(*DISC1*), a known genetic risk factor for SZ and major depressive disorder (MDD) (Cannon et al. 2005; Chen et al. 2007; Hashimoto et al. 2006; Hennah et al. 2003; Millar et al. 2000; Thomson et al. 2005), localizes to the centrosome by binding to *PCNT* (Miyoshi et al. 2004). Shimizu et al. showed that overexpression of the *DISC1*-binding regions of *PCNT* or the *DISC1* deletion mutant lacking the *PCNT*-binding region impaired the microtubule organization and they suggested that the *DISC1–PCNT* interaction played a key role in the microtubule network formation (Shimizu et al. 2008). Recently, single-nucleotide polymorphisms (SNPs) within the *PCNT* gene have been found to show allelic associations with SZ and MDD (Anitha et al. 2009; Numata et al. 2009). In addition, Mitkus et al. reported a trend for an increase mRNA levels of the *PCNT* gene in the dorsolateral prefrontal cortex of patients with SZ, compared with the control groups (Mitkus et al. 2006). In this study, case-controlled association analysis was performed in the Japanese population to determine if the *PCNT* gene is implicated in SZ.

Materials and Methods

Subjects

We used genomic DNA samples from 726 SZ patients: 406 male (mean age 48.6 ± 13.8 years), 320 female (mean age 49.2 ± 14.5 years) from the Tokushima University Hospital, affiliated psychiatric hospitals of the University of Tokushima, the Ehime University Hospital and the Osaka University Hospital in Japan. The diagnosis of SZ was made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of extensive clinical interviews and review of medical records. Seven hundred fifty-one controls, 422 male (mean age 45.5 ± 11.1 years) and 329 female (mean age 45.2 ± 10.5), were selected from volunteers who were recruited from hospital staff and students and company employees documented to be free from either psychiatric problems or past mental histories. All subjects were unrelated Japanese origin and signed written informed consent to participate in the genetic association studies approved by the institutional ethics committees.

Genotyping

We initially selected eight tagging SNPs by SNPBrowser 3.5 (De La Vega et al. 2006) (Applied Biosystems, Foster, CA, USA, Pair-wise $r^2 > 85\%$, MAF > 20%, Japanese population) (rs11702684, rs2249057, rs11701058, rs2839226, rs2839231, rs3788265, rs2073376, rs1010111) (Supplementary Table 1). After that, we selected rs2073380 additionally because eight tagging SNPs did not seem to cover the third block of the *PCNT* gene from HapMap data. Genotyping was performed using commercially available TaqMan probes for the *PCNT* gene with ABI Prism 7900 HT Sequence Detection System and ABI 7500 Real Time PCR System (Applied Biosystems). Haplotype block structure was determined using the HAPLOVIEW program (Barrett et al. 2005). Blocks were defined according to the criteria of Gabriel et al. (2002).

Statistical Analysis

Allelic and genotypic frequencies of patients and control subjects were compared using χ^2 test. The SNPAlyze 3.2Pro software (DYNACOM, Japan) was used to estimate haplotype frequencies, linkage disequilibrium (LD), permutation *P*-values (10,000 replications) and deviation from Hardy–Weinberg Equilibrium (HWE) distribution of alleles. Power calculations for our sample size performed using the G*Power program (Erdfelder et al. 1996). The criterion for significance was set at $P < 0.05$ for all tests.

Results

Genotypic and allelic frequencies of the *PCNT* gene are shown in Table 1. Genotypic distributions of these nine SNPs did not deviate significantly from HWE in either group ($P > 0.05$). No significant difference was observed in genotypic frequency between the controls and patients in eight SNPs. Although allelic distribution of rs11702684 was different between the two groups ($P = 0.042$), the difference did not reach statistical significance after permutation correction for multiple comparisons. In power calculations using the G*Power program, our sample size had >0.98 power for detecting a significant association (alpha < 0.05) when an effect size index of 0.2 was used.

Several papers reported that there were gender-specific genetic components involved in the pathology of SZ in the *DISC1* gene (Hennah et al. 2003; Chen et al. 2007) and the *DISC1*-related genes (Hennah et al. 2007; Pickard et al. 2007; Qu et al. 2008). In our study, when the data were subdivided on the basis of gender, allelic distribution of rs11702684 was different between the two groups in only male samples ($P = 0.033$). However, the difference did not survive statistical significance after permutation correction for multiple comparisons.

There were three LD blocks in the *PCNT* gene with rs2249057, rs11701058, rs2839226, and rs2839231 residing in block 1 and rs3788265 and rs2073376 residing in block 2, and rs2073380 and rs1010111 residing in block 3 (Gabriel et al. 2002, Fig. 1). These constructed marker haplotypes of blocks 1–3 were not associated with SZ (permutation $P = 0.184$, 0.137, and 0.601, respectively).

Table 1 Genotypes and allele frequencies of nine single SNPs in the PCNT gene in patients with SZ and controls

SNP	Diagnosis	Allele		*P*-value	Genotype			*P*-value	Frequency
rsl1702684		C	T		C/C	C/T	T/T		
	SC	913	515	0.042	296	321	97	0.085	0.361
	CT	892	588		265	362	113		0.397
		C	A		C/C	C/A	A/A		
rs2249057	SC	862	590	0.504	255	352	119	0.691	0.406
	CT	870	626		247	376	125		0.418
		C	T		C/C	C/T	T/T		
rs11701058	SC	669	783	0.181	153	363	210	0.297	0.461
	CT	728	772		168	392	190		0.485
		C	T		C/C	C/T	T/T		
rs2839226	SC	378	1072	0.111	47	284	394	0.19	0.261
	CT	353	1147		34	285	431		0.235
		A	G		A/A	A/G	G/G		
rs2839231	SC	408	1042	0.562	63	282	380	0.52	0.281
	CT	405	1085		53	299	393		0.272
		G	T		G/G	G/T	T/T		
rs3788265	SC	821	627	0.998	234	353	137	0.506	0.433
	CT	846	646		230	386	130		0.433
		A	G		A/A	A/G	G/G		
rs2073376	SC	445	1001	0.403	75	295	353	0.51	0.308
	CT	478	1006		77	324	341		0.322
		C	A		C/C	C/A	A/A		
rs2073380	SC	642	796	0.839	144	354	221	0.552	0.446
	CT	669	817		141	387	215		0.45
		A	G		A/A	A/G	G/G		
rs1010111	SC	1079	363	0.298	402	275	44	0.343	0.252
	CT	1141	351		428	285	33		0.235

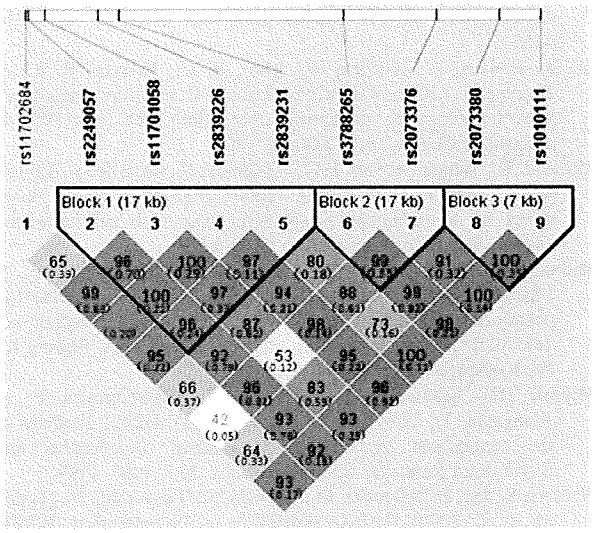

Fig. 1 LD and haplotype structure of the PCNT gene. Haplotype block structure was determined using the HAPLOVIEW program (Barrett et al. 2005). Blocks were defined according to the criteria of Gabriel et al. (2002). Each box represents the D' (r^2) values corresponding to each pair-wise SNP

Discussion

In this study, we examined the association of nine SNPs in the *PCNT* gene and SZ. No significant difference was observed between the controls and the patients in either allelic frequencies or genotypic distributions of nine SNPs after permutation correction for multiple comparisons. In the haplotypic analysis, we could not find any significant association in our subjects. This result was concordance with another study in a Caucasian population (Tomppo et al. 2009).

