2). The L.I. for patients after 6-month treatment with olanzapine [19.2 (13.1)] was significantly larger than that at baseline ($z=-2.0$, $p<0.05$) (Fig. 2), indicating a shift of the high current source density areas in the temporal regions to the left side.

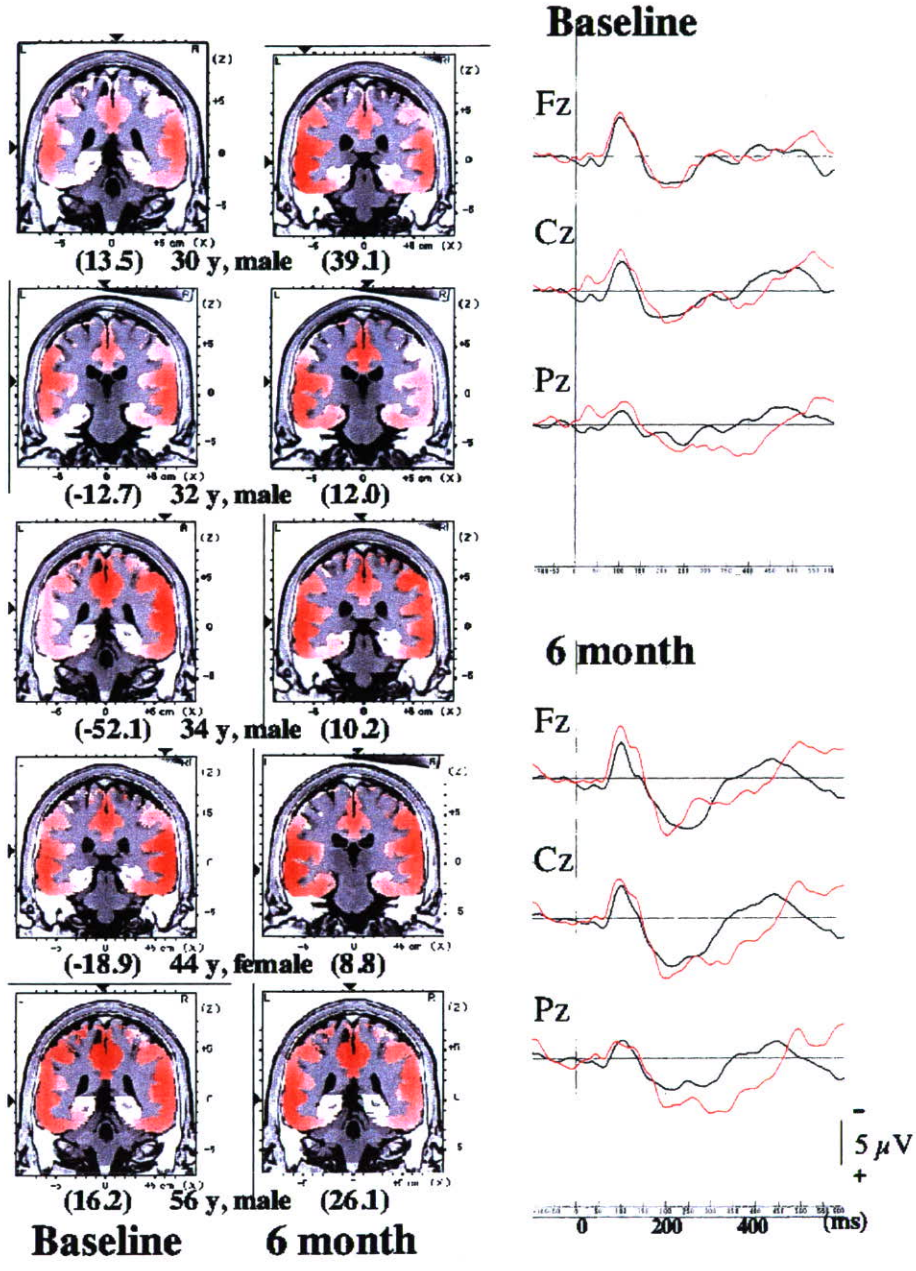

Fig. 2. Grand average of the ERPs (black and red lines represent the responses to non-target and target stimuli, respectively) and the LORETA images of P300 in response to the odd-ball auditory discrimination task in patients with schizophrenia before (Baseline) and after (6 months) treatment with olanzapine. Values in the parentheses represent the Laterality Index (see text).

P300 amplitudes were increased after switching to olanzapine in the patients (Fig. 2).

4. Discussion

The results of this study provide the first suggestion for a link between the change in the anatomical configuration of electrical brain activity and response to treatment with an antipsychotic drug in subjects with schizophrenia. LORETA images of P300 indicated recovery of the left dominant pattern of neural activity in the temporal lobes, specifically the Heschl gyri, in patients treated with olanzapine who showed improvement in psychopathology and performance on a test of verbal learning and memory, as well as the functional status.

The observed enhancement of verbal learning and memory, as measured by the AVLT, in patients treated with olanzapine is similar to Keefe et al. (2004), who reported improved scores of the California Verbal Learning Test (CVLT) after treatment with 5–20 mg/day olanzapine for 3 months in subjects with schizophrenia.

