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.

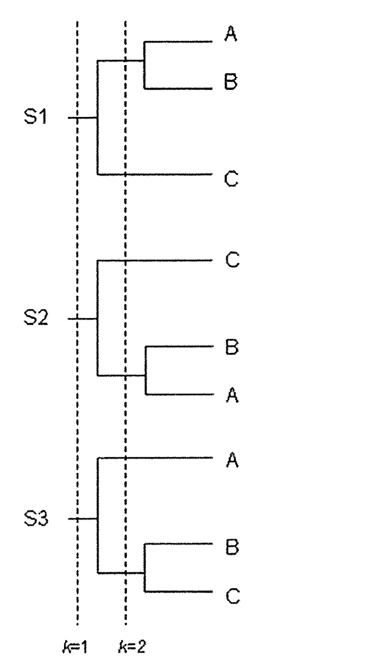
ADDTREE and HCA were performed to examine the semantic structures, using both Chan's algorithm (Chan et al., 1993a) and Crowe's algorithm (Crowe and Prescott, 2003). Thus, four types of analyses (2 cluster analyses × 2 algorithms) were conducted. The details of the former algorithm have been described 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.



	S1	S2	S3
k=1	(ABC)	(ABC)	(ABC)
k=2	(AB)(C)	(AB)(C)	(A)(BC)

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.

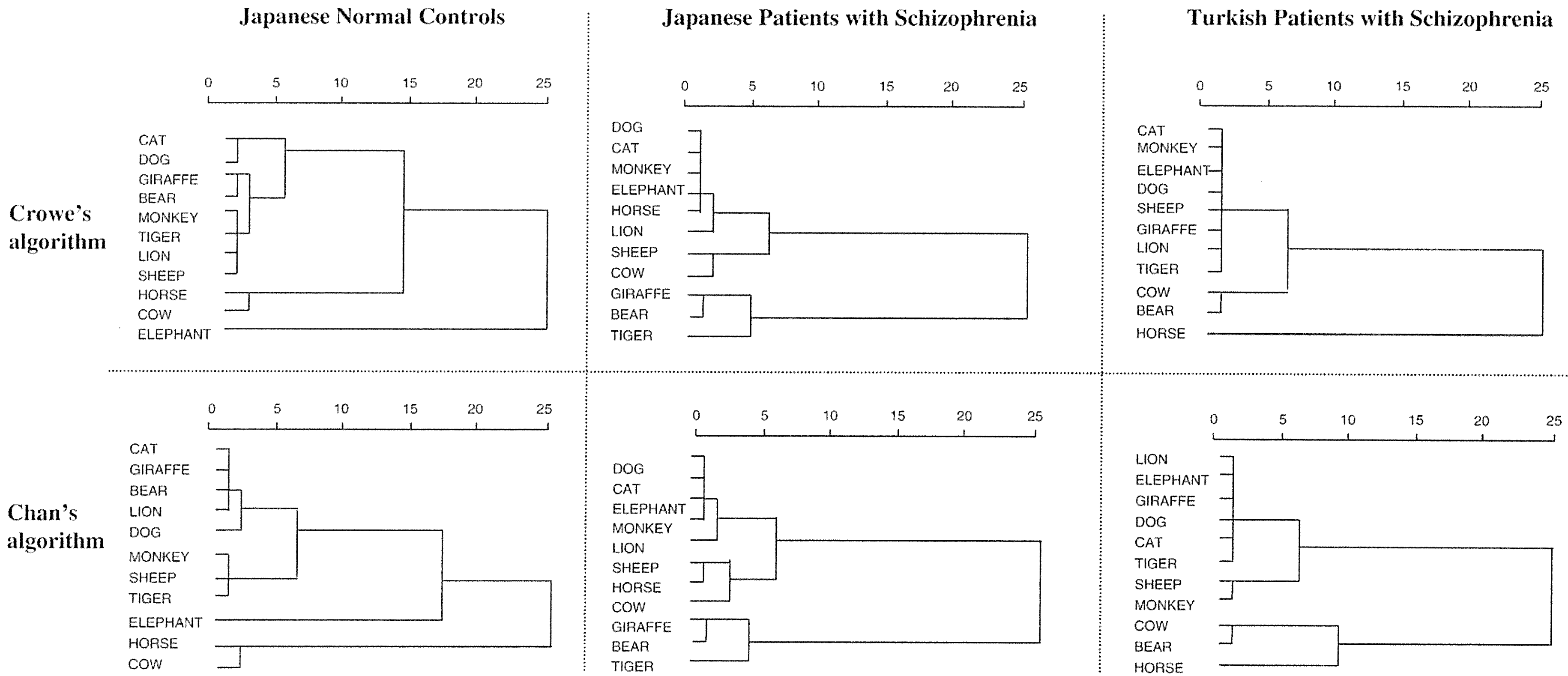


Fig. 2. Cluster structures as demonstrated by hierarchical cluster analysis in Japanese normal controls (left), Japanese patients with schizophrenia (middle), and Turkish patients with schizophrenia (right).

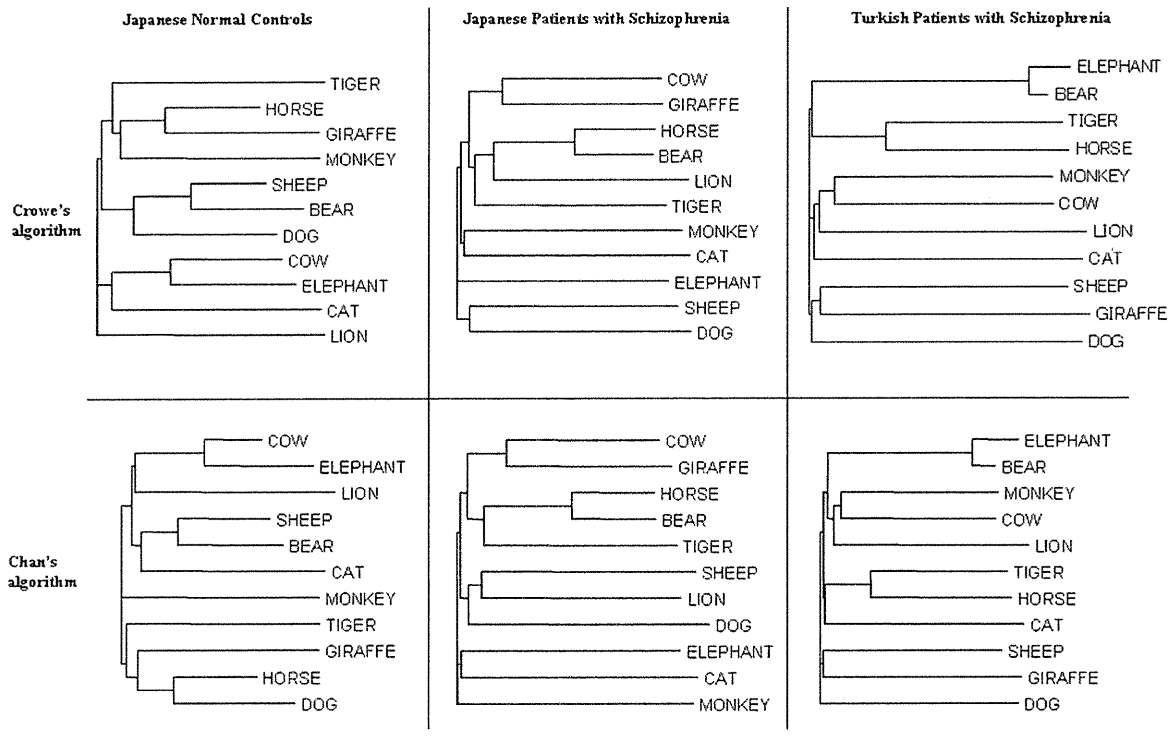


Fig. 3. Cluster structures as demonstrated by ADDTREE analysis in Japanese normal controls (left), Japanese patients with schizophrenia (middle), and Turkish patients with schizophrenia (right). The length of branches represents inter-item distances. Thus, normal controls have relatively shorter branches 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