During the preparation of this article, Anitha et al. reported that rs2249057 of the *PCNT* gene and haplotypes involving this SNP were significantly associated with SZ after correction for multiple comparisons in the Japanese population (Anitha et al. 2009). Although SNPs examined in our study contained rs2249057, we could not find any significant associations in our subjects. The statistical power of our study was sufficient to detect an association between the variants and SZ (SZ $n = 726$; control $n = 751$). Surprisingly, the control minor allele frequency of rs2249057 in Anitha's study (0.48) was higher than

those of our study, HapMap data, and ABI data (0.42, 0.40, and 0.41, respectively). This differing allele frequency between these two studies may be caused by samples' recruited areas. Anitha et al. used subjects from further east compared to ours. However, it is reported that there is no significant population stratification in Japanese (Arinami et al. 2005; Yamaguchi-Kabata et al. 2008).

There are several limitations in our study. First, we applied MAF > 20% when we selected the tagging SNPs and it is difficult to evaluate the association of rare variants in our study. Second, we cannot rule out a possibility that *DISC1–PCNT* interaction may be involved in the etiology of SZ. Third, our findings only represented the Japanese population and studies in other populations would still be warranted due to differing allele frequencies between populations.

Conclusions

In conclusion, we did not find any significant association between the *PCNT* gene and the SZ in the Japanese population. This gene may not play a major role independently in the etiology of SZ.

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Semantic memory deficits based on category fluency performance in schizophrenia: Similar impairment patterns of semantic organization across Turkish and Japanese patients

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Abstract

Patients with schizophrenia exhibit a wide range of cognitive dysfunction, including impairments in semantic memory and verbal fluency. Previous studies report that semantic memory, i.e. associated meaning of words or knowledge, is specifically disorganized in patients who use the English or Japanese language. The purpose of the present study was to determine if semantic memory, as evaluated by verbal fluency data, shows similar patterns of semantic disorganization in non-English-speaking patients who do (Turkish) or do not (Japanese) use an alphabetical language. Turkish (N=20) and Japanese (N=22) patients with schizophrenia, as well as Japanese normal controls (N=22), entered the study. As a measure of semantic memory organization, two types of cluster analyses, i.e. ADDTREE and hierarchical cluster analysis, were performed on category fluency task data. The cluster analyses revealed a greater similarity between the Turkish patients vs. Japanese patients comparison than the Japanese patients vs. Japanese controls comparison. The results provide further support to the concept that impaired semantic memory organization is one of the core features of schizophrenia, and is independent of the language system or cultural backgrounds.

Keywords: Verbal fluency; Semantic memory; Schizophrenia; Cluster analysis; Cognitive function

1. Introduction

Patients with schizophrenia exhibit a wide range of cognitive dysfunction in the domains of language, motor, memory and executive functions (Green et al., 2000). Among the domains of cognition, verbal memory is most severely impaired (Saykin et al., 1991). Disturbances of verbal memory are noticeable even in the prodromal stage of schizophrenia. A recent study demonstrated that verbal memory, as assessed by the California Verbal Learning Test (CVLT) and the Wechsler Memory Scale-Revised (WMS-R), is specifically impaired in subjects at high risk for the development of psychiatric disorders (Lencz et al., 2006).

Recently, several studies have found that higher order cognitive functions related to verbal abilities, such as

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semantic memory, are also impaired in patients with schizophrenia (Aloia et al., 1996; Moelter et al., 2001; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001; Sumiyoshi et al., 2005; Tallent et al., 2001). Semantic memory is defined as "stored representation of meaning of words and knowledge about the world" (Mckay et al., 1996), which represents an aspect of long-term memory related to verbal functions. Well-organized semantic memory is required to facilitate acquisition, storage, and retrieval of information, which enhances quality of life for patients (Sumiyoshi et al., 2006). Thus, further research into the pattern of disorganization of semantic memory in schizophrenia is useful for the development of an effective therapeutic strategy to improve functional outcomes of patients.

A number of previous studies used verbal outputs from the category fluency task (CFT) to estimate semantic memory organization (Aloia et al., 1996; Moelter et al., 2001; Paulsen et al., 1996; Rossell et al., 1999; Sumiyoshi et al., 2001; Sumiyoshi et al., 2005). Interestingly, the pattern of semantic memory disorganization has been suggested to be independent of the language system used by subjects. Thus, the size-ordered dimension, which is observed in normal controls, is absent in the semantic structures of English or Japanese speakers with schizophrenia (Paulsen et al., 1996; Sumiyoshi et al., 2001; Sumiyoshi et al., 2005).

So far, only a few studies have been conducted in non-English speaking subjects. Thus, Robert et al. (1998) investigated clustering (production of words within semantic subcategories) and switching (the ability to shift between clusters) scores, as measures of organization of semantic memory, in French patients, while Bozikas et al. (2005) reported data from Greek patients using the same methods. Although these previous results suggest an impairment of semantic memory in non-English-speaking patients, further investigations are required to determine the pattern of semantic disorganization in schizophrenia. Particularly, it is important to elucidate organization of semantic memory based on verbal fluency performance in subjects with cultural backgrounds that are different from those of Western European countries, as dissimilarity among category items may vary depending on the particular language used, as in the case for typicality (Rosch, 1975). Therefore, it could be argued that the difference in dissimilarity may result in a language- or culture-specific pattern of semantic memory organization.

Several methods have been developed to quantify the structure of semantic memory. Among them, multidimensional scaling (MDS) analysis and cluster analysis are most widely used, although other measures, e.g. Pathfinder (Paulsen et al., 1996) or clustering and switching scores (Bozikas et al., 2005; Troyer et al., 1997), have been used, depending on study purposes. MDS and cluster analyses can "visualize" internal semantic memory in the form of spatial or network structures. MDS analysis is a spatial model, placing each item as a point in a coordinate space where a metric distance between the points reflects subjective dissimilarities, i.e. to which degree a person estimates the difference of the meaning between two items (Kruskal and Wish, 1978). Cluster analysis, on the other hand, is a network model, locating each item in a group (subcluster) based on dissimilarities. Levels of nodes connecting sub-groups reflect the degree of dissimilarities among items. Thus, cluster analysis provides "coherence" among items, which is not obtained by MDS analysis.

Two types of cluster analysis have been developed. Hierarchical cluster analysis (HCA) elicits groupings of items as nested clusters, and demonstrates the degree of dissimilarities as "depth of nesting". Thus, HCA does not reflect actual dissimilarity values. For example, even if dissimilarity for a DOG–CAT pair is smaller than that for a LION–TIGER pair, their dissimilarities are regarded as equal. On the other hand, ADDTREE analysis can quantify the distance among items as the length of branches (Tversky, 1977), where longer branches represent larger inter-item distances. Thus, the length of a DOG–CAT branch would be shorter than that of a LION-TIGER branch.

The dissimilarity values should be obtained in order to perform semantic structure analyses. The order of verbal outputs from the CFT has been typically used for this purpose. Chan et al. (1993a) was a pioneer who formulated the conversion process from inter-item orders to dissimilarity values using parameters such as the number of generated exemplars and the number of subjects who produce certain pairs, and so on. Later, Crowe and Prescott (2003) developed an algorithm which includes parameters of within-list proximity and across-list similarity in order to avoid the distortion by a small amount of utterances. The latter algorithm was so created that it can be effectively applied to a relatively small number of words, or verbal outputs, in such cases as the study of infantile subjects. Thus, this algorithm is equally applicable to clinical samples that generally produce a limited number of verbal outputs.

The comparison of the semantic structures between individuals with different languages provides further support for the hypothesis that the degradation pattern of semantic structure is independent of languages or cultural backgrounds, and thus is a core deficit of schizophrenia.

Although the difference in semantic memory has been investigated mostly in subjects whose language systems are considerably different from each other (i.e. English vs. Japanese), little information is available from patients who use languages sharing similar features in several aspects (e.g. grammar, orthography), but use different characters (alphabets vs. non-alphabets). Therefore, the purpose of the present study was to compare semantic structures between subjects with schizophrenia who use Turkish or Japanese, two languages meeting the above criteria.

In this study, we conducted two types of cluster analyses, i.e. HCA and ADDTREE analyses, to evaluate semantic structures. Further, we applied a traditional (Chan et al., 1993a) algorithm and a more recently developed (Crowe and Prescott, 2003) algorithm to obtain dissimilarity values. These analytical procedures were adopted to test the hypothesis that Turkish and Japanese patients would elicit similarly disorganized semantic memory patterns, irrespective of the methods used for cluster analyses or the algorithms to obtain dissimilarity values.

