Various factors have been associated with LM test score differences. Abikoff *et al.* have already reported that age and education norms are generated for immediate, 30-min delayed and 24-h delayed recall in the LM of the WMS, and performance is more closely related to educational background.[6] Their sample ranged in age from 18 to 81 years, with a mean educational level of 13.96 years (range 6–18 years). The LM performance increase is somewhat more common with higher levels of education.[6,7] However, Abikoff *et al.* noted that "Although education was more highly related to scores than was age, small but significant relationships between age and verbal recall remained over and above the influence of education.[6]" The impact of age is most obvious in 24-h delayed recall, and drop-off in performance occurs over the age of 60 years. Therefore, the latest version of the WMS has paid attention to elderly participants in the form of advancing an elderly battery.

However, the WMS-R version is the only LM task that has been standardized for Japanese people, and the normative sample has been limited to the ages of between 16 and 74 years. The incidences of AD, combined dementia and other types of dementia rise with increasing age, particularly after the age of 85 years.[8] Although not only for young-old people, but also for old-old or oldest-old people, an amnestic state examination of high accuracy is required, because the Japanese versions of the WMS-R, LM-I and LM-II have not been adequately normalized for latter-stage elderly people. In the current study, normative data for the LM in Japanese elderly people aged 75 years and older were gathered.

Methods

Participants

A total of 50 (27 female and 23 male) participants without a history of dementia and symptomatic stroke events were recruited from the community and hospital populations living in two urban areas. All participants could attend the trial sites alone. The sample size determination was based on the original version of the WMS-R and the general recommendation on statistics in psychology and education, taking a sample of 50 and over per age group interval.[9] A total of 30 participants (60%) had no history of psychiatric problem as assessed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disoriders, Fourth Edition revised (SCID),[10] and they did not report clinical evidence of amnesia and ADL impairment. There is nothing to suggest that participants did not hear something at the time of auditory stimulus presentation in the study. They ranged in age between 75 and 87 years (mean ± SD: 79.3 ± 3.6 years), and in educational background between 6 and 18 years (mean ± SD: 11.7 ± 3.1 years).

The ethics committee of the Tokyo Metropolitan Institute of Gerontology and the Nagoya University School of Medicine approved the present study, and each participant signed a consent form after being sufficiently informed about the outline of the study by the principal investigator.

Tasks

Logical Memory (LM)-I and -II from the Japanese version of the WMS-R[11] were carried out. In the LM-I, participants were asked to immediately recall from the number of prose units twice: the first trial presented story A verbally, and the second trial presented story B verbally. In the LM-II, participants were asked to recall words from the two stories 30 min later. During the time delay, participants were asked to carry out the Mini-Mental State Examination (MMSE)[12] and some interference tasks.

In the present study, not all of the participants carried out every task item, other than LM-I, II and MMSE. As the purpose of the present study was to provide normative data for LM-I and -II, the sample size was kept the same; hence, missing data were not substituted. The results are based on the eight task scales.

Statistical analysis

All statistical analyses were carried out using SPSS 17.0 J. for Windows (SPSS, Chicago. IL, USA). Normative data are provided in the form of means and standard deviations (SD) broken down by sex, age and educational background. Correlation analyses between LM scores and various factors were carried out using the Pearson product-moment correlation coefficient. A *P*-value of less than 0.05 was considered significant. The percentile rank of each LM-I or -II score was calculated, after the Shapiro–Wilk test was carried out to check the normality of the sampling distribution.

Results

Sample characteristics

In the present sample, the mean ± SD score of MMSE (27.3 ± 2.2) reflected the expected distribution of general cognitive status for aged groups. The normative sample was confirmed to match closely the demographic profile of this population as reported in a recent census. Table 1 shows the percentiles of the normalization sample by age, sex and educational background compared with these population averages in Japan (Statistics Bureau 2010: Ministry of Internal Affairs and Communications). The results showed that the sample might have had a higher educational background than Japan's age-matched population.

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Table 1 Percentiles of the normalization sample by age, sex and educational background

Age (years)	Sex	Education 0–11 (years) Sample	Population (Japan)	12 (years) Sample	Population (Japan)	>13 (years) Sample	Population (Japan)
>75	Male	25.9	45.6	18.5	37.6	40.7	16.8
	Female	63.0	53.3	18.5	41.3	18.5	5.4
	Total	48.0	50.3	20.0	39.9	32.0	9.8

The estimated population was calculated excluding active students and unknown individuals of education backgrounds from total number.

Table 2 Performance of the sample aged 75 years and older

		Mean SD (min–max)
LM-I		15.5 ± 5.4 (5–8)
	Story A	8.3 ± 3.2 (3–16)
	Story B	7.4 ± 2.8 (2–14)
LM-II		9.9 ± 6.6 (0–25)
	Story A	5.0 ± 3.8 (0–13)
	Story B	4.9 ± 3.2 (0–12)

I, immediate recall; II, delayed recall; LM, Wechsler Memory Scale-Revised Logical Memory subtest.

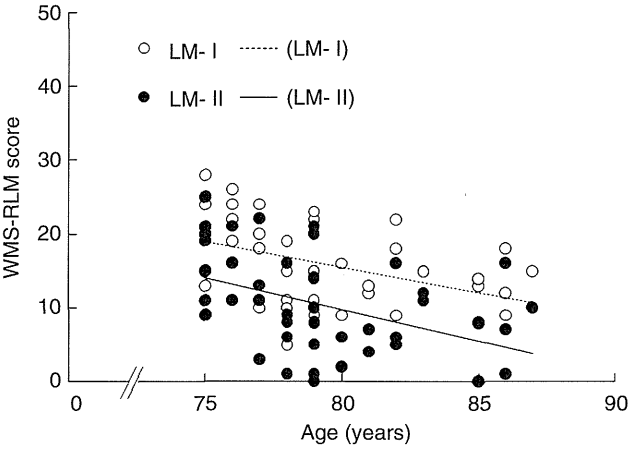

Figure 1 The scatter plot of Wechsler Memory Scale-Revised Logical Memory (WMS-RLM) subtest scores (y-axis) and age in years (x-axis). I, immediate recall; II, delayed recall; LM, Logical Memory subtest.