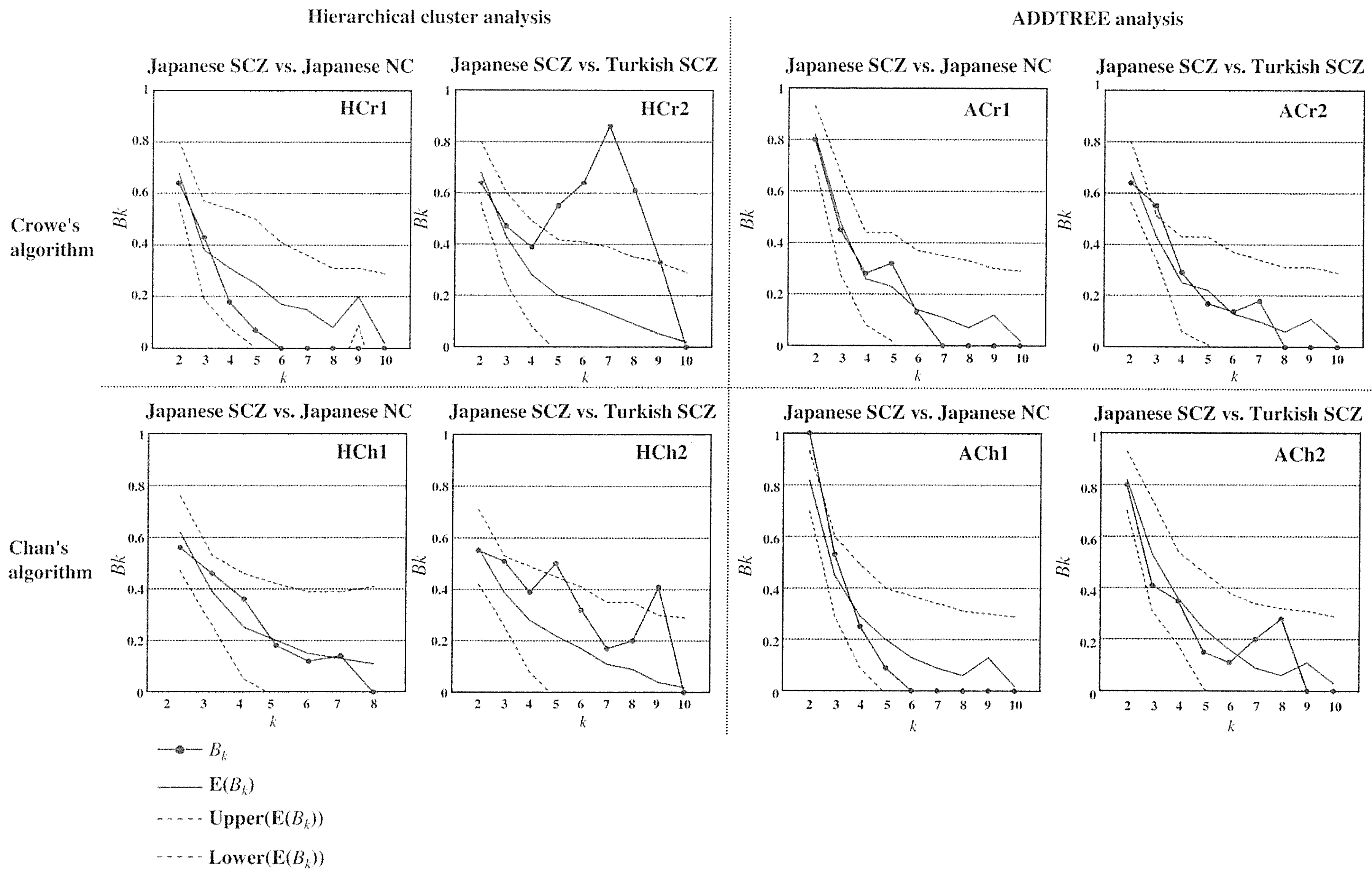


Fig. 4. B_k values obtained from comparisons between Japanese patients with schizophrenia and Japanese normal controls (HCr1, HCh1, ACr1, ACh1) and between Turkish patients and Japanese patients (HCr2, HCh2, ACr2, ACh2). HCr and HCh are abbreviations for hierarchical cluster analysis by Crow's algorithm 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.

Acknowledgement

This work was supported by a Grant-in-Aid from the Ministry of Education and Science of Japan (No. 18530502) to Dr. Chika Sumiyoshi, as well as a Young Investigator Award from NARSAD, a Pharmacopsychiatry Research Grant from the Mitsubishi Pharma Research Foundation, a fellowship from the Ministry of Education and Science of Japan, and a Grant-in-Aid for Scientific Research (No. 16591126, 19591345) from Japan Society for the Promotion of Science to Dr. Tomiki Sumiyoshi.

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Neuroscience Research 69 (2011) 252–257

Contents lists available at ScienceDirect

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Impaired ability to organize information in individuals with autism spectrum disorders and their siblings

Chika Sumiyoshi[a,*], Yuki Kawakubo[b,c,d], Motomu Suga[b], Tomiki Sumiyoshi[e], Kiyoto Kasai[b]

[a] *Faculty of Human Development and Culture, Fukushima University[1], Fukushima, Japan*
[b] *Department of Neuropsychiatry, Graduate School of Medicine, University of Tokyo[2], Japan*
[c] *Japan Science and Technology Agency (JST)[3], Japan*
[d] *Core Research of Evolutional Science & Technology (CREST)[4], Japan*
[e] *Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Science, Toyama, Japan*

ARTICLE INFO

Article history:
Received 4 October 2010
Received in revised form
19 November 2010
Accepted 22 November 2010
Available online 1 December 2010

Keywords:
Autism spectrum disorders
Wisconsin Card Sorting Test
Verbal learning task
Organizing of information
Cognitive function
Cognitive endophenotype

ABSTRACT

Despite rigorous research on disturbances of executive function and social cognition in autism spectrum disorders (ASD), little information has been available concerning higher cognitive functions, such as the ability to focus and associate relevant features to form categories, or 'organizing of information'. The purpose of this study was to investigate this issue by using the Wisconsin Card Sorting Test (WCST) and the Verbal Learning Task (VLT). Cognitive assessments were conducted in 22 individuals with ASD, 14 non-affected siblings, and 15 age-matched control subjects. Overall, individuals with ASD performed significantly worse on the WCST and VLT compared to their siblings and normal control subjects. Although siblings performed generally well on both tasks, they exhibited similar degree of perseverative responses in the WCST compared to the probands. A linear increase of the memory organization score in the VLT was also absent in siblings as well as the ASD group. These results suggest an impaired ability to organize information is one of the cognitive endophenotypes for ASD.

1. Introduction

High-functioning autism (HFA) and Asperger syndrome (AS) are defined as a part of autism spectrum disorders (ASD), characterized by difficulties in establishing social relationships, poor communication skills, lack of imaginative behavior, and repetitive stereotypic behaviors (American Psychiatric Association, 1994; World Health Organization, 1992). Although subjects with HFA or AS do not show a significant delay in intelligence, they have been reported to elicit disturbances of some domains of cognitive function, e.g. social cognition (Baron-Cohen et al., 1985) and executive function (Hill, 2004). For example, they perform poorly on various types of Theory of Mind tasks, ranging from perceptual (e.g. The Eyes Task), verbal (e.g. The Strange Stories) (Kaland et al., 2008a) to emotional ones (identification of emotional states of others) (Shamay-Tsoory, 2008). These results suggest the inability to recognize thoughts and feelings to understand how others act. Also, subjects with ASD have been reported to show impaired executive function, specifically, cognitive flexibility (Geurts et al., 2004) and inhibition (Happe et al., 2006).

Although previous studies have identified some aspects of cognitive disturbance associated with ASD, more specific assessments of higher cognitive functions would help further understand the psychopathology of the disorder. Specifically, 'organizing infor-

Abbreviations: ASD, autistic spectrum disorders; WCST, Wisconsin Card Sorting Test; VLT, verbal learning task; SCR, stimulus category repetition.