2. Methods

2.1. Subjects

The subjects comprised 20 Turkish patients and 22 Japanese patients. The Turkish patients were recruited from the Outpatient Clinic of Hacettepe University Department of Psychiatry while the Japanese patients were recruited from the University of Toyama Hospital. The study protocol was approved by Ethics Committees of both Universities. All patients met DSM-IV criteria for schizophrenia. Diagnosis was made by experienced psychiatrists using structured interview, medical history, and all available information. Patients known to be abusing alcohol or other illicit drugs, or those with epilepsy, brain damage, or neurologic disorders, were excluded from the study. Psychiatric symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) for Turkish patients and by the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) for Japanese patients.

Twenty-two Japanese normal healthy volunteers participated in the study as control subjects. They were matched with the patient groups as to the demographic variables and education. This adjustment was made to study the net difference in the semantic memory structure.

Demographic and clinical profiles are summarized in Table 1. Written informed consent was obtained from all subjects.

Table 1
Demographic and cognitive variables.

	Japanese normal controls (N=22)	Japanese schizophrenia (N=22)	Turkish schizophrenia (N=20)
Age (years)	31.09 (10.27)	31.48 (10.07)	27.80 (6.95)
Male/female	11/11	11/11	13/7
Education (year)	14.14 (1.36)	13.89 (2.36)	12.65 (2.22)
Neuroleptic dose (mg/day)[a]	–	11.48 (9.55)	0.00 (0.00)
Onset age (years)	–	22.00 (8.67)	21.30 (4.18)
Duration (years)	–	8.82 (8.80)	6.00 (5.64)
SAPS—total score	–	8.23 (9.53)	–
SANS—total score	–	8.59 (11.91)	–
PANSS (Positive)	–	–	18.35 (6.51)
PANSS (Negative)	–	–	19.50 (6.21)
PANSS (General)	–	–	35.85 (10.26)
CFT[b]	17.14 (2.94)	16.09 (3.13)	15.70 (2.93)
LFT[c]	10.77 (3.01)	9.18 (2.58)	8.45 (3.35)

Values represent mean (standard deviation).
CFT, Category Fluency Task; LFT, Letter Fluency Task.
SAPS, Scale for the Assessment of Positive Symptoms;
SANS, Scale for the Assessment of Negative Symptoms.
PANSS, Positive and Negative Syndrome Scale.
[a] Haloperidol equivalent.
[b] Number of words produced in the Category Fluency Task (CFT) with "ANIMAL".
[c] Means of words produced for given letters in the Letter Fluency Task (LFT) (see Section 2).

2.2. Design and procedure

The VFTs were conducted following the standard norm (Spreen and Strauss, 1998). Subjects were asked to orally produce as many words as possible in 1 min. "ANIMAL" was used as the suggested category in the CFT. For the LFT, "A", "E", and "Z" were used for Turkish patients, while "KA" and "TA" were used for Japanese subjects, based on previous studies (Sumiyoshi et al., 2001; Sumiyoshi et al., 2005).

2.3. Statistical analysis

Multivariate analysis of variance (MANOVA) was conducted to examine group differences in demographic and clinical variables. Age and education were compared among the three groups while onset and duration were compared between Turkish patients and Japanese patients. Performance on the VFTs (CFT and LFT) was analyzed using two-way analysis of variance (ANOVA) with Group (Turkish patients vs. Japanese patients vs. Japanese controls) as the between-subjects factor, and Task type (CFT vs. LFT scores) as within-subject factor. The number of verbal outputs for ANIMAL naming was used for the CFT score. The LFT score was calculated by

Table 2
Frequency of ANIMAL exemplars.

Japanese normal controls (N=22)		Japanese schizophrenia (N=22)		Turkish schizophrenia (N=20)	
DOG	22	DOG	21	DOG	14
CAT	21	CAT	20	GIRAFFE	14
MONKEY	21	MONKEY	20	BIRD	13
LION	20	TIGER	15	CAT	13
GIRAFFE	19	LION	14	LION	12
ELEPHANT	18	BEAR	13	HORSE	11
TIGER	18	ELEPHANT	13	SNAKE	11
BEAR	14	GIRAFFE	13	BEAR	8
SHEEP	13	HIPPO	11	DONKEY	8
HORSE	11	RABBIT	11	ELEPHANT	8

averaging the outputs for "KA" and "TA" for Japanese patients and "A", "E" and "Z" for Turkish patients.

ADDTREE and HCA were performed to examine the semantic structures, using both Chan's algorithm (Chan et al., 1993a) and Crowe's algorithm (Crowe and Prescott, 2003). Thus, four types of analyses (2 cluster analyses × 2 algorithms) were conducted. The details of the former algorithm have been described in previous studies (Chan et al., 1993a; Paulsen et al., 1996; Sumiyoshi et al., 2001), and the latter have been reported by Crowe and Prescott (2003). To compare cluster structures among the groups, the same cluster items should be chosen. Although it is desirable to choose the most frequent items, they varied among the groups (Table 2). Thus, we chose 11 items (BEAR, CAT, COW, DOG, ELEPHANT, GIRAFFE, HORSE, LION, MONKEY, SHEEP), which more than a quarter of subjects in each group produced. ADDTREE analysis and HCA were performed using SYSTAT (version 11.0) and SPSS (version 13.0), respectively. The average linkage method was adopted for HCA. To estimate similarities across the cluster structures, B_k values, as developed by Fowlkes and Mallows (1983), were calculated. Briefly, B_k values represent an isomorphic relation of cluster items, and are determined by the number of the items commonly included in each level of clustering between two clusters. A large value indicates similar groupings of items. Fig. 1 shows a simple example for comparison of cluster structures; the B_k value at k=2 level between S1 and S2 would be greater than that between S1 and S3, or S2 and S3, as the same sub-clusters (A, B) are included within S1 and S2. A whole picture of cluster similarity between two clusters is obtained by plotting B_k values at each level. The expected value and its upper and lower limits were calculated for each B_k value according to previous studies (Crowe and Prescott, 2003; Fowlkes and Mallows, 1983). Statistical significance of B_k values was defined as those greater than the upper limit (Fowlkes and Mallows, 1983).

To compare metric similarities among semantic structures, the correlation analyses were conducted for dissimilarity matrices derived from Chan's algorithm and those by Crowe's algorithm. Three pairs, i.e., Turkish patients vs. Japanese patients, Turkish patients vs. Japanese normal controls, and Japanese patients vs. Japanese normal controls, were formed, all of which had two dissimilarity matrices by the two algorithms. Thus, six (3 pairs × 2 dissimilarity matrices) correlation analyses were performed.

3. Results

3.1. Demographic and clinical profiles

The means and S.D.s of demographic and clinical variables are shown in Table 1. MANOVA for demographic variables showed no overall difference among the three groups (Wilks' lambda=0.90, F=1.58, df=4, 120, P=0.18). Also, clinical profiles did not significantly differ between Turkish patients and Japanese patients (Wilks' lambda=0.96, F=0.92, df=2, 39, P=0.41). These results suggest that demographic and clinical backgrounds were similar among the three groups.

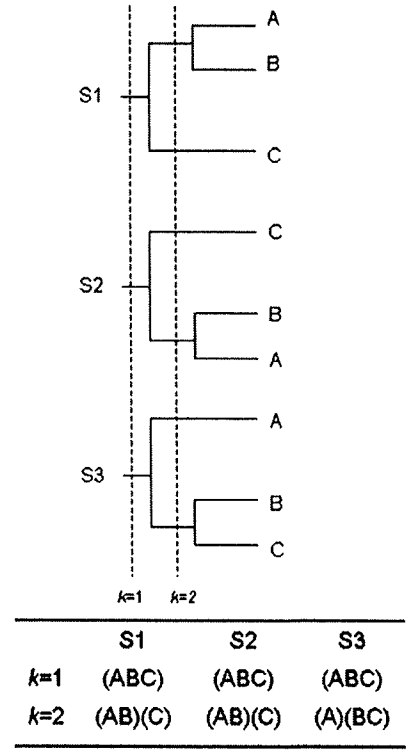

Fig. 1. Schematic representation for cluster structure comparisons. The same groupings exist between S1 and S2 at k=2 level, but not between S1 and S3 or between S2 and S3.