Reference data of the normal group

Mean scores (SD) of the sample were 15.5 (5.4) on LM-I and 9.9 (6.6) on LM-II. Table 2 summarizes the performance of the sample. To check the normality of the sampling distribution, coefficients of skewness and kurtosis were calculated for each trial. In the LM-I, the skewness value was 0.19 and the kurtosis value was –0.89; in the LM-II, the skewness value was 0.32 and the kurtosis value was –0.82. The distributions of the LM-I and -II scores satisfied the normality assumption using the Shapiro–Wilk test ($P > 0.05$).

Characteristics and performances

To examine the effect of sex on performance, unpaired t-tests comparing the LM-I and -II scores in male and female participants were carried out. In both the LM-I and -II, no significant difference was found. The mean scores (SD) of the male group were 15.6 (5.5) on the LM-I and 10.8 (6.4) on the LM-II, compared with 16.3 (5.5) on the LM-I and 10.0 (6.8) on the LM-II in the female group.

To examine associations between age (years) or educational background (years) and LM scores, correlation analyses were carried out. The LM-I and LM-II scores were moderately correlated with age ($r = -0.44$, $P < 0.01$; $r = -0.45$, $P < 0.01$), and the LM-I score was moderately correlated with educational background ($r = 0.36$, $P < 0.05$). There was no significant correlation between the LM-II score and educational background ($r = 0.23$, not significant.). The figures show scatter plots of the WMS-R LM scores and age in years (Fig. 1), or years of education (Fig. 2). Considering that the sample had a moderate to high education, partial correlation analyses between age (years) and LM scores were carried out. The LM-I and LM-II scores were moderately correlated with age ($r = -0.36$, $P < 0.05$; $r = -0.40$, $P < 0.01$).

Discussion

In the current study, LM normal performances of healthy Japanese people aged 75 years and older were surveyed, and the effects of sex, age and education on performance were identified. The means, SD and distribution features of the LM-I and -II of the WMS-R are presented for Japanese old-old people.

The sample had mean (SD) scores of 15.5 (3.2) on the LM-I and 9.9 (6.6) on the LM-II. According to

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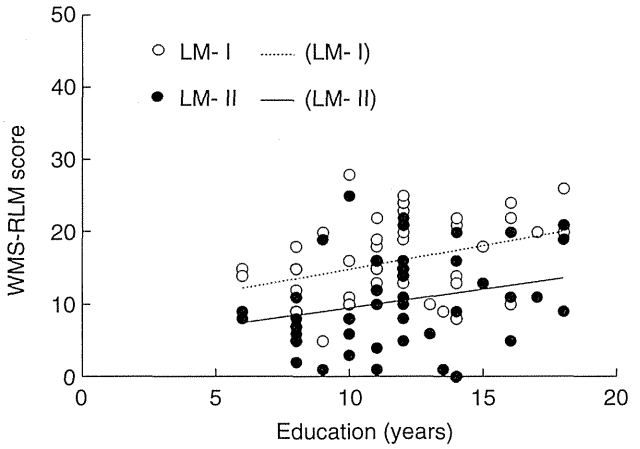

Figure 2 The scatter plot of Wechsler Memory Scale-Revised Logical Memory (WMS-RLM) scores (*y*-axis) and years of education (*x*-axis). I, immediate recall; II, delayed recall; LM, Logical Memory subtest.

Sugishita,[11] people in each age group (16–17 years ($n = 50$), 20–24 years ($n = 54$), 35–44 years ($n = 56$), 55–64 years ($n = 50$), 65–69 years ($n = 52$) and 70–74 years ($n = 54$)) had the following scores: on the LM-I, 27.7 (7.2), 26.6 (6.4), 25.1 (7.5), 22.0 (7.1), 19.5 (6.8) and 18.5 (7.5), respectively; and on the LM-II, 24.9 (7.7), 22.8 (6.7), 20.7 (7.6), 16.8 (7.0), 15.3 (7.0) and 13.2 (6.8), respectively. These results are consistent with previous data, and indicate an age-related decrease in LM task performance.[6,13] Considering the Flynn effect, the present data should not be compared directly with the previous data by Sugishita.[11] It is recommended that a larger study for the normalization of LM in older people be carried out.

Furthermore, the study showed that the LM-I and -II scores were moderately negatively correlated with age in a healthy sample aged 75 years and older. In particular, the LM-II score reflected the individual difference associated with age, independent of educational background. The result also confirms the age-related changes in memory functions. This finding, that the LM-II was *not* correlated with education leaves room for interpretation. Although the present sample from among community-dwelling older adults had generally better health and education, high-risk MCI persons might have been present in definite proportions, or the normal population might have individuals who, despite educational levels, may have been less able in cognitive abilities throughout their life.[14,15] According to the Mayo clinic's team, the LM-II data were *not* correlated with education in a community-based healthy sample.[15] They noted that the education-WMS performance association in the restricted age range of their older sample did not reflect true underlying relationships between the intelligence quotient (IQ) and task performance, and they recommended that WMS norms be stratified by IQ. The education-LM performance association might reflect these confounding factors.

Although the present sample was chosen to closely match the demographic profile of the Japanese population, the sample might have had a higher educational background than the age-matched population, especially among males. Community-based surveys in rural areas should also be carried out at the same time as surveys in urban areas. Thus, the sample bias is inappropriate for determining the "range of normal" memory functioning in an older population.[15] Norms stratified to be representative of the general population have great diagnostic value. However, the present result showed that the aging-related memory decline was observed in highly educated people, who had a greater likelihood of preserving cognitive function than people with low educational achievement. The result suggests that normalization of LM must be carried out for latter-stage elderly Japanese people. To establish the norms for the Japanese version of the LM, a further community-based study using the Intelligence Scale in parallel will be necessary. In addition, it will be necessary to compare between the LM norms based on the separately-carried out condition and that based on the completely-carried out WMS-R condition, and to normalize the latest version of WMS in Japanese people, because the latest version has a short battery for ages 65–90 years (the Older Adult Battery), including the new LM composed of the 14-paragraph-story (story A) and the 25-paragraph-story (story B).