* Corresponding author at: Faculty of Human Development and Culture, Fukushima University, 1 Kanayagawa Fukushima, Fukushima 960-1296, Japan. Tel.: +81 24 548 8161; fax: +81 24 548 8161.

E-mail addresses: sumiyoshi@educ.fukushima-u.ac.jp (C. Sumiyoshi), yukik-tky@umin.ac.jp (Y. Kawakubo), mosuga-tky@umin.net (M. Suga), sumiyo@med.u-toyama.ac.jp (T. Sumiyoshi), kasaik-tky@umin.net (K. Kasai).

[1] The AQ is a self-report questionnaire consisting of five domains of questions regarding the psychopathology of ASD: social skills, attention switching, attention to detail, communication, and imagination.

[2] The CARS is a behavior rating scale completed by clinician or parents based on subjective observation. The scale contains 15 items (e.g. relationship to people, imitation, and so on) and each item is rated with 1 (normal for child's age) to 4 (severely abnormal).

[3] This BAP scale covers three domains of autism, i.e. 'communication impairment', 'social dysfunction', and 'stereotyped and repetitive behavior'. Each domain includes items coded as either 'presence' or 'absence' of autistic symptoms. A subject would be classified as BAP if his/her total score of each domain exceeds the designated cut-off point.

[4] There were two outliers in the %PEM, deviating 2SD from the average of the ASD group. We re-analyzed the data excluding these deviations but the main results have remained the same.

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doi:10.1016/j.neures.2010.11.007

mation', i.e. the process of focusing and associating relevant information to form categories, appears to be worth investigating, as they are assumed to be pertinent to some cardinal traits, such as inflexible and perseverated behavior or restricted interests (Kenworthy et al., 2005).

The Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) has been used to provide a good measure to evaluate the focusing process. This test consists of four stimulus types, and requires subjects to detect sorting principles from stimulus cards and categorize a response card. The task proceeds through the shifts of sorting principles, i.e. color, form and number. Successful performance on the WCST depends on the ability to detect the correct sorting principle on the basis of feedback, and maintain the principle until it is replaced by a new one.

From 1980s onward, more than 30 studies have been conducted to examine the WCST performance in individual with ASD. The majority of them have reported the degradation in performance on some measures of the task (generally, the number of categories achieved and perseverative errors. For review, Hill (2004), Pennington and Ozonoff (1996), for recent studies, Ambery et al., 2006; Geurts et al., 2004; Hill, 2004; Hill and Bird, 2006; Kaland et al., 2008b; Lopez et al., 2005; Pennington and Ozonoff, 1996; Sergeant et al., 2002; Voelbel et al., 2006; Winsler et al., 2007). Studies targeting adults with ASD, however, have been relatively limited (Ambery et al., 2006; Ciesielski and Harris, 1997; Lopez et al., 2005; Rumsey, 1985; Rumsey and Hamburger, 1988, 1990). Most of these investigations have reported poor achievement of the task in adults with ASD, as has been observed in the studies for younger samples. Ambery et al. (2006), for example, has reported that adults with ASD produced substantially greater perseverative errors, indicating that the ability to find and utilize relevant features of in-coming information may not have been well developed in people with ASD.

There is also paucity of information as to the ability to associate information for category formation in individuals with ASD, besides the findings from free-recall task (Tager-Flusberg, 1991) and the California Verbal Learning Task (CVLT; Delis et al., 1987). Both tasks are similar in that they require subjects to learn orally presented word lists and let them recognize the association of presented stimulus; the association process is evaluated to calculate the difference in the number of recalled words between related (members of a particular category) and unrelated word lists in the free-recall task, or by the number of voluntarily re-organized category-wise responses in the CVLT. Subjects with ASD have been reported to fail to achieve better in the related lists compared to the unrelated lists in the free-recall paradigm, unlike IQ-matched normal controls (Bowler et al., 1997). On the other hand, a study with the CVLT (Minshew and Goldstein, 1993) has not detected clear differences in the semantic cluster ratio, a measure of category formation, between subjects with ASD and normal controls.

Given the mixed results from these verbal learning tasks, more sensitive methods to evaluate the ability to associate information for categorization is needed. The Verbal Learning Task (VLT; Gold et al., 1992; Yamashita et al., 2000), which has been used in the studies of schizophrenia, would be appropriate for this purpose. The VLT consists of three types of word lists: the Random, Blocked, and Semi-blocked lists. The Random list consists of semantically unrelated nouns while the Blocked and Semi-blocked lists contain category exemplars. In the Blocked list, the words are presented on a category-basis, while the words of the same category are never presented consecutively in the Semi-blocked list. One of the strength of the VLT is the inclusion of the SCR (Stimulus Category Repetition; Bousfield and Bousfield, 1966), which quantifies the category-wised responses in the Semi-blocked list. With this measure, the process of category-formation is directly evaluated.

To determine if the deficits of organizing information, discussed above, are cognitive traits specific to ASD, i.e. a cognitive endophenotype, it would be worthwhile to investigate this cognitive ability in biological relatives. A number of studies have reported that several domains of cognitive function are, to some extent, disturbed in first-degree relatives of individuals with ASD (Bailey et al., 1998; Dorris et al., 2004): executive function (Delorme et al., 2007; Hughes et al., 1999; Kawakubo et al., 2009), central coherence (Baron-Cohen and Hammer, 1997; Baron-Cohen et al., 2006; de Jonge et al., 2006; Fombonne et al., 1997), and Theory of Mind (Smalley and Asarnow, 1990; Szatmari et al., 1993). As to the processes of organizing information, however, clear results have not been obtained. For instance, Ozonoff et al. (1993) has reported that sibling of ASD exhibited no distinct impairments in the overall performance on the WCST. On the other hand, studies using the intradimensional/extradimensional (ID/ED) set-shifting task, a categorization task akin to the WCST, have reported that parents (Hughes et al., 1997) and siblings (Hughes et al., 1999) of ASD probands performed poorly compared with those of typically-developed children. Apart from those contradicted findings for the ability to focus on relevant information, little is known about the process for category formation, at least under the verbal leaning task paradigm, in siblings of individuals with ASD.

The purposes of the current study were two-fold: first, the ability to organize information, specifically focusing and associating the relevant features to form categories, were investigated in subjects with ASD using the WCST and the VLT. The two tasks have been typically used as the measure for executive function (flexibility) and verbal learning (or working memory), respectively. The simultaneous implementation of these two tests, however, would be useful to evaluate the two processes of organizing of information; the percentage of perseverative errors of Milner (%PEM) in the WCST provide the index for the focusing process while the SCR in the VLT represents the one for the association process. Second, the possibility that the deficits of the two cognitive processes are ones of the cognitive markers, i.e. endophenotypes, of ASD was examined by administrating these tasks to siblings of subjects with ASD.

2. Method

2.1. Subjects

Twenty-two individuals with ASD (M/F = 19/3), 14 non-affected siblings (M/F = 8/6), and 15 age-matched normal controls (M/F = 11/4) entered the study. Male/female ratio was not significantly different among the groups ($\chi^2 = 4.01$, $df = 2$, *n.s.*). Subjects in the ASD group met DSM-IV criteria for autistic disorder ($N = 8$), Asperger disorder ($N = 12$) or pervasive developmental disorder not otherwise specified (PDD-NOS) ($N = 2$).

Individuals with ASD and their siblings were recruited from outpatient clinics in the following institutions: Departments of Neuropsychiatry and Child Psychiatry, University of Tokyo Hospital and Mie Prefectural Asunaro Hospital for Children and Adolescent Psychiatry. Participants from public symposia on ASD which took place at The University of Tokyo were also included. Healthy controls were mainly recruited from hospital staff members, their acquaintances and children, and college students. Exclusion criteria were neurological illness, traumatic brain injury with any known cognitive consequences and loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and alcohol/substance abuse or addiction. Besides, based on the Structured Interview Schedule of DSM-IV Axis I Disorders Research Version Non-patient Edition (SCID-I/NP), normal controls were excluded if they or their first-degree relatives had a history of DSM-IV axis I disorders. IQs were evaluated with the WISC-III or WAIS-R (IQ range: normal controls; 87–120, siblings; 90–118, ASD; 58–114). The full

Table 1
Demographic and clinical data.