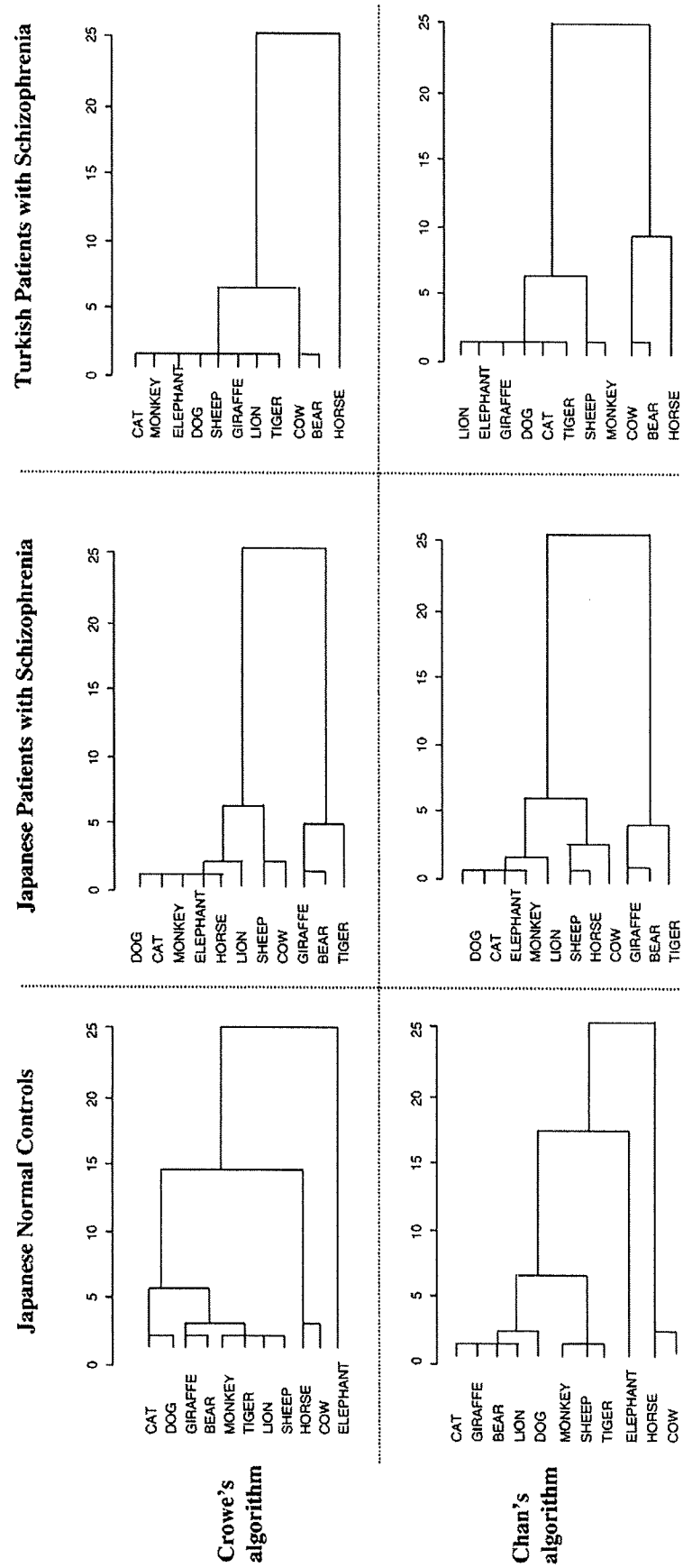

Fig. 2. Cluster structures as demonstrated by hierarchical cluster analysis in Japanese normal controls (left), Japanese patients with schizophrenia (middle), and Turkish patients with schizophrenia (right).

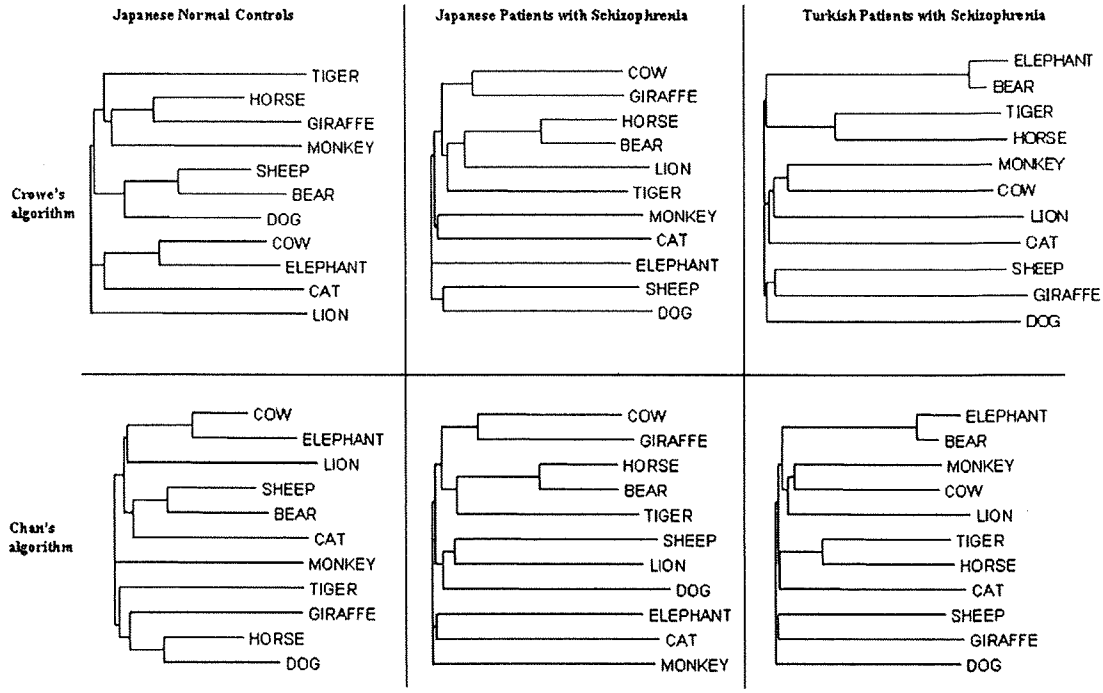

Fig. 3. Cluster structures as demonstrated by ADDTREE analysis in Japanese normal controls (left), Japanese patients with schizophrenia (middle), and Turkish patients with schizophrenia (right). The length of branches represents inter-item distances. Thus, normal controls have relatively shorter branches in most sub-clusters compared with Turkish or Japanese patients with schizophrenia, suggesting that semantic structures of the two patient groups are not firm.

3.2. Verbal fluency scores

The mean and S.D. of the VFT scores are shown in Table 1. ANOVA revealed that Group (F=3.29, df=2, 61, P=0.04) and Task (CFT vs. LFT; F=219.99, df=1,61, P<0.0001) factors were significant. Subsequent analysis for Group factor by Bonferroni/Dunn method detected a significant difference between Turkish patients and Japanese normal controls (P=0.016), while the differences between Turkish patients and Japanese patients (P=0.46) and between Japanese patients and Japanese normal controls (P=0.08) were not significant. No significant interaction effect was obtained between the two factors (F=0.31, df=2, 61, P=0.73).

3.3. Cluster analyses

The results of HCA and ADDTREE analyses are shown in Figs. 2 and 3, respectively. In ADDTREE analysis, two goodness-of-fit measures, Stress and R-square values, were obtained (Table 3). Both measures vary in a range of 0–1. For the Stress value, 0 means best possible fit. For the R-square value, 1 indicates the best representation of data. All Stress values in the current study were in the range of 0.02–0.07, which satisfies Kruskal's (1964) guideline. In addition, all R-square values are more than 0.60, comparable to values obtained in previous studies (Aloia et al., 1996; Sumiyoshi et al., 2005; Sumiyoshi et al., 2006). The two patient groups and Japanese normal controls showed similar values for these two measures, indicating that dissimilarity data from these three groups fit equally well with ADDTREE analysis.