The present estimated values based on LM scores of people aged 75 years and older, which are currently based on the population aged less than 75 years, show that current percentile ranks underestimate the memory ability of people aged 75 years and older. Furthermore, the present study obviously showed that the LM-I and LM-II scores were correlated with age. These results suggest the necessity of normative data on the Japanese version of the WMS-R LM subtest for each 5-year interval for the population aged 75 years and older, like the original version. In the future, for old-old people, it will be necessary to carry out a survey to establish norms of the WMS-R LM for each 5-year interval.

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Disclosure statement

No potential conflicts of interest were disclosed.

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Research Article

Evaluation of Factors Affecting Continuous Performance Test Identical Pairs Version Score of Schizophrenic Patients in a Japanese Clinical Sample

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Aim. Cognitive impairment in schizophrenia strongly relates to social outcome and is a good candidate for endophenotypes. When we accurately measure drug efficacy or effects of genes or variants relevant to schizophrenia on cognitive impairment, clinical factors that can affect scores on cognitive tests, such as age and severity of symptoms, should be considered. To elucidate the effect of clinical factors, we conducted multiple regression analysis using scores of the Continuous Performance Test Identical Pairs Version (CPT-IP), which is often used to measure attention/vigilance in schizophrenia. *Methods.* We conducted the CPT-IP (4-4 digit) and examined clinical information (sex, age, education years, onset age, duration of illness, chlorpromazine-equivalent dose, and Positive and Negative Symptom Scale (PANSS) scores) in 126 schizophrenia patients in Japanese population. Multiple regression analysis was used to evaluate the effect of clinical factors. *Results.* Age, chlorpromazine-equivalent dose, and PANSS-negative symptom score were associated with mean d′ score in patients. These three clinical factors explained about 28% of the variance in mean d′ score. *Conclusions.* As conclusion, CPT-IP score in schizophrenia patients is influenced by age, chlorpromazine-equivalent dose and PANSS negative symptom score.

1. Introduction

Schizophrenia is a complex, heritable psychiatric disorder, affecting approximately 1% of the general population. The heritability of schizophrenia is estimated to be 64% [1]. Genes relevant to schizophrenia or variants that may modulate risk for the disease have been identified using both linkage and candidate-based or whole-genome association studies [2–5]. A complementary approach examines the genetics of schizophrenia from the neurobiological perspective with neurocognitive endophenotypic markers of putative brain function. The underlying brain dysfunctions (and related endophenotypes) are more stable, trait-like markers that can be used to refine the psychiatric diagnosis. This approach is further motivated by the need to elucidate pathophysiological pathways after candidate variants are established [6].

The Consortium on the Genetics of Schizophrenia is a 7-site collaboration that examines the genetic architecture of quantitative endophenotypes in families with schizophrenia. The authors suggested that the Continuous Performance Test Identical Pairs Version (CPT-IP), Degraded Stimulus Continuous Performance Test (DS-CPT), Verbal Declarative Memory Test, Working Memory Test, and Penn Computerized Neurocognitive Battery are the most appropriate tests to evaluate endophenotypes relevant to schizophrenia. Furthermore, the heritability of attention/vigilance using sample comprised of 30 healthy families was estimated to be 0.39 and 0.49 based on verbal and spatial CPT-IP scores, respectively

[7]. The effect size was 1.18 when schizophrenia patients and controls were compared. Accordingly, the comparison between the first-degree relatives of schizophrenic patients and controls resulted in smaller effect size (0.54) [6].

CPT-IP is included as a core test in major psychological batteries used to evaluate cognitive functioning of psychiatric patients, such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia and the Consensus Cognitive Battery (MCCB) for schizophrenia. Cognitive impairment is one of the core symptoms of schizophrenia and is associated with impaired quality of life and poor outcome [8–10]. The CPT-IP test used to evaluate one of the cognitive endophenotypes related to schizophrenia. Specifically, CPT-IP can measure the attention/vigilance deficit that is commonly found in schizophrenic subjects and those who are at risk for the disorder [11].

Biological phenotypes (e.g., cognitive or central executive functions) are thought to more closely reflect the effects of genetic variation compared with manifested psychiatric illness; therefore, endophenotype studies have proven to be more robust and require smaller sample sizes than purely diagnosis-based studies. When genetic effects on cognitive performance are evaluated, it is important to consider measurement errors [12] as well as the effect of clinical factors that may strongly affect CPT-IP scores. In that regard, except for several reports that have evaluated the association between age and Positive and Negative Symptom Scale (PANSS) scores on cognitive performance [13], there are no comprehensive studies that looked for relevant covariates that may influence CPT-IP scores. We conducted an analysis of factors that can affect CPT-IP scores (e.g., sex, age, education years, onset age, duration of illness, chlorpromazine equivalent dose, and PANSS scores) using a Japanese population-based sample.

2. Methods

2.1. Participants. This study was approved by the Ethics Committee of each participating institute, and written informed consent was obtained from each participant. Patients were included in the study if they (1) met DSM-IV criteria for schizophrenia, (2) were physically healthy, and (3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy, or known mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with patients and families and review of medical records. The rate of the samples excluded due to a lack of consensus was less than 5%. All subjects were unrelated to each other, living in the central area of the mainland of Japan, and self-identified as Japanese. The study included 126 unrelated Japanese patients with schizophrenia (mean age, 44.4 ± 13.3 years; 80 males and 46 females).

2.2. Measurement Settings. There are a variety of CPTs, the more commonly used being CPT-X/AX, DS-CPT, and CPT-IP [11]. CPT-IP has evolved over the course of the New York High-Risk Project [14]. In CPT-IP, the target is defined as the second stimulus in any pair of identical stimuli. The benefit of using CPT-IP instead of the other tests is due to the structure and simplicity of the examination. In other words, no number or number sequence is specified, as in the X/AX design, and the subject does not need to memorize each stimulus presented as in the DS-CPT, which can increase the information-processing load. We used CPT-IP program Release 4.0 (NewCPT.exe, Copyright 1982–2004 by Barbara A. Cornblatt, All Rights Reserved). The PC monitor was 10.4′ and letter size was at least 2.2 × 1.5 cm [7]. The distance between the subjects and the monitor was at least 50 cm.