	Controls	Siblings	ASD[a]
Male/female	11/4	8/6	19/3
Age	29.7(6.4)	24.5 (4.0)	26.5(7.4)
Education	15.9(2.1)	15.3(1.6)	12.5(1.8)**
CARS	–	15.6(0.8)	31.2 (6.1)‡
AQ-J	16.3 (5.6)	22.7 (5.52)	30.6 (8.6)†
Medication (mg/day)[b]	–	–	220.8 (347.7)
IQ[c]	99.7(8.6)	101.2(10.4)	94.1(17.8)

Note: ASD, autism spectrum disorders; CARS, Childhood Autism Rating Scale; AQ-J, Autism-Spectrum Quotient Japanese version.
[a] Missing data in education = 7, CARS = 1, AQ-J = 10.
[b] Chlorpromazine equivalent dose.
[c] Estimated IQ, controls and siblings; Full IQ, ASD.
** $p<0.01$; compared to controls and siblings.
‡ $p<0.01$; compared to siblings.
† $p<0.05$; compared to siblings.

version was administered to subjects with ASD and siblings while the abbreviated one (i.e. Information, Similarities, Picture Completion, and Digit Symbol-Coding) was applied to normal controls. Although 4 subjects with ASD had IQs of less than 70, they were included in the study as they had completed at least high school education (i.e. more than 12 years). In fact, the directions of principal results, presented later, did not change even if data from those cases were excluded. The Ethical Committee of The University of Tokyo Hospital approved this study (receipt No. 630-5). The Mie Prefectural Asunaro Hospital for Children and Adolescent Psychiatry delegated the ethical review to the ethical committee of The University of Tokyo Hospital because they did not have an institutional review board. Written informed consent was obtained from all participants.

The Autism-Spectrum Quotient Japanese version (AQ-J; Kurita and Koyama, 2006)[5] was administered to probands, siblings, and normal controls. In addition, subjects with ASD and siblings were assessed by the Childhood Autism Rating Scale-Tokyo Version (CARS-TV; Kurita et al., 1989)[6] by trained child psychiatrists. One-way ANOVA for AQ-J yielded a significant group difference ($F=9.65$, $df=2, 25$, $p<0.01$). Multiple comparisons with the Tukey method revealed that the ASD group elicited a significantly higher score than other two groups ($p<0.05$). As to CARS, *t*-test revealed a significantly higher score for the ASD group compared to siblings ($t=9.23$, $df=17$, $p<0.01$). These results indicate that the ASD group and other two groups were clinically independent. In fact, no siblings were found to elicit autistic features as evaluated by the Broader Autism Phenotype (Le Couteur et al., 1996).[7] All but one on the ASD subjects received medication, with eight of them treated with antipsychotics (risperidone = 4; pimoizide = 2; haloperidol = 2). Other medications included mood stabilizers (e.g. valproate = 6, lithium = 3), benzodiazepines (e.g. bromazepam = 3, nitrazepam = 2, triazolam = 2), anti-depressants (e.g. fluvoxamine = 4, paroxetine = 3), and anti-parkinson drugs (e.g. biperiden = 5, trihexyphenidyl = 2). Demographic and clinical profiles of participants are summarized in Table 1.

2.2. Design and procedure

WCST. A computerized version of the WCST (WCST-64: Computer Version-2 Research Edition, Psychological Assessment Resources, Inc.) was used. Subjects were requested to sort cards according to one of the implicit principles (i.e. color, shape, and number), which is altered after 10 consecutive correct responses. A test session was terminated when 6 shifts had been completed. Three variables, (1) number of categories achieved (CA), (2) the percentage of perseverative errors of Milner (%PEM), and (3) reaction time (RT), were analyzed.

VLT. The Japanese version of the VLT (JVLT; Yamashita et al., 2000) was used. This task consists of three 16-word lists: Random list, Blocked list, and Semi-blocked list. The Random list consists of 16 unrelated nouns. Other two lists contain four exemplars from four taxonomic categories (the Blocked list: stationery, animal, musical instruments, and sports; the Semi-blocked list: vehicles, seasoning, flower, and countries). In the Blocked list, exemplars in the same category were presented consecutively, while they were never given serially in the Semi-blocked list. Thus, in the Semi-blocked list, the list items would be re-organized in a category-wise manner, if a subject voluntary formed categories to be utilized as recalling cues.

Three trials were conducted and each trial included the Random, Blocked, and Semi-blocked lists. The lists were presented in the fixed order of the Random, Blocked, and Semi-blocked lists. Every word in the lists was presented orally in 1 s basis, and subjects were instructed to learn them. The VLT scores were calculated for each type of list as the average of the three trials. In addition, for the Semi-blocked lists, Stimulus Category Repetition (SCR; Bousfield and Bousfield, 1966) was calculated. SCR is defined as the total number of exemplars in the same category consecutively recalled in each trial. Thus, it was considered to be an index of the degree to which a subject associates information based on implicitly given categories (Koh et al., 1976).

2.3. Statistical analyses

Multivariate analysis of variance (MANOVA) was conducted to examine group differences for demographic variables (age, education, IQ) and three measures of WCST (CA, %PEM, RT). The arcsine transformation and logarithmic transformation were applied for %PEM and RT, respectively. The VLT scores were analyzed by three-way ANOVA with Group (normal controls vs. siblings vs. ASD) as between-subject factor, and Block (Random vs. Blocked vs. Semi-blocked) and Trial (1st vs. 2nd vs. 3rd) as within-subjects factor. The SCR scores were examined by two-way ANOVA, with Group (normal controls vs. siblings vs. ASD) as between-subjects factor and Trial (1st vs. 2nd vs. 3rd) as within-subjects factor. The correlation analyses were conducted between the CARS Total scores and the measures of the WCST and VLT to examine the relationship between the severity of symptoms and cognitive performances.

3. Results

3.1. Demographic variables

Demographic and clinical data are shown in Table 1. MANOVA indicated an overall difference among the three groups (*Wilks' lambda* = 0.52, $F=4.45$, $df=6, 68$, $p<0.01$). Subsequent univariate analyses revealed that the ASD group showed a significantly shorter education period than did other two groups ($F=13.22$, $df=2, 39$, $p<0.01$), while Age ($F=2.26$, $df=2, 48$, *n.s.*) and IQ ($F=2.29$, $df=2, 44$, *n.s.*) did not differ among the groups.

[5] The AQ is a self-report questionnaire consisting of five domains of questions regarding the psychopathology of ASD: social skills, attention switching, attention to detail, communication, and imagination.
[6] The CARS is a behavior rating scale completed by clinician or parents based on subjective observation. The scale contains 15 items (e.g. relationship to people, imitation, and so on) and each item is rated with 1 (normal for child's age) to 4 (severely abnormal).
[7] This BAP scale covers three domains of autism, i.e. 'communication impairment', 'social dysfunction', and 'stereotyped and repetitive behavior'. Each domain includes items coded as either 'presence' or 'absence' of autistic symptoms. A subject would be classified as BAP if his/her total score of each domain exceeds the designated cut-off point.

Table 2
Performance on the Wisconsin Card Sorting Test (WCST) and Verbal Learning Task (VLT).

	Controls	Siblings	ASD
WCST			
CA	6.0(1.7)	5.9(0.5)	4.2 (2.2)
%PEM	9.9 (4.5)	12.1 (9.2)	24.1 (19.5)
RT (min)	1.6(0.3)	1.8(0.8)	2.1(1.1)
JVLT			
Random	9.9(3.6)	10.1 (3.0)	8.6(3.6)
Semi-blocked	11.8(3.3)	12.9 (2.7)	10.0 (4.0)
Blocked	13.8 (2.9)	13.8(2.5)	11.2(4.3)
SCR1	3.0(2.4)	4.6 (2.8)	3.5 (3.2)
SCR2	6.7 (4.3)	7.6(3.8)	5.8 (4.0)
SCR3	8.9(4.3)	8.9(4.5)	5.9 (4.8)

Note: ASD, autism spectrum disorders; WCST, Wisconsin Card Sorting Test; JVLT, Japanese Verbal Learning Task; CA, categories achieved; %PEM, percentages of Milnere-type perseverative errors; RT, reaction time; SCR, stimulus category repetition.