As to the structure of the ADDTREE clusters, relatively longer branches were found *within* sub-clusters while they were shorter *between* sub-clusters, specifically in the two patient groups (Fig. 3). Because such a construction represents weak connection of items within a sub-cluster, the results indicate that the cluster construction in the patient groups is not firmly organized.

Meanwhile, the analyses of B_k values exhibited *structural similarities* between the two patient groups.

Table 3
Summary of the Stress and R-squared values in ADDTREE analysis.

	Chan's algorithm		Crowe's algorithm	
	Stress	R-squared	Stress	R-squared
Turkish schizophrenia	0.02	0.92	0.02	0.95
Japanese schizophrenia	0.05	0.70	0.05	0.70
Japanese normal controls	0.06	0.65	0.07	0.63

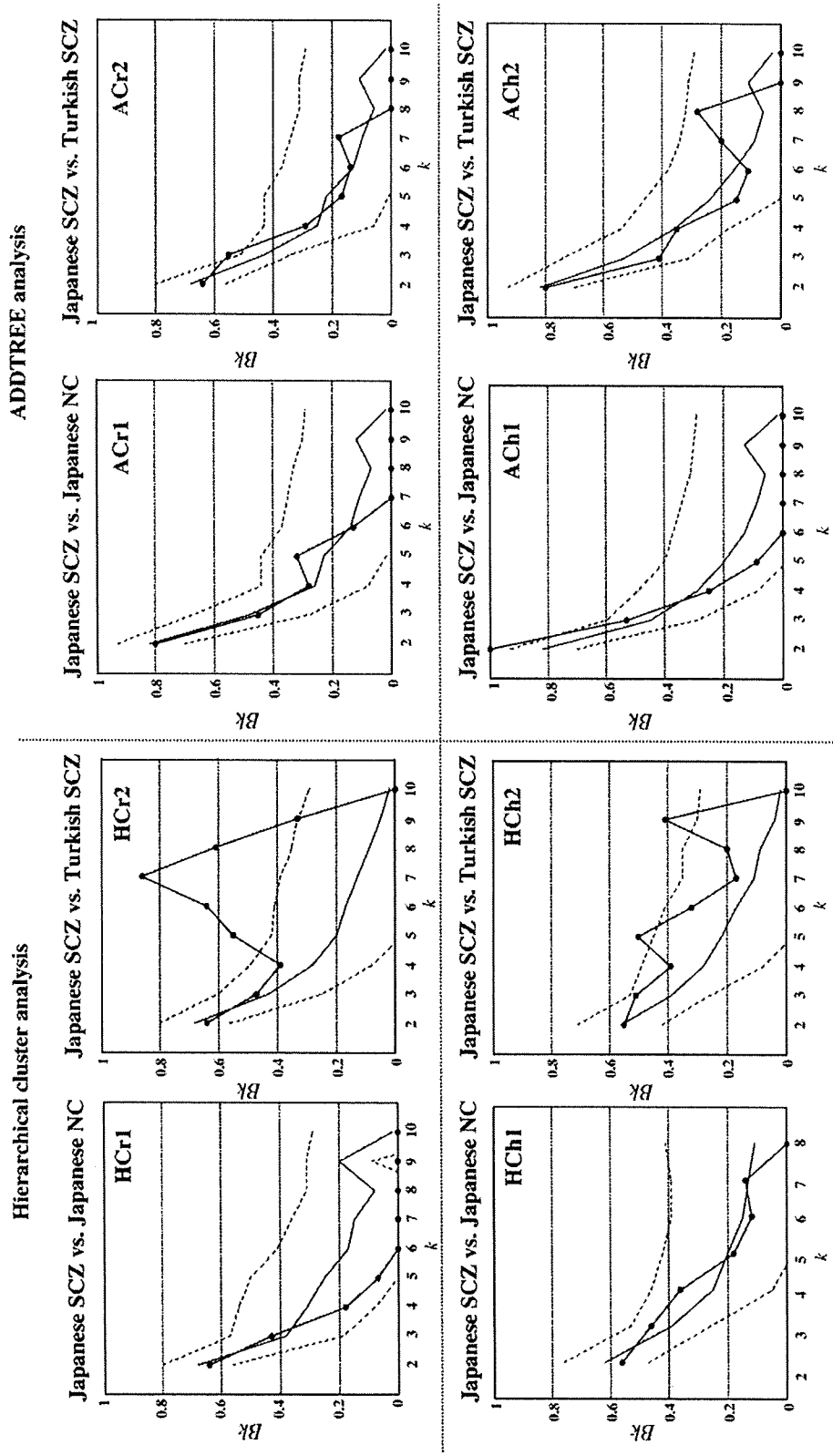

Fig. 4. B_k values obtained from comparisons between Japanese patients with schizophrenia and Japanese normal controls (HCr1, HCh1, ACr1, ACh1) and between Turkish patients and Japanese patients (HCr2, HCh2, ACr2, ACh2). HCr and HCh are abbreviations for hierarchical cluster analysis by Crow's algorithm and Chan's algorithm, respectively. ACr and ACh are abbreviations for ADDTREE analysis by Crow's algorithm and by Chan's algorithm, respectively. E(B_k) and Upper(E(B_k))/Lower(E(B_k)) represent an expected value and its upper/lower limits, respectively. SCZ, schizophrenia; NC, normal controls.

Portrayals of B_k values for the Japanese patients vs. Japanese normal controls comparison and the Turkish patients vs. Japanese patients comparison are presented in Fig. 4 (where HCr and HCh are abbreviations for hierarchical cluster analysis by Crow's algorithm and Chan's algorithm, respectively, and ACr and ACh are abbreviations for ADDTREE analysis by Crow's algorithm and by Chan's algorithm, respectively). The B_k values did not exceed the upper limit of expected values (see dotted lines of Upper (E(B_k)) in Fig. 4) in most comparisons. However, in the two comparisons between Turkish patients and Japanese patients (HCr2 and HCh2), the B_k values exceeded the expected values (E(B_k)) at several k levels (e.g. HCr2: k=5–9; HCh2: k=5, 9). The result suggests greater similarities in the Turkish patients vs. Japanese patients comparison as compared with the Japanese controls vs. Japanese patients comparison.

In order to quantify this trend, we calculated the difference in B_k values (Turkish patients vs. Japanese patients comparison minus Japanese patients vs. Japanese normal controls comparison). As shown in Table 4, only a few values were negative, suggesting that the B_k values in the Turkish patients vs. Japanese patients comparison were larger than those in the Japanese patients vs. Japanese normal controls comparison. Overall, these findings suggest that cluster structures were more similarly organized between the two patient groups than between Japanese patients and normal controls.

3.4. Correlation analysis

As shown in Table 5, the correlations for all group combinations with Chan's algorithm were significant (Table 5, upper-triangular part), although this was not replicated with Crowe's algorithm (Table 5, lower-triangular part). It should be noted that the strongest correlation was obtained between Turkish patients and Japanese patients. Thus, the result partially supports the findings from the B_k analyses, which showed relatively greater similarity of semantic structures between Turkish patients and Japanese patients than between Japanese patients and Japanese normal controls.

Table 4
B_k value differences between Turkish patients/Japanese patients comparison and Japanese patients/Japanese normal controls comparison.

k	HCr2–HCr1	HCh2–HCh1	ACr2–ACr1	ACh2–ACh1
2	0.00	−0.01	−0.16	−0.20
3	0.04	0.05	0.10	−0.12
4	0.21	0.03	0.01	0.10
5	0.48	0.32	−0.15	0.06
6	0.64	0.20	0.01	0.11
7	0.86	0.03	0.18	0.20
8	0.61	0.20	0.00	0.28
9	0.33	0.41	0.00	0.00
10	0.00	0.00	0.00	0.00

HCr and HCh are abbreviations for hierarchical cluster analysis by Crow's algorithm and Chan's algorithm, respectively.

Table 5
Summary of correlations for dissimilarities by the two algorithms.

	Dissimilarities with Chan's algorithm		
	Japanese normal controls	Japanese schizophrenia	Turkish schizophrenia
Japanese normal controls		0.32*	0.29*
Japanese schizophrenia	0.15		0.55**
Turkish schizophrenia	0.02	0.18	
	Dissimilarities with Crowe's algorithm		

*P<0.05, *P<0.01 by Pearson's method.