Stimuli were flashed on the screen at a constant rate of 1 per set, with a stimulus "on" time of 50 msec and a stimulus "off" time of 950 msec. Stimuli were four-digit numbers and were presented 150 times. In each 150 trial conditions, 30 of the trials (20%) were target trials and required a response. Target trials were those on which the second of a pair of two identical stimuli appeared. Responses to target trials were scored as hits [7]. Condition also included a number of catch trials on which the stimulus presented was similar but not identical to that of the preceding trial. Responses to catch trials were considered a specific type of commission error, referred to as false alarms. There were 30 catch trials (20%) in our test. The remaining trials in both conditions were 90 randomly distributed fillers. Responses to filler trials, referred to as random errors, were also considered to be commission errors but were analysed independently of false alarms. We conducted the four-digit CPT-IP two times, with a resting time between the two examinations of 1 min. Mean d′ score was defined as the mean of first and second d′ score.

2.3. Clinical Factors. Chlorpromazine (CPZ) equivalent dose was calculated according to standard methodology based on a Japanese clinical sample [15, 16]. The PANSS was used to evaluate the severity of symptoms in patients [17].

2.4. Statistical Analysis. IBM SPSS Statistics Version 19 was used for all analyses. Intraclass correlation coefficient was calculated in d′, hits, false alarm, and random errors. Multiple regression was performed for the analysis of mean of d′ score using clinical information (sex, age, education years, onset age, duration of illness, CPZ equivalent dose of antipsychotics, and PANSS score) (positive, negative and general psychopathology). Multiple regression models were analysed using forward-backward stepwise selection. Multiple correlation coefficient adjusted for the degree of freedom (R_a^2), analysis of variance (ANOVA) P-value, and Durbin-Watson ratio were calculated to evaluate the extent of model fitting. The significance level was set at $P = 0.05$.

3. Results

Clinical profile of participants is shown in Table 1. The intraclass correlation coefficient (ICC) of the mean d′ score was 0.71 (Table 2). In multiple regression analysis, age, CPZ equivalent dose, and PANSS-negative symptom score were significantly associated with mean d′ score (Table 3). Durbin-Watson ratio indicated the absence of spurious

Table 1: Participants profile.

	Patients (n = 126)	
Sex		
Male	80	
Female	46	
	Mean	SD[a]
Age (y)	44.4	13.3
Education years (y)	12.4	2.4
Onset age (y)	26.7	10.0
Duration of illness (y)	17.6	13.0
Chlorpromazine equivalent dose (mg/day)	631.9	434.0
PANSS score		
Positive (7–49)	16.3	5.2
Negative (7–49)	19.0	5.5
General psychopathology (16–112)	36.2	9.3
Total (30–210)	71.6	17.7
Clinical diagnosis		
Paranoid type	46	
Disorganized type	3	
Catatonic type	1	
Residual type	65	
Unknown	11	
Polytherapy		
Antipsychotics		
Monotherapy	26	
Risperidone	62	
Olanzapine	16	
Aripiprazole	17	
Other atypical drug	3	
Typical drug	2	

[a]standard deviation.

Table 2: Measurement results of 4-digit CPT-IP.

P	Patients (n = 126)		
	Mean	SD[a]	ICC[b]
d′			
1st	1.29	0.84	0.71
2nd	1.55	0.96	
mean	1.42	0.84	
Hits (0–30)			
1st	18.4	7.2	0.77
2nd	19.6	6.9	
False alarms (0–30)			
1st	6.3	4.6	0.70
2nd	5.7	4.7	
Random errors (0–90)			
1st	4.8	8.9	0.53
2nd	3.5	4.9	

[a]standard deviation
[b]intraclass correlation coefficient.

regression. Although no strong correlation (>0.8) was observed in all clinical parameters, the Pearson's correlation between age and duration of illness was high (0.72).

4. Discussion

CPT-IP is a major neurocognitive examination used to assess cognitive impairment among psychiatric patients. Included as a subtest in the MCCB, CPT-IP scores are often used to assess drug efficacy in clinical trials or endophenotypes in genetic studies. Confounding factors, such as measurement error or influence of clinical data, can hamper interpretation of results. Thus, to elucidate the effects of clinical data (age, sex, education years, duration of illness, onset age, CPZ equivalent dose, and PANSS score) on CPT-IP score in schizophrenia patients, we performed a multiple regression analysis in Japanese people suffering from schizophrenia.

4.1. Main Findings. Age and PANSS-negative symptom score were statistically associated with mean d′ score in schizophrenia patients. This finding is in concordance with a previous study [18]. Additionally, our results suggest that CPZ-equivalent dose affects CPT-IP score. Overall, using a relatively large Japanese clinical sample of schizophrenia, we showed that age, CPZ-equivalent, dose and PANSS-negative symptom score can have a major effect on the CPT-IP scores and therefore should be taken into the account when interpreting results obtained from patients with schizophrenia. Age, CPZ-equivalent dose, and PANSS negative symptom score explained about 28% of the variance in mean d′ score.

4.2. Limitations. There are several limitations that should be considered when interpreting the results of the present study. Multiple regression analysis findings in schizophrenia patients would benefit if we had been able to obtain more clinical information, such as IQ score and duration of untreated psychosis. As we could not find significant effects of sex, age at disease onset, duration of illness, and PANSS-positive and general psychopathology score in this study, weak effects of these factors might be observed when the sample size is increased.

5. Conclusion

We investigated how covariates (age, CPZ-equivalent dose, and PANSS-negative symptom score) affect mean d′ score of CPT-IP. This is the first study using a single independent large Japanese schizophrenia sample set, known as homogeneous in terms of genetic makeup. Our study suggested that those effects should be carefully considered especially when CPT-IP is performed to detect small effect size factors which are expected to be found in case of common risk variants associated with schizophrenia or cognitive-enhancing drugs. Thus, as CPT-IP is likely to be an endophenotypic measure in molecular genetic studies of schizophrenia in the post-genome-wide association study era [19, 20], our data show

Table 3: Multiple regression analysis of mean d′ score.