The location of high current source density areas of P300 observed in the control subjects (Fig. 1) is consistent with the results of a recent study by Mulert et al. (2004) who found left dominant lateralized activations in response to the auditory odd-ball task in brain areas including the bilateral superior temporal gyrus and bilateral temporo-parietal junctions. The absence of this activation pattern in the patients at baseline (Fig. 2) may be in line with previous observations (Heidrich and Strik, 1997; Nieman et al., 2002) indicating the left temporal lobe dysfunction in schizophrenia. For example, Heidrich and Strik (1997) examined performance on neuropsychological tests sensitive to functional brain asymmetries and P300, as elicited with an odd-ball paradigm in subjects with schizophrenia. They found a negative correlation between performance on the verbal paired associates subtest of the Wechsler Memory Scale and right-sided lateralization of the P300 maximum. Similarly, Nieman et al. (2002) reported a positive correlation between reduction in P300 amplitude and poor performance on the CVLT, suggesting a link between P300 abnormality and impaired function of the left temporal lobe. These previous findings may be relevant to the amelioration of neural activity in the left temporal regions, presented here, in the patients whose verbal learning and memory improved after treatment with olanzapine (Fig. 2).

The limitations of the current study include the fact that the findings were based on a small sample size, which is prone to type-I and type-II errors. For example, inclusion of more patients could have detected additional brain areas sensitive to treatment with olanzapine with regard to the ERP measures. Further investigations with a larger number of subjects are required to confirm the observations reported here.

5. Conclusions

In conclusion, we have reported a shift of the distribution for focus of electrical brain activity, as demonstrated by the LORETA images of the P300 potential, in patients with schizophrenia whose verbal memory and functional status improved during treatment with olanzapine. Our findings deserve replications in a larger study.

Acknowledgements

Supported by a Grant-in-Aid for Scientific Research (No. 16591126, 16530445 and 17591201) from the Japan Society for the Promotion of Science, as well as a research grant from Eli Lilly Japan.

The authors thank Dr. Lisha Niu, Ms. Chieko Takamiya, Ms. Kuniko Tanaka, and Ms. Rie Abe for help in data collection. Part of this work was presented at a symposium in the 8th World Congress of Biological Psychiatry in Vienna, Austria, on July 29th, 2005.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington DC: APA; 1994.

Heidrich A, Strik WK. Auditory P300 topography and neuropsychological test performance: evidence for left hemispheric dysfunction in schizophrenia. Biol Psychiatry 1997;41:327–35.

Kawasaki Y, Maeda Y, Higashima M, Nagasawa T, Koshino Y, Suzuki M, et al. Reduced auditory P300 amplitude, medial temporal volume reduction and psychopathology in schizophrenia. Schizophr Res 1997;26:107–15.

Keefe RS, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Sitskoorn MM, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 2004;161:985–95.

Matsui M, Yuuki H, Kato K, Kurachi M. Impairment of memory organization in patients with schizophrenia or schizotypal disorder. J Int Neuropsychol Soc in press.

Meltzer HY, Sumiyoshi T. Atypical antipsychotic drugs improve cognition in schizophrenia. Biol Psychiatry 2003;53:265–7.

Mulert C, Pogarell O, Juckel G, Rujescu D, Giegling I, Rupp D, et al. The neural basis of the P300 potential. Focus on the time-course of the underlying cortical generators. Eur Arch Psychiatry Clin Neurosci 2004;254:190–8.

Nieman DH, Koelman JH, Linszen DH, Bour LJ, Dingemans PM, Ongerboer de Visser BW. Clinical and neuropsychological correlates of the P300 in schizophrenia. Schizophr Res 2002;55:105–13.

Niznikiewicz MA, Patel JK, McCarley R, Sutton J, Chau DT, Wojcik J, et al. Clozapine action on auditory P3 response in schizophrenia. Schizophr Res 2005;76:119–21.

Nohara S, Suzuki M, Kurachi M, Yamashita I, Matsui M, Seto H, et al. Neural correlates of memory organization deficits in schizophrenia: a single photon emission computed tomography study with 99m-Tc-ethyl-cysteinate dimmer during a verbal learning task. Schizophr Res 2000;42:209–22.

Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799–812.

Pascual-Marqui RD. Review of methods for solving the EEG inverse problem. Int J Bioelectromagn 1999;1:75–86.

Sumiyoshi T, Jayathilake K, Meltzer HY. The effect of melperone, an atypical antipsychotic drug, on cognitive function in schizophrenia. Schizophr Res 2003;59:7–16.

Talairach J, Tournoux P. Co-Planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Towle VL, Bolanos J, Suarez D, Tan K, Grzeszczuk R, Levin DN, et al. The spatial location of EEG electrodes: locating the best-fitting sphere relative to cortical anatomy. Electroencephalogr Clin Neurophysiol 1993;86:1–6.

Umbricht D, Javitt D, Novak G, Bates J, Pollack S, Lieberman J, et al. Effects of clozapine on auditory event-related potentials in schizophrenia. Biol Psychiatry 1998;44:716–25.