4. Discussion

The purpose of the present study was to determine if Turkish and Japanese patients with schizophrenia exhibit similar patterns of impairment in semantic structures. We conducted two types of cluster analyses (HCA and ADDTREE) using two versions of algorithms (Chan's algorithm and Crowe's algorithm) to obtain dissimilarities matrices from VFT data. While the results obtained by these cluster analyses were not exactly the same, the general trend was that the two patient groups elicited topologically similar semantic structures. Thus, B_k values for the Turkish patients vs. Japanese patients comparison were larger than those for the Japanese patients vs. Japanese normal controls comparison (Table 4). In addition, ADDTREE analysis revealed that semantic memory in the two patient groups was not firmly organized, as indicated by loose connections *within* sub-clusters.

The reason for the lack of firm cluster structures in Japanese normal controls may be due to an attempt to match the demographic and other variables (i.e. education and the number of words produced in the VFTs) of the control subjects with those of the Japanese patients. In fact, ANOVA revealed that the VFT scores did not differ between the two groups. However, it should be noted that the cluster structure of Japanese patients was more similar to that of Turkish patients than to that of Japanese control subjects, despite the fact that the performance on the VFTs by the Japanese patients was comparable to that by the Japanese normal controls.

The analyses of the metric feature of semantic structures also exhibited a relatively greater similarity between Turkish patients and Japanese patients than between Japanese patients and Japanese normal controls. Thus, the dissimilarity matrices of the two patient groups with Chan's algorithm were significantly correlated with the highest value (Table 5). Similarly, correlations between Turkish patients and Japanese patients with Crowe's algorithm tended to be higher than those between Japanese patients and Japanese normal controls, although they did not reach significance. While a previous study (Prescott et al., 2006) found a high correlation between schizophrenia patients and normal control subjects (Chan's algorithm: 0.67, Crowe's algorithm: 0.75), this finding was not replicated in the current study.

Interestingly, category items frequently produced in the CFT by Japanese patients were similar to those by control subjects, in spite of dissimilarity of semantic structures (Table 2). The result suggests that typicality (common animal names) and dissimilarity (feature-based semantic association) are independently affected, and that the latter is more vulnerable to the pathological process of schizophrenia.

The impaired semantic structure in patients with schizophrenia may be explained by abnormal neural development. The neurodevelopmental hypothesis of schizophrenia (Rapoport et al., 2005) predicts that the cognitive impairment is already evident in the premorbid stage of the illness. This concept is supported by our previous study (Sumiyoshi et al., 2001), which reports more severely impaired semantic structure in patients with an earlier onset of illness.

Cohort studies (Chen et al., 2000; Keefe et al., 1994) also provide evidence for the notion that an abnormal neural development underlies irregular semantic structures. Thus, Chen et al. (2000) investigated the cognitive function of family members of patients with schizophrenia, and found that the CFT performance was specifically impaired in non-psychotic siblings of schizophrenia subjects, while the performance on other tasks was spared. Similarly, Phillips et al. (2004) reported that young patients, who were close to illness onset, exhibit a severe disturbance exclusively in the performance on the CFT but not the LFT. These results indicate that the normal development of semantic association, which affects CFT performance, is disturbed in subjects who are vulnerable to developing schizophrenia.

The specific pattern of deficits in the performance on the CFT also lends support to the hypothesis that an abnormal neural development underlies impaired semantic organization in subjects with schizophrenia. In the normal course of development, perceptual dimensions (e.g. size) appear first in the semantic structure, followed by knowledge-based dimensions (e.g. domesticity, predation) (Howard and Howard, 1977). In patients with Alzheimer's disease, these events have been suggested to progress in the opposite direction, i.e., the knowledge-based dimensions deteriorate before perceptual-based dimensions are affected (Chan et al., 1993a; Chan et al., 1993b). On the other hand, deterioration of semantic structure in schizophrenia is likely to exhibit a different pattern, i.e., the perceptual dimension is more vulnerable than the knowledge-based dimension (Paulsen et al., 1996; Sumiyoshi et al., 2001). This pattern of degradation indicates an irregular development of the semantic structure in individuals vulnerable to developing schizophrenia, which may arise from an abnormal neural development.

A number of researchers have reported that the impaired performance on the CFT is not totally explained by deficits in executive function (Bozikas et al., 2005; Goldberg et al., 1998; Gourovitch et al., 1996; Rossell et al., 1999). Thus, these authors have found a greater decrease in verbal outputs in the CFT than in the LFT, the latter representing mainly executive function. Our results presented here did not show such a pattern in VFT performance in the patient groups; performance on the CFT is better than that on the LFT in all groups. This may be due to the fact that Japanese orthography and Turkish orthography are different from that of English. Accordingly, we previously found that the execution of the LFT is more severely impaired in Japanese patients with schizophrenia than in English-speaking patients (Sumiyoshi et al., 2004). This is probably due to the inflexible correspondence between phonemes and graphemes and/or the lack of phonological clusters in the Japanese orthography. The association between phonemes and graphemes is basically one-to-one in the Japanese orthography, unlike the English counterpart whose correspondence is one-to-many. Furthermore, the lack of "phonemic cluster", i.e. coherence of words characterized with specific associations between phonemes and graphemes[1], makes word searching more demanding. Without phonemic clusters, as in the Japanese language, subjects have to rely on exhaustive searching (i.e. enumeration of all possible combinations of syllables to find a lexical word). Thus, unlike English-speaking subjects, performance on the

[1] Three criteria for organization of clusters have been proposed in previous studies (Robert et al., 1998; Troyer et al., 1997). They are: (1) first letter, words beginning with same first two letters, such as "prick", "prison" and "prism"; (2) vowel sounds, words differing only by a vowel sound such as "seat", "sight", and "sought"; and (3) homonyms, the same oral shape but with different spelling, such as "some" and "sum".

LFT would be considerably impaired in Japanese patients, which may be the case for Turkish patients as well.

Although the patients studied in this study showed a comparable degree of disturbances in the CFT and LFT, a distinct neuropsychological substrate other than executive function is likely to underlie the performance on the former task. It is assumed that the unstructured semantic memory in the two patient groups, as revealed by ADTREE analysis and B_k values, prevented effective word search or retrieval, which is necessary for animal naming.

In summary, we have reported impaired semantic organization in patients with schizophrenia, based on analyses of the word order produced in the CFT. Importantly, this study was the first to demonstrate isomorphic cluster structures in Turkish and Japanese patients with schizophrenia. These results suggest impaired organization of long-term semantic memory in schizophrenia is independent of the language system or cultural backgrounds.

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Effect of perospirone on P300 electrophysiological activity and social cognition in schizophrenia: A three-dimensional analysis with sLORETA

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ABSTRACT

The purpose of this study was to determine if perospirone, a second generation antipsychotic drug and partial agonist at serotonin-5-HT_{1A} receptors, enhances electrophysiological activity, such as event-related potentials (ERPs), in frontal brain regions, as well as cognitive function in subjects with schizophrenia. P300 current source images were obtained by means of standardized low resolution brain electromagnetic tomography (sLORETA) before and after treatment with perospirone for 6 months. Perospirone significantly increased P300 current source density in the left superior frontal gyrus, and improved positive symptoms and performance on the script tasks, a measure of verbal social cognition, while verbal learning memory tended to be improved. There was a significant correlation between the changes in P300 amplitude on the left frontal lead and those in social cognition. These results suggest the changes in three-dimensional distribution of cortical activity, as demonstrated by sLORETA, may mediate some of the actions of antipsychotic drugs. The distinct cognition-enhancing profile of perospirone in patients with schizophrenia may be related to its actions on 5-HT_{1A} receptors.

1. Introduction

Reduction of P300 amplitudes of event-related potentials (ERPs) has been consistently reported in subjects with schizophrenia, as well as other psychiatric conditions (Kawasaki et al., 1997; Sumiyoshi et al., 2006; Higuchi et al., 2008; for review, see Kawasaki et al., 2007). Several previous studies investigated the effect of antipsychotic drugs on P300 in patients with schizophrenia. For example, treatment with clozapine, the prototype of the second generation antipsychotic drugs (SGAs), has been found to increase P300 amplitudes (Niznikiewicz et al., 2005; Umbricht et al., 1998), without affecting deficits in mismatch negativity and N200 components (Umbricht et al., 1998).