Multiple regression analysis						
Forward-backward stepwise selection						
Clinical factors	Patients (n = 126) Setting: P_{in} = 0.05, P_{out} = 0.1					
	PRC[a]	S-PRC[b]	VIF[c]	95% CI[d] Lower	Upper	P value
Age (y)	−0.031	−0.45	1.04	−0.041	−0.020	**<0.001**
CPZ-equivalent dose (mg/day)	−0.00038	−0.21	1.01	−0.001	<0	**0.012**
PANSS-negative symptom score (7–49)	−0.026	−0.16	1.04	−0.052	<0	**0.017**
Intercept	3.54	—	—	2.89	4.19	<0.001
$\hat{R}^{2e}$			0.28			
ANOVA P value			**<0.001**			
Durbin-Watson ratio			1.93			

[a]partial regression coefficient
[b]standardized partial regression coefficient
[c]variance inflation factor
[d]confidence interval
[e]multiple correlation coefficient adjusted for the degrees of freedom.

that careful assessment of confounding factors is essential for interpretation of findings.

Authors' Contribution

T. Koide and B. Aleksic contributed equally to this work.

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Wisconsin Card Sorting Test scores and clinical and sociodemographic correlates in Schizophrenia: multiple logistic regression analysis

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ABSTRACT

Objectives: This study investigated what clinical and sociodemographic factors affected Wisconsin Card Sorting Test (WCST) factor scores of patients with schizophrenia to evaluate parameters or items of the WCST.

Design: Cross-sectional study.

Setting: Patients with schizophrenia from three hospitals participated.

Participants: Participants were recruited from July 2009 to August 2011. 131 Japanese patients with schizophrenia (84 men and 47 women, 43.5 ±13.8 years (mean±SD)) entered and completed the study. Participants were recruited in the study if they (1) met DSM-IV criteria for schizophrenia; (2) were physically healthy and (3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy or mental retardation. We examined their basic clinical and sociodemographic factors (sex, age, education years, age of onset, duration of illness, chlorpromazine equivalent doses and the positive and negative syndrome scale (PANSS) scores).

Primary and secondary outcome measures: All patients carried out the WCST Keio version. Five indicators were calculated, including categories achieved (CA), perseverative errors in Milner (PEM) and Nelson (PEN), total errors (TE) and difficulties of maintaining set (DMS). From the principal component analysis, we identified two factors (1 and 2). We assessed the relationship between these factor scores and clinical and sociodemographic factors, using multiple logistic regression analysis.

Results: Factor 1 was mainly composed of CA, PEM, PEN and TE. Factor 2 was mainly composed of DMS. The factor 1 score was affected by age, education years and the PANSS negative scale score. The factor 2 score was affected by duration of illness.

Conclusions: Age, education years, PANSS negative scale score and duration of illness affected WCST factor scores in patients with schizophrenia. Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

ARTICLE SUMMARY

Article focus

- To investigate relationships between Wisconsin Card Sorting Test (WCST) factor scores and clinical and sociodemographic factors in Japanese patients with schizophrenia using multiple logistic regression analysis.
- To show distribution of each WCST score for patients with schizophrenia.

Key messages

- Age, education years, positive and negative syndrome scale negative scale score and duration of illness affected two WCST factor scores.
- Using WCST factor scores may reduce the possibility of type I errors due to multiple comparisons.

Strengths and limitations of this study

- We conducted principal component analysis and identified two WCST factors. Components of two WCST factors in this study were similar to previous studies.
- This is the first study to investigate relationships between WCST factor scores and clinical and sociodemographic factors in patients with schizophrenia.
- We identified a clinical and sociodemographic factor (duration of illness) that affected the WCST factor 2 score. This is a new finding.

INTRODUCTION

Cognitive impairment in patients with schizophrenia has been evaluated as an indicator of outcome regarding social functioning and quality of life.[1 2] It is reported that cognitive performance in patients with schizophrenia declines from prodrome to onset of schizophrenia (first episode).[3] Moreover, it is reported that decline of cognitive performance exists before onset of schizophrenia.[3] Many studies using brain imaging suggest that neurobiological changes in the brain are related to

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the cognitive impairment in schizophrenia.[4–6] Therefore, some researchers regard cognitive impairment, rather than positive and negative symptoms, as the core pathology of schizophrenia.[7]

However, there are several problems when analysing cognitive impairment in schizophrenia. First, positive and negative syndromes modify cognitive performance.[8 9] Second, intelligence level, intelligence profile (verbal IQ and performance IQ), and educational level could affect cognitive impairment in patients with schizophrenia.[10–12] In brief, many factors have the potential to affect cognitive impairment in patients with schizophrenia. It is necessary to clarify the relationship between cognitive performance in patients with schizophrenia and clinical and sociodemographic factors in order to investigate what factors affect cognitive impairment in patients with schizophrenia.

Many neurocognitive tests have been used in order to evaluate cognitive performance in schizophrenia. The Wisconsin Card Sorting Test (WCST) is a neurocognitive test using cards and is one of the most frequently used executive function measures.[13] A functional brain imaging study showed widespread activation across frontal and non-frontal brain regions during WCST performance.[14] It has been reported that each WCST score was related with social functioning in patients with schizophrenia.[15–17]

Recent reports suggest that WCST performance may decline during disease progression from prodrome to onset of schizophrenia. A steady (non-significant) progression of impairment on WCST perseverative errors (PE) was demonstrated from basic symptom at-risk (BS), ultra high-risk (UHR) and first-episode (FE) groups (BS: z=−0.74; UHR: z=−0.88; FE: z=−0.97).[3] However, negative and depressive symptoms may modify WCST performance in patients with schizophrenia,[9 18] and many other factors (eg, premorbid IQ) may modify WCST scores.[11]

Factor structures of WCST in patients with schizophrenia have been investigated using principal component analysis and factor analysis of WCST scores.[19–21] Differences in cognitive performance of WCST scores (categories achieved (CA) and PE) were shown between patients with schizophrenia and healthy controls (Cohens' d=0.91 and 0.53) in one meta-analysis, but age, education years and other clinical and sociodemographic factors were not matched in the statistical analysis.[10] In another previous study, age and education years affected CA and PE scores.[22] In a different study, age affected PE score but education years did not affect either CA or PE scores.[10] Additional two studies showed age of onset affected PE score[23] and the positive and negative syndrome scale (PANSS) negative scale score affected CA score in patients with schizophrenia.[9] These findings indicate that it is important to consider all clinical and sociodemographic factors to clarify which affect WCST scores in patients with schizophrenia.