3.2. Performance on the WCST

Mean and SD for variables of the WCST are summarized in Table 2. MANOVA demonstrated significant overall group difference (*Wilks' lambda* = 0.71, $F = 2.70$, $df = 6, 86$, $p < 0.05$). Subsequent univariate analyses revealed main effects of CA ($F = 8.31$, $df = 2, 45$, $p < 0.01$) and %PEM ($F = 5.20$, $df = 2, 45$, $p < 0.01$),[8] but not RT ($F = 0.10$, $df = 2, 45$, *n.s.*). Multiple comparisons showed a significantly lower CA score for the ASD group compared to other two groups ($p < 0.01$). As for the %PEM, the difference was found only between the ASD group and normal controls. Siblings did not differ from either group.

3.3. Performance on the VLT

Mean and SD for variables of the VLT are shown in Table 2. ANOVA showed a significant Block × Group interaction effect ($F = 2.54$, $df = 4, 96$, $p < 0.05$) on the VLT scores. Simple main effects of Group were significant for the Blocked ($F = 4.137$, $df = 2, 144$, $p < 0.05$) and Semi-blocked ($F = 5.87$, $df = 2, 144$, $p < 0.01$), but not the Random ($F = 1.72$, $df = 2, 144$, *n.s.*) lists condition. Multiple comparisons yield significant differences in the Blocked lists condition in the order of controls = siblings > ASD ($p < 0.05$). For the Semi-blocked lists condition, on the other hand, the difference was only found in siblings > ASD ($p < 0.01$).

ANOVA revealed a significant Trial × Group interaction effect ($F = 3.14$, $df = 4, 86$ $p < 0.05$) on the SCR score. Therefore, simple main effect for the Trial condition was examined, which yielded significant results for all groups (normal controls: $F = 49.86$, $df = 2, 129$, $p < 0.01$; siblings; $F = 27.23$, $df = 2, 129$, $p < 0.01$; ASD; $F = 10.22$, $df = 2, 129$, $p < 0.01$). Multiple comparisons revealed a stepwise enhancement on the SCR score (3rd trial > 2nd trial > 1st trial) in normal controls ($p < 0.01$), while the difference was detected only between the first two trials (2nd trial > 1st trial) in siblings ($p < 0.01$) and ASD patients ($p < 0.01$).

3.4. Correlation analyses

No measures in the WCST were significantly correlated with the CARS total score (CA: $r = -0.34$, $df = 19$, *n.s.*; %PEM: $r = -0.12$; RT: $r = 0.15$ $df = 18$, *n.s.*). The same result was obtained in the VLT (Random: $r = -2.66$; Blocked: $r = -0.14$; Semi-blocked: $r = -0.21$, $df = 20$, *n.s.*; SCR1: $r = -0.06$; SCR2: $r = -0.23$; SCR3: $r = -0.16$, $df = 15$, *n.s.*).

[8] There were two outliers in the %PEM, deviating 2SD from the average of the ASD group. We re-analyzed the data excluding these deviations but the main results have remained the same.

4. Discussion

The purpose of the current study was to investigate the ability to organize information in individuals with ASD and their siblings. Specifically, the two cognitive processes in that ability, i.e. focusing on relevant features and associating them to form categories, were examined using the WCST and VLT.

Overall, individuals with ASD performed poorly on the WCST and VLT, as shown by the significantly worse scores on most measures of the tasks (Table 3). Specifically, greater %PEM in the ASD group is in accordance with a previous study (Kenworthy et al., 2005), representing the poor ability to focus on the relevant information in subjects with ASD using other tasks (i.e. the Object Assembly, the Rey-Osterrrieth Complex Figure, the Story Sentence Memory, and letter fluency with "F, A, S". Similarly, the lack of an increase in the SCR supports the result from the free-recall task (Bowler et al., 1997), reporting the failure to associate category members in subjects with ASD. Both %PEM and the SCR scores did not correlate with the CARS score in the ASD group. Thus, it is possible that degradation in the cognitive process, such as focusing and associating relevant information, is intrinsic to the symptomatology of ASD irrespective of severity of the illness.

The poor cognitive performance in subjects with ASD cannot be attributed entirely to their shorter education period. First, the IQ level in subjects with ASD on the whole was not significantly different from those in siblings and normal controls, as shown by the analysis of the demographic variables. In addition, the RT in the WCST and performance on the Random List condition in the VLT were equivalent to those for normal controls and siblings. In all, these results suggest that general intelligence, visuo-motor skills, attention, and memory capacity, were relatively uniform among the three groups studied here.

Generally, the sibling group performed almost as equally well as the normal control group; however, there were some noticeable similarities between siblings and subjects with ASD (Table 3, highlighted in bold). First, siblings have failed to show the linear increase in the SCR score in the VLT. Second, the %PEM for siblings was not significantly smaller than that for the ASD group, although it did not differ from that of normal controls, either (Table 3). This result is worth noting as siblings performed better than individuals with ASD on other measures, such as the CA. In all, the results from the two tasks are likely to reflect the limited ability of siblings to focus and conceptualize categories using updated information.

The tendency of 'weak central coherence' may explain the current results for the subjects with ASD. 'Central coherence' is a cognitive trait to extract meaning, gist, and gestalt from given stimuli (Frith and Happe, 1994). Impairment of this ability, or 'weak central coherence', leads to an inclination to focus on individual parts of information without integrating them (Happe and Frith, 2006). This may be related to increased perseverative responses in subjects with ASD; once their attention has been captured by a particular dimension of features, shifting it according to negative feedback would become difficult.

The weak central coherence trait also seems to be related to higher cognitive function such as category formation and organization (Plaisted, 2001); in order to form a category, it is necessary to extract a commonality from each piece of information and ignore idiosyncratic features. This cognitive process may be disturbed in people with ASD, leading to the restriction in forming categories. The lack of an increase in the SCR scores may be accounted for by this cognitive deficit.

Interestingly, the tendency related to weak central coherence has also been reported in first-degree relatives of patients with ASD, especially their fathers (Happe et al., 2001). This seems to be consistent with our observations that siblings of subjects with ASD failed to show a steady increase of the SCR in the VLT, suggesting

Table 3
Summary of performances on the WCST and JVLT.

WCST		JVLT			
		SCORE		SCR	
CA	Controls = Siblings > ASD	**Blocked**	Controls = Siblings > ASD	**Normal controls**	SCR1 > SCR2 > SCR3
%PEM	Controls < ASD Controls = siblings **Siblings = ASD**	**Semi-blocked**	Siblings > ASD Controls = Siblings	**ASD**	**SCR1 = SCR2 > SCR3**
RT	Controls = Siblings = ASD	**Random**	Controls = Siblings = ASD	**Siblings**	**SCR1 = SCR2 > SCR3**

Note: ASD, autism spectrum disorders WCST; Wisconsin Card Sorting Test; JVLT, Japanese Verbal Learning Task; SCR, stimulus category repetition.

that degradation in the ability to associate information is one of the cognitive markers, i.e. endophenotypes for people vulnerable to ASD.

It is hypothesized that attenuated neural activities in parahippocampal regions may be responsible for the difficulties in organizing information in subjects with ASD. The left parahippocampal regions, including parahippocampal gyrus, has been suggested to play an important role in sorting, relating, and sending information to hippocampus (Eichenbaum, 1997; Sumiyoshi et al., 2006; Vargha-Khadem et al., 1997). Thus, dysfunction of these regions is assumed to impair the ability to systemize incoming information. In fact, several idiosyncrasies around parahippocampal regions have been reported in individuals with ASD. For example, Boucher et al. (2005) found a smaller parahippocampal volume in patients with ASD compared to normal controls, as well as weaker correlational activities between this region and the hippocampal region.