Perospirone is a novel SGA marketed in Japan for the treatment of schizophrenia, which shows high affinities for dopamine (DA)-D_2 and serotonin-5HT_{2A} receptors, as well as partial agonist activity at 5-HT_{1A} receptors (Kato et al., 1990). Araki et al. (2006b) reported the advantage of switching from previous medications to perospirone for enhancing memory organization, a cognitive domain related to frontal lobe function in subjects with schizophrenia, while the switch to perospirone did not affect verbal learning and memory (Araki et al., 2006a,b; Mori et al., 2004). These findings point to a distinct cognition-enhancing profile of perospirone.

Several lines of recent research on impaired cognition in schizophrenia have focused on real-world functional performance, as evaluated by neuropsychological tests of social cognition, such as script tasks (Matsui et al., 2006; Sumiyoshi et al., 2008). Performance on these tasks measures the ability of subjects to evaluate component actions of social situations, and is related to frontal lobe activity (Crozier et al., 1999). So far, no attempt has been made to determine whether treatment with antipsychotic drugs enhances performance on script tasks in patients with schizophrenia.

Low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1999), and more recently, standardized LORETA (sLORETA) (Pascual-Marqui, 2002) have been developed to provide three-dimensional images of electrical brain activity. For example, LORETA current source images with 19 or more electrodes have been shown to provide good estimates of the localization for activated brain regions identified with functional magnetic resonance imaging (Mulert et al., 2004).

We previously reported that 6-month treatment with olanzapine increased the P300 current source density in left temporal brain regions, as demonstrated by LORETA, and enhanced verbal learning and memory,

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as measured by a word memory test, in subjects with schizophrenia (Sumiyoshi et al., 2006; Higuchi et al., 2008). These findings suggest the advantage of localizing P300 generators with LORETA/sLORETA methods to more precisely evaluate changes in anatomical configuration of neural activities in response to treatment with antipsychotic drugs.

Postmortem studies report that the 5-HT_{1A} receptor density is increased in prefrontal cortical areas, such as Area 10, in subjects with schizophrenia (Hashimoto et al., 1991; Sumiyoshi et al., 1996). This may represent up-regulation secondary to diminished 5-HT_{1A}-receptor stimulation (Hashimoto et al., 1991; Sumiyoshi et al., 1996). This concept is in agreement with clinical observations that augmentation therapy with 5-HT_{1A} partial agonists, e.g. buspirone and tandospirone, enhanced the performance on some neuropsychological tests representing frontal lobe function in patients with schizophrenia (Sumiyoshi et al., 2001, 2007).

On the basis of the above-reviewed findings, it was hypothesized that neural activity in frontal cortical regions would be enhanced by treatment with antipsychotic drugs with agonist actions at 5-HT_{1A} receptors, such as perospirone, in patients with schizophrenia. A previous study (Araki et al., 2006a) reported no significant changes in P300 amplitudes, as measured by conventional ERP methods, in subjects treated with perospirone. The primary purpose of this study, therefore, was to determine whether P300 current source density in the frontal cortex, as evaluated by the sLORETA method, would be increased during treatment with perospirone. We also sought to determine if there is an association between enhancement of P300 activity and improvement of performance on script tasks.

2. Methods

2.1. Subjects

Twenty out-patients meeting DSM-IV criteria for schizophrenia [male/female = 11/9; mean (S.D.) age = 31.9 (9.6), range 21–49 years] participated in the study. The mean age of onset and the mean duration of illness for these subjects were 23.3 (6.6) and 7.7 (6.8) years, respectively, with 13.7 (1.6) years of education. All subjects were right-handed, and were treated at the University of Toyama Hospital. Diagnosis was made based on the Structured Clinical Interview for DSM-IV (SCID) by experienced psychiatrists. A psychiatric and treatment history was obtained from the subjects, informants, and medical records. Subjects with a 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. This protocol was approved by the Committee on Medical Ethics of the 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: haloperidol ($N=4$), risperidone ($N=3$), nemonapride ($N=3$), olanzapine ($N=2$), or sulpiride ($N=1$). Seven subjects were neuroleptic-free. The mean (S.D.) risperidone-equivalent antipsychotic dose was 2.5 (4.2) mg/day.

Immediately after the baseline assessment, perospirone was administered. The treating psychiatrists adjusted the dose to optimize improvement in psychopathology, while attempting to keep the side effects of the drug tolerable. For the subjects who had already been treated with other antipsychotic drugs, the antipsychotic medication was switched stepwise to perospirone monotherapy during the initial 6 weeks. Concomitant medications were restricted to benzodiazepines. Six months after the start of the treatment with perospirone, the clinical and neuropsychological assessments were repeated.

2.2. Clinical assessments

The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) were administered by an experienced psychiatrist (T.I.) who was not informed of medication status. At baseline, the subjects had mean (S.D.) scores of 19.3 (17.2) and 44.8 (18.9) for the SAPS and SANS, respectively.

2.3. Neuropsychological evaluation

Administration of the script tasks was based on previous reports (Matsui et al., 2006; Sumiyoshi et al., 2008). Scores for the total of the three tasks (i.e. Recall, Frequency Judgment, Sequencing) were evaluated, based on previous reports (Matsui et al., 2006; Sumiyoshi et al., 2008). Verbal learning and memory were evaluated with the Japanese Verbal Learning Test (Higuchi et al., 2008; Matsui et al., 2007; Sumiyoshi et al., 2006).

2.4. ERP recording

ERPs were recorded at the time of the clinical assessment using an auditory odd-ball paradigm, based on an established method (Kawasaki et al., 2007; Sumiyoshi et al., 2006; Higuchi et al., 2008). Electroencephalograms (EEGs) were recorded with a 32-channel DC-amplifier (EEG-2100 version 2.22J, Nihon Kohden Corp., Tokyo, Japan). 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 (higher) target tones. All subjects responded correctly to the 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 = 0.16–120 Hz, 60 Hz notch filter). Gain was set at 10 K. Eye movement artifacts (blinks and eye movements) were rejected off-line, corresponding to 15.2 (9.9) trials per recording. 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. EEG responses 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).

2.5. sLORETA analysis

Current source analysis of P300 was conducted using the sLORETA software (Pascual-Marqui, 2002), which is available at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm. By this method, the maximum of the current density obtained at a given moment was taken as the source of the particular component. We calculated sLORETA images for each ERP in the time frame 250–500 ms post-stimulus.

The head model for the inverse solution (Volume conductor model) uses the electric potential lead field computed with the boundary element method applied to the MNI152 template (Fuchs et al., 2002; Jurcak et al., 2007). The MNI brain volume was scanned at 5 mm

Table 1
Effect of perospirone on psychopathology and cognition.

Variables	Baseline	6 month	t	ES
SAPS	19.3 (17.2)	12.1 (15.7)	3.05**	0.80
SANS	44.8 (18.9)	47.5 (23.4)	0.54	0.16
Script tasks	25.6 (3.6)	28.3 (1.7)	2.91**	0.84
JVLT	8.3 (4.03)	11.4 (8.4)	1.61†	0.46

** $P<0.01$, * $P<0.05$, †$P<0.10$ compared with baseline values. SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; JVLT, Japanese Verbal Learning Test.

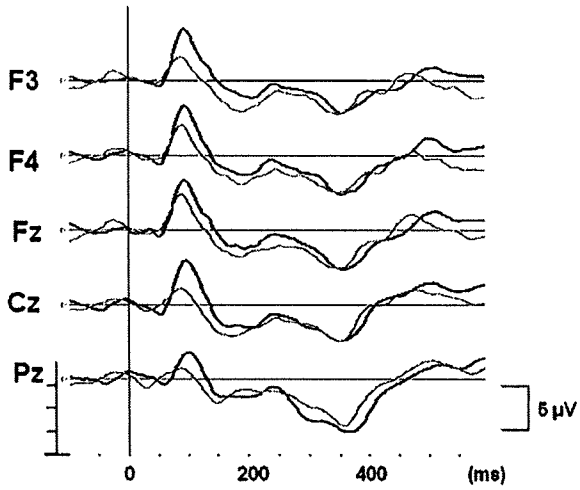

Fig. 1. Grand average of ERP waveforms before (black lines) and after (red lines) treatment with perospirone in patients with schizophrenia.

resolution. This produced 6239 cortical grey matter voxels (Mazziotta et al., 2001).