In previous studies, the Wechsler Adult Intelligence Scale Full Scale IQ (FSIQ) showed significant correlations ($p<0.05$) with CA, perseverative errors in Milner (PEM) and Nelson (PEN) and TE scores, while items 3 and 16 of the Brief Psychiatric Rating Scale showed significant correlations ($p<0.05$) with CA, PEN and TE scores.[24] Affective flattening and blunting and avolition-apathy on the Scale for the Assessment of Negative Symptoms showed significant correlations ($p<0.05$) with CA, PEM, PEN, TE and difficulties of maintaining set (DMS) scores of Wisconsin Card Sorting Test Keio version (KWCST) in Japanese patients with schizophrenia (n=33).[24] However, there is no previous study that investigated other clinical and sociodemographic factors (except IQ and negative symptoms) affecting KWCST scores. Therefore, we investigated clinical and sociodemographic factors affecting scores of KWCST[25] (Japanese computerised version[26]) in Japanese patients with schizophrenia.

METHODS AND PROCEDURES

Participants

The study included 131 unrelated Japanese patients with schizophrenia (age 43.5±13.8 (mean±SD), 84 men and 47 women) from three hospitals. The recruitment took place from both the outpatient department and the acute/chronic wards in three hospitals. Fifty-one outpatients (15 acute phase patients and 36 chronic phase patients) and 55 inpatients (37 acute phase patients and 18 chronic phase patients) were recruited. Twenty-five patients were unspecified (outpatients or inpatients: 20 acute phase patients and 5 chronic phase patients). Participants were recruited from July 2009 to August 2011. Profiles of all the patients are shown in table 1. In total, 104 patients (78%) were receiving concomitant medications, which could include benzodiazepines, barbiturates, anticholinergics, mood stabilisers and antidepressants.

This study protocol was approved by Nagoya University Graduate School of Medicine and Nagoya University

Table 1 Profiles of patients with schizophrenia

	Patients with schizophrenia (n=131)	
	Male	Female
Sex	84	47
	Average	(SD)
Age (year)	43.5	(13.8)
Education (year)	12.4	(2.4)
Age of onset (year)	26.3	(10.0)
Duration of illness (year)	17.0	(12.8)
Chlorpromazine equivalent doses (mg)	618.4	(391.1)
PANSS scale		
Positive (7–49)	16.5	(5.3)
Negative (7–49)	19.3	(5.6)
General (16–112)	36.6	(9.4)
Total (30–210)	72.4	(18.1)

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Hospital Ethics Review Committee, and written informed consent was obtained from each participant. Participants were recruited for the study if they (1) met DSM-IV criteria for schizophrenia; (2) were physically healthy and (3) had no mood disorders, substance abuse, neurodevelopmental disorders, epilepsy or mental retardation. Consensus diagnoses were made by at least two experienced psychiatrists according to DSM-IV criteria on the basis of unstructured interviews with patients with schizophrenia (or their family members) and review of patients' medical records. Less than 5% of participants were excluded due to a lack of consensus. All subjects were unrelated to each other and lived in the central area of the mainland of Japan. A general characterisation and psychiatric assessment of the subjects is available elsewhere.[27–29]

Measurement settings

The WCST mainly assesses executive function, including cognitive flexibility in response to feedback.[30] KWCST is the Japanese version of the WCST modified by Kashima.[25] KWCST consists of a card version and a computerised version, both of which have been used to investigate cognitive performance in patients with schizophrenia.[31 32] In KWCST, there are two levels of instruction.[33] The subject is told that, at the first level, this is a test of classification based on any of the three categories of colour, shape or number, and that, at the second level, the tester's categories change when the subject continues to get correct answers at fixed times. The computerised version uses instruction through letters on the monitor and the synthetic sound of the computer in order to prevent potential bias derived from a confrontation test. We selected specific indicators (CA, PEM, PEN, TE and DMS) of KWCST in this analysis, given that these indicators were investigated in previous studies.[31 32] The computerised programme investigates these indicators at the second level only if the CA score at the first level is equal or less than 3. We got data for the following five indicators [32 34] at the first and second levels in this study.

1. CA: the number of categories for which six consecutive correct responses are achieved (maximum CA is 8).
2. PEM: the number of incorrect responses in the same category as the immediately preceding correct response after the tester's categories change (maximum PEM is 47).
3. PEN: the number of incorrect responses in the same category as the immediately preceding incorrect response (maximum PEN is 47).
4. TE: the total number of incorrect responses (maximum TE is 48).
5. DMS: the number of times an incorrect response occurs after 2–5 consecutive correct responses (maximum DMS is 16).

We analysed KWCST (Japanese computerised version;[26] Shimane University, Shimane, Japan) scores at the first level of the patients with schizophrenia. Psychiatrists in three hospitals performed the KWCST assessment.

Clinical and sociodemographic factors

We investigated sex, age, education years, age of onset, duration of illness, chlorpromazine (CPZ) equivalent doses and PANSS scores as clinical and sociodemographic factors. Age was calculated based on the day we evaluated KWCST scores. Education years were calculated from elementary school entrance to the graduation or dropout of the last institution of higher education, which consisted of junior high school, senior high school, vocational school, junior college and university and graduate school. Age of onset was the age at onset of schizophrenia in each patient and was based on review of medical records. Duration of illness was defined from age of onset to age at the time of study. CPZ equivalent doses were the identified dose ratios of each antipsychotic in relation to 100 mg of CPZ.[35] CPZ equivalent doses in this study were calculated based on the method by Inagaki and Inada.[36 37] PANSS is a standardised scale for evaluating positive and negative symptoms of schizophrenia and was used to evaluate severity of schizophrenia in the patients.[38]

Statistical analysis

Clinical profiles of the patients with schizophrenia are shown in table 1. We investigated correlations of the five indicators of the KWCST (CA, PEM, PEN, TE and DMS) in patients with schizophrenia by Spearman's Rank Correlation Test.