A key issue for future research is the developmental course of the knowledge structure, that is, semantic association in the long-term memory, in individuals with ASD. Given that the ability to organize information is impaired, knowledge structure would suffer from insufficient maturation in subjects with ASD, as has been reported in children with William's syndrome (Johnson and Carey, 1998). Although several attempts have been already made to address this issue (Dunn et al., 1996), further research is expected to clarify the link between the limited ability to organize information and the development of knowledge structure in individuals with ASD and those who are vulnerable to the disorder.

Finally, several limitations for the present study should be mentioned. First, it would be worthwhile to relate some cognitive measures studied here, e.g. %PEM and SCR, to endophenotypes of ASD in replication studies with a larger sample of ASD probands and their siblings. Second, although clinical variables such as intelligence did not significantly affect current findings, evaluation with more adjusted samples would be desirable in future studies.

5. Conclusion

The current study has identified the limited ability to organize information in individuals with ASD, extending the previous observations that they performed poorly on most of the measures of the WCST and verbal learning compared with normal controls. In addition, their siblings showed similar impairments on the measures of organizing of information derived from these tasks, suggesting that the deficits of this cognitive ability is one of the cognitive endophenotypes of ASD.

Acknowledgements

This study was supported in part by grants from the Ministry of Health, Labour, and Welfare (Health and Labour Sciences Research Grants, Research on Psychiatric and Neurological Diseases and Mental Health, H19-kokoro-ippan-012, H20-kokoro-ippan-001 & H20-3 to KK), and from the JSPS/MEXT (No. 20023009 & 21249064 to KK). A part of this study was also the result of "Development of biomarker candidates for social behavior" carried out under the Strategic Research Program for Brain Sciences by the MEXT (to KK) and of Core Research for Evolutional Science and Technology (CREST) of Japan Science and Technology Agency (JST) (YK was supported by this grant). We thank all the subjects and their families for participation in the study, and Dr. Hisami Nishida and Drs. Michiko Minowa, Kei-ichiro Watanabe and Hitoshi Kuwabara for their clinical assessments and recruitment. Thanks also goes to Alan Milby for improving the quality of the manuscript.

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日本神経精神薬理学雑誌（Jpn. J. Neuropsychopharmacol.）31：251-257（2011）

〔特集：認知機能障害に対する治療をどう評価するか〕

統合失調症患者における機能的転帰：MATRICS Consensus Cognitive Battery との関連

住　吉　チ　カ[*1]

[*1] 福島大学人間発達文化学類

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統合失調症患者における機能的転帰：MATRICS Consensus Cognitive Battery との関連*

住 吉 チ カ[*1]

[*1] 福島大学人間発達文化学類

要約：統合失調症患者の機能的転帰について，Measurement and Treatment Research to Improve Cognition in Schizophrenia（MATRICS）の研究動向に沿いつつ論じた．同研究組織が開発した認知機能検査バッテリー MATRICS Consensus Cognitive Battery（MCCB）に対し，日常生活や社会生活で発揮される認知機能の指標が co-primary measures として要請されてきた．本稿ではまず，機能的転帰の各階層，すなわち neuropsychological performance，functional capacity，functional performance について説明した．その上で，functional capacity が co-primary measures のターゲットとされたこと，またその評価に performance-based approach と interview-based approach による手法が検討されていることについて述べた．さらに functional performance の意義についても，その評価が患者の社会予後の評価に重要であること，およびその評価尺度である community functioning measures が MCCB の妥当性検証に用いられてきたことについて述べた．最後に，機能的転帰の測度，すなわち co-primary measures や community functioning measures を英語以外の言語に移植する際に生じる諸問題について考察した．

キーワード：統合失調症，MATRICS Consensus Cognitive Battery，機能的転帰，Co-primary measures，Community functioning measures

Measurement and Treatment Research to Improve Cognition in Schizophrenia（MATRICS）は，2003年に始められた統合失調症における認知機能の改善のための測定と治療研究である（http://www.matrics.ucla.edu/）．MATRICS 発足の背景には，1）統合失調症の認知機能が機能的転帰（functional outcome）に影響することが明らかになったこと，それゆえ 2）認知機能の改善が抗精神病薬の治療ターゲットとされたこと，しかし，3）治療薬による認知機能改善効果を包括的に評定し得る標準的な検査バッテリーが確立していなかったこと，が挙げられる（Green and Nuechterlein, 2004; Green et al, 2004b）．標準的バッテリー開発のために，MATRICS 神経認知委員会（MATRICS Neurocognition Committee）が組織され，専門家（精神科医，心理学者等）のコンセンサスに基づいて MATRICS Consensus Cognitive Battery（MCCB）の開発が進められた（Nuechterlein et al, 2008）．そして現在に至るまで，MATRICS-PASS（MATRICS Psychonomic and Standardization Study）により，MCCB の標準化，および信頼性妥当性の検証などの研究が行われてきた（Kern et al, 2008）．

MCCB は，神経心理学的検査で測り得る基本的な認知機能の指標（primary measure）である．この開発課程で primary measure に対応する機能的転帰の指標（co-primary measures/community functioning measures）についても研究が進められてきた（Green et al, 2008）．このような MATRICS の動向は，機能的転帰の概念を理論的に整理することにも寄与してきたと思われる．

本総説ではまず，統合失調患者の機能的転帰について考察する．次に機能的転帰の2つのレベル，functional capacity と functional performance について，筆者らの研究も含めつつ述べる．最後に，これら機能的転帰の各国・言語への移植における課題点を挙げる．

I. 機能的転帰

機能的転帰とは，社会生活における予後を意味し，具体的には，自立した生活（金銭・服薬の管理など）から，就労，社交・娯楽の充実にわたる広汎な活動を意味する（Green et al, 2000）．これらについて健常者と同レベルに至るまで，いくつかの段階が想定される（図1）．機能的転帰の基盤となるのは，神経心理学的検査の遂行（neuropsychological performance）である．このレベルの認知機能課題は通常，日常生活とは直接関連しないものが多く（文字・数字列の暗記や記号操作など），これのみで患者の社会的予後を予測するのは難しい．そこで，社会生活への適応度に応じた機能的転帰の評価レベルが必要となる（Green et al, 2004a）．

第一段階が functional capacity であり，主要な生活技能を遂行し得るレベルである．具体的には統制された条件下（検査場面等）で，電話応対や金銭管理などの日常生活技能をシミュレーションできる段階である．次の段階は functional performance であり，実際の社会生活が円滑に営める状態に至ることである．具体的には，日常生活におけ

* 本論文は第40回日本神経精神薬理学会（2010年9月，仙台）におけるシンポジウム講演の記録である．
[*1] 〒960-1296 福島市金谷川1
E-mail: sumiyoshi@educ.fukushima-u.ac.jp
（別刷請求先：住吉チカ）

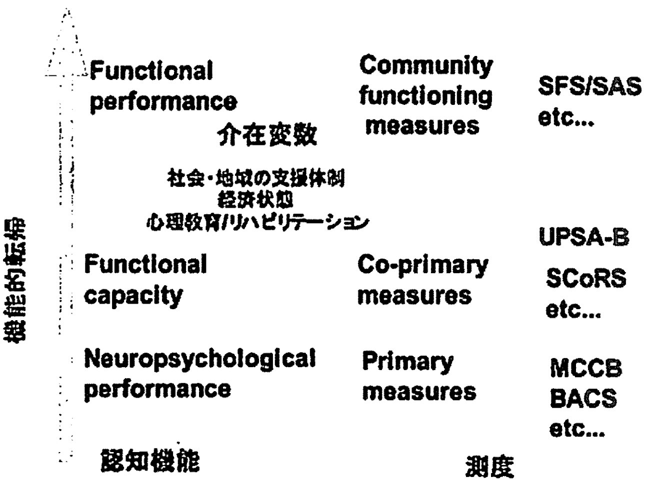


図1 機能的転帰の階層と測度.