2.6. Data analysis

Differences in P300 current source density between baseline and 6 months after treatment with perospirone were assessed by voxel-by-voxel comparison with paired t-tests (two-tailed) for 6239 voxels per each sLORETA image, followed by adjustments for multiple comparisons. Comparisons of clinical variables were conducted with paired t-tests (one-tailed). Correlational analysis was performed by Spearman's rank correlation test. Statistical analyses were conducted using SPSS 15.0 software package. Significance was considered when the *P*-value was less than 0.05.

3. Results

Twelve patients (male/female = 8/4) completed the 6-month study, whereas eight dropped out after baseline assessment. The reasons for drop-out for these eight subjects were as follows: non-compliance with treatment ($N=2$), symptom exacerbations ($N=2$), refusal to have further cognitive testing ($N=2$), and lost to follow-up ($N=2$). Data from the 12 subjects were used for subsequent analyses. On completion of the study, mean dosage of perospirone was 18.3 (11.9) mg/day (range 8–32 mg/day).

As shown in Table 1, treatment with perospirone significantly enhanced performance on the script tasks and reduced SAPS scores with large effects sizes. SANS scores did not change significantly, while the improvement of performance on the JVLT was marginally significant with a moderate effect size. The percentage of reduction of SANS + SAPS Total score at endpoint vs. baseline was 13.5 (45.6) (range: −58.5–100).

Fig. 1 shows grand averages of ERP waveforms in the completer subjects before and after treatment with perospirone. P300 amplitudes and latency at Fz, Cz, Pz, F3, and F4 leads were not significantly changed during treatment. On the other hand, comparison of P300 current source density between baseline and 6-month evaluations revealed a significantly enhanced neural activity ($t=4.17$, corrected $P=0.001$) in the left superior frontal gyrus [Area 10; (X, Y, Z) = (−25, 55, 30 mm)], as demonstrated in Fig. 2.

Based on the findings with sLORETA analysis, we further investigated the relationship between the changes in P300 amplitudes at the left frontal lead (F3) and those in performance on the script tasks during treatment, and found a significant positive correlation between these two variables ($Rs=0.726$, $P=0.027$).

4. Discussion

To our knowledge, this study is the first to investigate the effect of an antipsychotic drug on three-dimensional distribution of the P300 generator using the sLORETA method in subjects with schizophrenia. Treatment with perospirone for 6 months was associated with an increase in P300 current density in the left prefrontal cortex. Performance on the script tasks was improved during treatment, which was positively correlated with the changes in P300 amplitudes on the left frontal lead. Positive symptoms were also improved during treatment with perospirone. The effect sizes of the script tasks and positive symptoms were satisfactorily large.

The mechanisms by which perospirone enhanced P300 activity in the prefrontal cortex and social cognition may include 5-HT_{1A} agonist potency of perospirone (Kato et al., 1990). The 5-HT_{1A} receptor density has been reported to be increased in the left prefrontal cortex of subjects with schizophrenia (Sumiyoshi et al., 1996), which may represent up-regulation secondary to diminished 5-HT_{1A} receptor stimulation (Sumiyoshi and Meltzer, 2004). This hypothesis is in agreement with our current observations that perospirone specifically enhanced P300 current density in this brain region, and improved performance on the script tasks, representing an aspect of frontal lobe function (Crozier et al.,

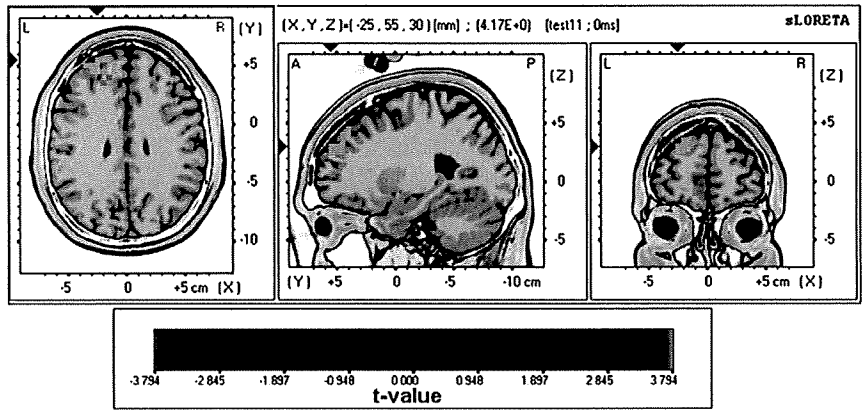

Fig. 2. Effect of perospirone on P300 electrophysiological activity in patients with schizophrenia as demonstrated by sLORETA images. Differences in the P300 current source density between before and after treatment are indicated.

1999; Matsui et al., 2006; Sumiyoshi et al., 2008), in patients with schizophrenia.

Some of the subjects studied here had been pre-treated with other SGAs, such as risperidone and olanzapine. We previously reported olanzapine enhanced P300 current density in the left superior temporal gyrus in subjects with schizophrenia, as demonstrated by LORETA (Sumiyoshi et al., 2006; Higuchi et al., 2008). As these SGAs are devoid of a noticeable affinity for 5-HT_{1A} receptors (Sumiyoshi et al., 2007), our observations with perospirone further indicate that stimulation of 5-HT_{1A} receptors may mediate the ability of this agent to increase P300 current source density in the left prefrontal cortex.

A major limitation of this study was that the subjects were rather heterogeneous in terms of premedication. Also, a relatively small group of subjects due to a rather large drop-out rate made it difficult to draw definite conclusions about, for example, the effect of perospirone on verbal learning and memory.

In summary, the results of this study provide further support for the usefulness of (s)LORETA imaging of electrophysiological activities to elucidate neural mechanisms underlying the effect of antipsychotic drugs on cognitive function in schizophrenia. The ability of perospirone to improve social cognition may be related to its actions on 5-HT_{1A} receptors.

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ORIGINAL INVESTIGATION

Long-term effects of neonatal MK-801 treatment on prepulse inhibition in young adult rats

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Abstract
Rationale Blockade of *N*-methyl-D-asparate (NMDA) receptors has been shown to produce some of the abnormal behaviors related to symptoms of schizophrenia in rodents and human. Neonatal treatment of rats with non-competitive NMDA antagonists has been shown to induce behavioral abnormality in a later period.
Objectives The aim of this study was to determine whether brief disruption of NMDA receptor function during a critical stage of development is sufficient to produce sensorimotor-gating deficits in the late adolescence or early adulthood in the rat.
Methods Male pups received the NMDA receptor blocker MK-801 (0.13 or 0.20 mg/kg), or an equal volume of saline on postnatal day (PD) 7 through 10. The animals were tested twice for prepulse inhibition (PPI) and locomotor activity in pre- (PD 35-38) and post- (PD 56-59) puberty.
Results Neonatal exposure to both doses MK-801 disrupted PPI in the adolescence and early adulthood. Low-dose MK-801 elicited long-term effects on startle amplitudes, whereas high-dose MK-801 did not. Neither dose of MK-801 showed a significant effect on spontaneous locomotor activity, whereas the high dose attenuated rearing.
Conclusions The results of this study suggest neonatal exposure to MK-801 disrupted sensorimotor gating in the adolescence and early adulthood stages. These findings indicate that rats transiently exposed to NMDA blockers in neonatal periods are useful for the study of the pathophysiology and treatment of schizophrenia.

Keywords NMDA receptor · MK-801 · Neonatal · Prepulse inhibition · Locomotor activity · Rat · Animal model · Schizophrenia

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Introduction

Non-competitive antagonists at the *N*-methyl-D-asparate (NMDA) receptor have been shown to induce schizophrenia-like symptoms, i.e., positive and negative symptoms, and cognitive dysfunction in normal subjects (Jentsch and Roth 1999). These observations lead to the concept that rodents treated with NMDA receptor antagonists provide an animal model of schizophrenia (Bubenikova-Valesova et al. 2008; Jentsch and Roth 1999). In accord with this view, numerous studies reported that NMDA receptor antagonists, such as phencyclidine (PCP), MK-801, and ketamine, produce behavioral changes reminiscent of symptoms of schizophrenia i.e. hyperlocomotion, stereotypy, information-processing deficits, impairments of cognitive function and social interactions (Breese et al. 2002; Bubenikova-Valesova et al. 2008; Moghaddam and Jackson 2003).