Principal component analysis

The principal component model was based on Pearson's correlation matrix. We showed the Pearson's product moment correlation coefficients between the five indicators of WCST in supplementary table S1 (web-only file). WCST factors were identified by principal component analysis of the five indicators without rotation. Factors were retained using the eigenvalue >1 criterion.

Main analysis

In the main analysis, we investigated what clinical and sociodemographic factors affected WCST factor scores in a multiple logistic regression analysis. Our reasoning for not using multiple linear regression is explained in supplementary information S1 (web-only file). The dependent variables were WCST factor scores and independent variables were the following candidate clinical and sociodemographic factors: sex, age, education years, age of onset, duration of illness, CPZ equivalent doses and PANSS (positive, negative and general psychopathology scale) scores. We made a dummy conversion variable (1 or 0) for sex. We converted factor scores into categorical variables (1 or 0), using cut-off values that were median values of the factor scores. The median was chosen as a cut-off point for dependent variables based on reasons explained in supplementary information S2

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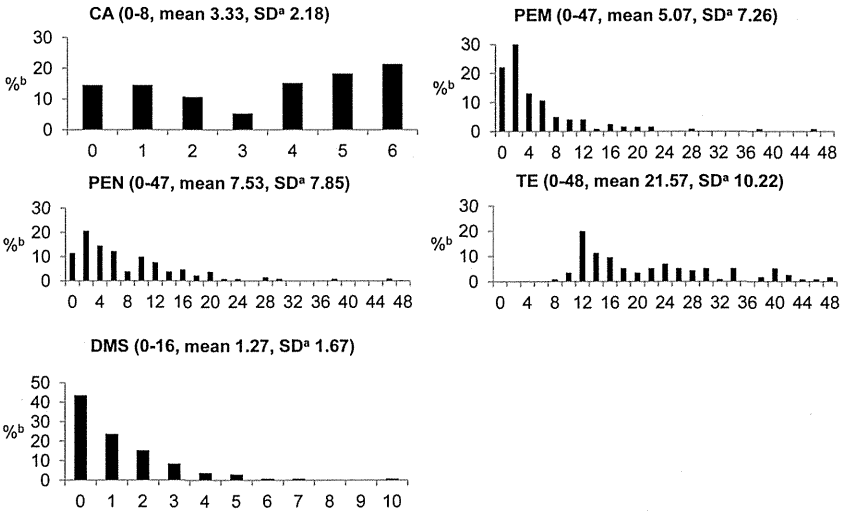

Figure 1 Distribution of Wisconsin Card Sorting Test scores in patients with schizophrenia (n=131). None of the distribution was normal distribution. CA, categories achieved; DMS, difficulties of maintaining set; PEM, perseverative errors in Milner; PEN, perseverative errors in Nelson; TE, total errors;. (A) SD. (B) Percentage of cases.

(web-only file). In our multiple logistic regression analysis, we did additional two tests. First, we did an omnibus test of model coefficients versus a model with intercept only. This test detects whether a model is significant ($p<0.05$) or not; this is a test of the null hypothesis that adding any variables to the model has not significantly increased our ability to predict the dependent variable. A model is useless if the p value in omnibus test was >0.05. Second, we did a Hosmer and Lemeshow goodness of fit test, which shows how well the model fits the data with $p>0.05$ indicating good fit; this is a test of the null hypothesis that there is a linear relationship between the predictor variables and the log odds of the criterion variable. The hit rate in multiple logistic regression analysis is a measure how well a model predicts the dependent variable.

Subanalysis

In the subanalysis, we also investigated what clinical and sociodemographic factors affected the five indicators of WCST in the multiple logistic regression analysis. We used multiple logistic regression analysis in the subanalysis in order to compare the results between main and subanalysis. In this analysis, the dependent variables were the five indicators of WCST and independent variables were the candidate clinical and sociodemographic factors. We compared the results of the multiple logistic regression analysis with the results of previous studies.[9 10 23]

Software

IBM SPSS statistical software (IBM Japan, Tokyo, Japan), V.19 was used for analyses. The significance level was set at p=0.05 using a two-tailed t test.

RESULTS

Distribution of the WCST (CA, PEM, PEN, TE and DMS) scores in patients with schizophrenia is shown in figure 1. The numbers of patients in the following analyses were CA n=131, PEM n=122, PEN n=131, TE n=115 and DMS n=131 because of missing values in the data.

Spearman's rank correlation coefficients between the five indicators of WCST are shown in table 2. Although no strong correlation (>0.8) was observed in any of these clinical and sociodemographic factors, the Spearman's correlation between PANSS negative scale score and PANSS general psychopathology scale score was high (0.74).

Principal component analysis

Two factors (1 and 2) were identified in principal component analysis of the five indicators of WCST. Factor 1 mainly consisted of CA, PEM, PEN and TE, and accounted for 65.6% of the total variance. Factor 2 mainly consisted of DMS and accounted for 23.2% of the total variance (table 3 and figure 2). We converted the factor 1 and factor 2 scores into categorical variables (1 or 0) using cut-off values. The cut-off values were the median values (factor 1:−0.299; factor 2:0.080). We used these categorical variables as dependent variables in multiple logistic regression analysis.

Table 2 Correlation coefficients for WCST scores in patients with schizophrenia

		Patients with schizophrenia (n=131)				
		CA	PEM	PEN	TE	DMS
Correlation coefficient†	CA	–	–	–	–	–
	PEM	−0.70**	–	–	–	–
	PEN	−0.79**	0.73**	–	–	–
	TE	−0.88**	0.71**	0.89**	–	–
	DMS	−0.58**	0.30*	0.28*	0.30*	–

*p<0.01.
**p<0.001.
†Spearman's rank correlation coefficient.
CA, categories achieved; DMS, difficulties of maintaining set; PEM, perseverative errors in Milner; PEN, perseverative errors in Nelson; TE, total errors; WCST, Wisconsin Card Sorting Test.