る自己管理，社交，良好な対人関係を保持し得る状態である．Functional capacity と functional performance は，認知能力における「コンピテンス（competence）」と「パフォーマンス（performance）」の関係に類似している（Harvey and Velligan, 2011）．すなわち検査場面におけるロールプレイで，適切に金銭勘定や電話応対ができることは，これらの行動を実行できる潜在能力を示唆する．しかし現実場面の買い物や職場では，周囲や対人関係によるプレッシャー，ストレスなどから，必ずしもその能力が十分に発揮できるとは限らない（Green et al, 2004a）．

米国食品医薬品局（Food and Drug Administration; FDA）は，精神病治療薬の効果の評価において，「neuropsychological performance の改善は必要条件だが十分条件ではない」として，製薬会社や臨床現場にとり，表面的妥当性（face validity）を持つ機能的転帰の指標が必要であるという見解を示した（Buchanan et al, 2010）．つまり，primary measure である MCCB に対し，co-primary measures として機能的転帰の指標を要請したといえる．しかし MATRICS 発足当初は，co-primary measures の概念が明確に確立していなかったと思われる（Buchanan et al, 2010; Green et al, 2004b）．そこで，MCCB に最も適した co-primary measures の検討も同バッテリーの開発とともに始められることになった．

II. Co-Primary Measures

精神病治療薬の効果が最も直接的に primary measure に反映されるとすれば，co-primary measures は可能な限り primary measure と連動して改善することが望まれる．そこでまず，機能的転帰のどのレベルに co-primary measures を置くかが重要な問題となる．理想的には，functional performance レベルの転帰，すなわち実際の社会生活における就業・学業・家事・社会生活・対人関係の実践についての評価が，理想的な co-primary measures として望まれる（Green et al, 2004a, 2004b）．しかし実際には，このレベルの転帰に対しては，介在要因として環境・社会要因（患者の心理教育・地域経済状態・家庭や地域社会における援助体制の在り方など）が影響するため（図1），認知機能の改善に連動した転帰のみを評価するのは難しい．そこで，functional performance に至る途中段階（intervening step）として，functional capacity のレベルが co-primary measures に相応しいと判断された（Green et al, 2004a）．先に述べたように，functional capacity レベルで測定される認知機能は，患者が日常的な課題を遂行し得る（can do）能力を意味し，実際に社会生活でその能力が発揮できる（actually does）ことを保証するものではない（Bowie et al, 2006; Green et al, 2004a）．しかし，然るべき機会と動機付けがあれば発揮されるものであり，functional performance を直接評価する代替になると考えられた．

Functional capacity レベルの転帰の評価について，performance-based approach と interview-based approach による手法が検討されてきた（Buchanan et al, 2010）．前者は，実際の生活場面において主要な認知・社会的技能（金銭・服薬の管理，公共機関の利用，電話をかける等）のシミュレーションにより，転帰の状態を評価する．主な検査バッテリーとして，Maryland Assessment of Social Competence（Bellack et al, 1994），Test of Adaptive Behavior in Schizophrenia（TABS; Velligan et al, 2007），Independent Living Scales（Loeb, 1996），University of California at San Diego（UCSD）Performance-Based Skills Assessment（UPSA; Patterson et al, 2001），その簡略版として UPSA Brief Version（UPSA-B; Mausbach et al, 2007）が挙げられる．

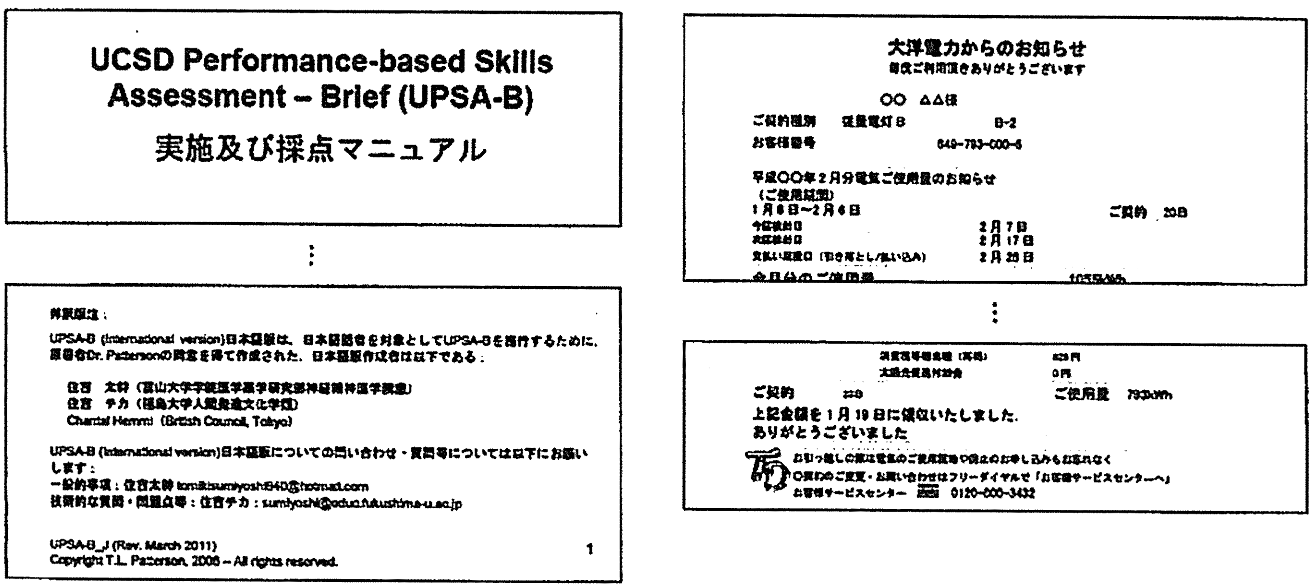
一方，interview-based approach では，治療者の評価，あるいは患者や介護者への構造的インタビューによって，functional capacity の状態を評価する．具体的には，治療者・介護者あるいは本人が，認知機能の状態や，認知機能障害による日常生活の質の低下についての項目を評価する．このような interview-based approach の代表的なものとして，Schizophrenia Cognition Rating Scale（SCoRS; Keefe et al, 2006），Clinical Global Impression of Cognition of Schizophrenia（CGI-CogS; Ventura et al, 2008）が挙げられる．

Performance-based approach，interview-based approach ともに，co-primary measures として最も相応しい評価尺度や検査バッテリーの選定が，MATRICS Co-primary and Translation（MATRICS-CT）を中心に進められてきた（Buchanan et al, 2010）．同組織は，co-primary measures に望まれる条件[1]を挙げ，それらに基づいて performance-based approach による検査バッテリーとして Maryland Assessment of Social Competence と UPSA，interview-based approach による評価尺度として，SCoRS と CGI-CogS を選んだ．これらの有効性について予備的研究を行っ

た結果，1）上記4バッテリー・尺度はすべて検査-再検査信頼性を満たす，2）神経心理学的検査との関連は performance based のバッテリーの方が大きい，3）上記4つはすべて community functioning との関連はそれほど大きくない（relatively modest），4）interview-based の尺度ではより欠損値が生じやすい，ことを明らかにしている（Green et al, 2008）.

さらに MATRICS-CT は，Validation of Intermediate Measure Study（VIM）を組織し，より系統立てた手法で co-primary measures に相応しい評価尺度や，バッテリーの選定・有効性の検証を進めている．この研究では，interview-based approach の指標として Cognitive Assessment Interview（CAI）や CGI-CogS，performance-based approach の指標として，TABS や UPSA を含むそれぞれ数種の co-primary measures が検討対象とされた（(Buchanan et al, 2010）．VIM は，performance based の co-primary measures では UPSA が，また簡略版では TABS と UPSA が，co-primary measures として望ましい要件[1]を最も多く満たすことを確認している（Green et al, 2008; Harvey and Velligan, 2011）．しかし現時点で，interview-based，performance-based 両アプローチともに，co-primary measure として単一の標準的評価尺度・バッテリーは確定されていないと思われる（Buchanan et al, 2010）.

このように，MCCB の開発と連動して co-primary measures の研究も精力的に進められてきた．MCCB の日本語版の作成とともに，本邦でも上記 co-primary measures のいくつかは，すでに導入が試みられている．例えば，interview-based によるものとして SCoRS-J（兼田ら，2010, 2011），performance-based のものとして UPSA-B_J が挙げられる（住吉ら，2011b; 図2）．UPSA-B は，広汎な生活技能を評価する UPSA に対し，金銭出納技能とコミュニケーション技能に絞ったものである（表）．その日本語版である UPSA-B_J は，後で述べるように，UPSA-B の国際版を基に日本の経済・社会・文化状況を考慮した調整が施


UCSD Performance-based Skills Assessment – Brief (UPSA-B)
実施及び採点マニュアル

UPSA-B (International version)日本語版は、日本語話者を対象としてUPSA-Bを施行するために、原著者Dr. Pattersonの同意を得て作成された．日本語版作成者は以下である：

住吉 太幹（富山大学大学院医学薬学研究部神経精神医学講座）
住吉 チカ（福島大学人間発達文化学類）
Chantal Hemmi (British Council, Tokyo)

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一般的事項：住吉太幹 tomikisumiyoshi840@hotmail.com
技術的な質問・問題点等：住吉チカ：sumiyoshi@educ.fukushima-u.ac.jp

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図2 UPSA-B_J の表紙（左）・請求書（右）.

表 UPSA-B_J と Modified SFS/SAS for MATRICS PASS_J の評価領域

	UPSA-B_J		Modified SFS/SAS for MATRICS PASS_J	
	金銭出納技能	コミュニケーション技能	SFS パート	SAS パート
評価領域	金銭勘定 請求書の読み取り	電話をかける 電話による予約変更	引きこもり 自立-実行 自立-能力 娯楽 社会参加 就労	労働（勉学・家事）時間 （仕事の）認知的複雑性 （仕事の）遂行の障害

[1] 優良な co-primary measures が満たすべき条件として以下が挙げられている：1）検査-再検査信頼性（test-retest reliability），2）反復使用における有用性（utility as repeated measures），3）機能的転帰との関連性（relationship to functional status），4）耐用性/実際性（tolerability/practicality），5）欠損値数（number of missing data），および 6）神経心理学検査における遂行との関連性（degree of correlation with cognitive performance）（Green et al, 2008, supplement）.

されている.

III. Community Functioning Measures

前節で述べたように，neuropsychological performance の改善に伴う functional performance の向上を，的確に測ることは難しい．しかし社会的予後の評価の観点から，functional performance を評価するのは重要だと考えられる．このレベルの機能転帰は，就労，対人関係，社交生活等を評価領域に含み，精神症状（引きこもりなど）を鋭敏に反映し得ること，またそれゆえに心理社会療法の効果について有効な指標となり得るからである（Burns and Patrick, 2007）．このような観点からここ 20 年間，community functioning measures についての研究も精力的に進められてきた（レビューとして Burns and Patrick, 2007）．

Functional performance の具体的な測度として，community functioning measures が対応するが，これは social functioning，social adjustment，および social adaptation などの評価尺度を包括するものと考えられる．Burns（Burns and Patrick, 2007）は，1990〜2006 年間に開発された 301 の community functioning measures の中から，統合失調症患者の社会機能評価研究，および抗精神病薬の無作為化比較臨床試験で最も多く使用され，かつ妥当だと思われる 20 の評価尺度を挙げている．それらはいずれも有用性が高いと考えるが，本稿では MCCB との関連から，Modified SFS/SAS for MATRICS-PASS について述べる．これは MATRICS-PASS のために，Social Functioning Scale（SFS; Birchwood et al, 1990）と Social Adjustment Scale（SAS; Weissman and Bothwell, 1976）を組み合わせ作成されたものである（図 3）．前者は上記 20 の尺度中，使用頻度 3 位，後者は 8 位に相当する（SAS にはいくつかバージョンがあり，SAS-II の場合）．

Co-primary measures の概念・必要性があまり明確ではなかった MCCB 開発当初は，MCCB に対応した機能的転帰として，functional capacity よりむしろ functional performance が想定されていたと思われる．実際，MCCB の妥当性検証の研究[2] では，community functioning measures である Modified SFS/SAS for MATRICS-PASS が，内容的妥当性を検討するために用いられている[3]．

先述のように Modified SFS/SAS for MATRICS-PASS は，社会機能尺度 SFS（Birchwood et al, 1990）に修正を施した Modified SFS と，社会適応尺度 SAS（Weissman and Bothwell, 1976）を修正した Modified SAS（Subotnik et al, 2003）から労働／学校機能尺度を抽出し，組み合わせたものである（図 3）．MATRICS-PASS は，標準化研究の一環として Modified SFS/SAS for MATRICS-PASS を統合失調症患者に施行し，主成分分析から，労働・自立した生活・日常的機能の社会領域の 3 成分を抽出している．そして 176 人の統合失調症患者を対象に，Modified SFS/SAS for MATRICS-PASS と MCCB の遂行成績との関連を調べた結果，Modified SFS/SAS for MATRICS-PASS の総合得点および各領域得点と，MCCB の課題間にそれほど高い相関は見いだされなかった．しかし，仕事領域は，MCCB の遂行と比較的高い相関を示した．この結果は先行研究と類似しており，MCCB の機能的転帰の予測妥当性を間接的に支持すると考えられた．

筆者らも MCCB-J 作成と並行して，Modified SFS/SAS for MATRICS-PASS の日本語版（Modified SFS/SAS-J MATRICS-PASS 用）の作成を開始した（表，図 4）．本邦において既に日本語版 SFS（根本ら，2008）が作成されていたことを考慮し，Modified SFS/SAS-J MATRICS-PASS 用における SFS パートを日本語版 SFS の形式に揃えた．また，患者の負担や実施の効率性を考慮し，自己記入式を採用した．採点方法を含め現在改良を重ねているが，予備的な分析の結果，MCCB-J の標準得点と SFS の総得点間に線形的な関係を見いだしている（図 5）．この結果は，少なくとも本邦では，MCCB-J で測定される neuropsychological performance の改善が，ある程度患者の社会的転帰を予測し得る可能性を示唆している．

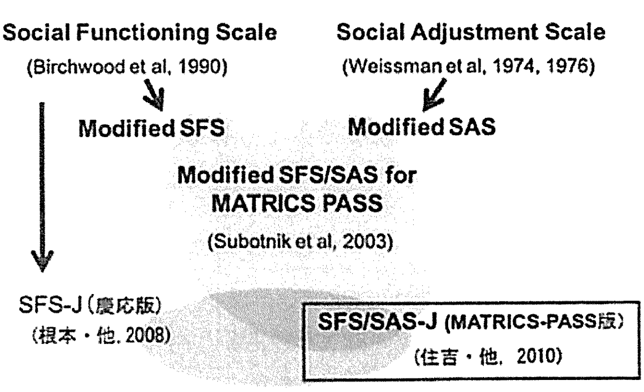

図 3　Modified SFS/SAS for MATRICS-PASS_J の背景.

[2] この研究では，MCCB の内容的妥当性について，「機能的転帰の予測妥当性」，「神経薬理の妥当性」，「精神症状の予測妥当性」を挙げ，これらのうち最も相応しいものを，専門家（精神医学・心理学 74 名）のコンセンサスにより確定した（Kern et al, 2004）．コンセンサス調査の結果，評価値の中央値は，機能的転帰の予測妥当性＞神経薬理的妥当性＞精神症状の予測妥当性の順に高く，この結果を受けて MATRICS-PASS は，「機能的転帰の予測妥当性」を最も重要な妥当性に据えた．

[3] MATRICS Consensus Cognitive Battery Manual（Nuechterline and Green, 2006）では，MCCB の妥当性について，「内容的妥当性」（その検査は測定対象をどれだけ反映し得るか）を強調している（Chapter 3 Reliability and Validity）．一方で，基準関連妥当性（その検査が同じ機能を測る他検査と同様の機能を測っているか）も妥当性の重要な側面であり，これについて，筆者らのグループでは BACS-J（Kaneda et al, 2007）等により検討が進められている．