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Table 3 Factor loadings in principal component analysis in patients with schizophrenia (n=131)

	Factor 1	Factor 2
WCST score		
CA	−0.89	0.36
PEM	0.84	0.27
PEN	0.92	0.27
TE	0.93	0.13
DMS	0.29	−0.93
Variance (%) explained by each factor	65.6	23.2
Cumulative explained variance (%)	65.6	88.9

Factor analysis was based on principal component method without rotation.
Two factors were retained using the eigenvalue >1 criterion.
CA, categories achieved; DMS, difficulties of maintaining set; PEM, perseverative errors in Milner; PEN, perseverative errors in Nelson; TE, total errors; WCST, Wisconsin Card Sorting Test.

Main analysis

Age, education years and PANSS negative scale score significantly affected factor 1 score, and the duration of illness significantly affected factor 2 score in patients with schizophrenia (table 4). The details of the results from the multiple logistic regression analyses are shown in supplementary table S2 (web-only file). p Values in an omnibus test of model coefficients versus a model with intercept only were statistically significant ($p<0.05$) for all the models in WCST factor scores. In the Hosmer and Lemeshow goodness of fit test, all the models fit the data adequately with $p>0.05$. Factor 1 score may be predicted precisely by this model considering hit rate (0.77).

CPZ equivalent doses did not affect the WCST scores. PANSS positive scale score did not affect the WCST scores; whereas PANSS negative scale score did.

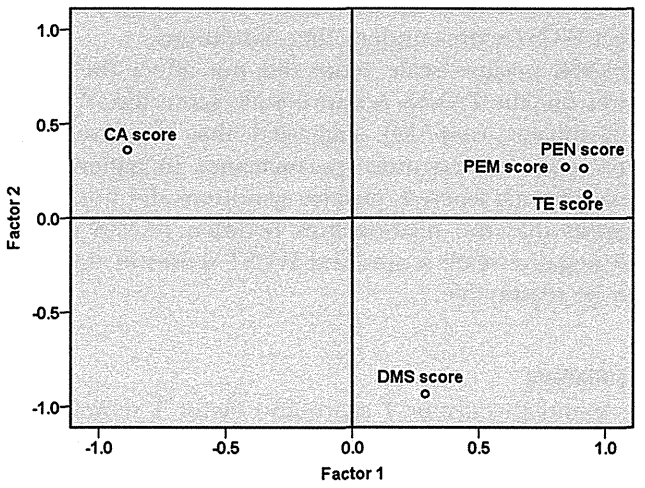

Figure 2 Component plot in principal component analysis of Wisconsin Card Sorting Test scores in patients with schizophrenia (n=131). Abbreviations: CA, categories achieved; DMS, difficulties of maintaining set; PEM, perseverative errors in Milner; PEN, perseverative errors in Nelson; TE, total errors.

Subanalysis

In the subanalyses, age, education years and PANSS negative scale score significantly affected CA score. Age and education years significantly affected PEM, PEN and TE scores, and age significantly affected DMS score in patients with schizophrenia. The details of these results are shown in supplementary tables S3 and S4 (web-only file); supplementary table S4 includes the results of previous studies. p Values in the omnibus test of model coefficients versus a model with intercept only were statistically significant ($p<0.05$) for all the models for each WCST score, and all the models fit the data adequately in the Hosmer and Lemeshow goodness of fit test.

DISCUSSION

This study is the first to investigate the relationships between WCST factor scores and clinical and sociodemographic factors in Japanese patients with schizophrenia by multiple logistic regression analysis. We showed the distribution of each WCST score (figure 1). We conducted principal component analysis and identified two factors. The components of these two factors were similar to previous studies.[19–21] Thus, we could reduce the number of WCST outcomes from five indicators to two factors (table 3). In assessment of cognitive function in patients with schizophrenia, using the WCST factor scores may reduce the possibility of type I errors due to multiple comparisons. We analysed the relationship between these two factors and clinical and sociodemographic factors with multiple logistic regression analysis. We found that age, education years, PANSS negative scale score and duration of illness affected the two WCST factor scores.

Principal component analysis

Our study showed that factor 1 mainly consisted of CA, PEM, PEN and TE and factor 2 mainly consisted of DMS. In the previous studies with principal component analysis and factor analysis of WCST scores in patients with schizophrenia, categories complete (CC; an indicator examining numbers of categories achieved in the same way as CA), PE (an indicator examining perseveration in the same way as PEM and PEN) and TE mainly constituted one factor. Failure to maintain set (FMS; an indicator examining difficulty of maintaining set, similar to DMS) mainly constituted another factor.[19–21] Our results resembled the results of the principal component analysis and factor analysis of WCST in these previous studies.[19–21]

Factor 1, which included representative indicators (CC, PE, etc), was named as 'general executive functioning' in a previous study.[21] Therefore, factor 1 in our study also may represent general executive functioning. In our study, factor 1 score showed a high contribution ratio of the total variance (65.6%) in principal component analysis of WCST scores in patients with schizophrenia. WCST factor scores calculated by principal component analysis may be useful for reducing the

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Table 4 Clinical and sociodemographic factors for WCST scores of patients with schizophrenia in the current study (main analysis) and for previous studies

	Patients with schizophrenia (n=131)				
	Main analysis		Previous studies		
	Factor 1 score	Factor 2 score	CA†	PE†	TE†
Sex			n/a	n/a	n/a
Age	***		ns‡	O‡	n/a
Education years	**		ns‡	ns‡	n/a
Age of onset			ns§	O§	n/a
Duration of illness		*	ns‡	ns‡	n/a
Chlorpromazine equivalent doses			n/a	n/a	n/a
PANSS score					
Positive (7–49)			ns¶	n/a	n/a
Negative (7–49)	*		O¶	n/a	n/a
General (16–112)			ns¶	n/a	n/a
Hit rate	0.77	0.58	n/a	n/a	n/a

*p<0.05.
**p<0.01.
***p<0.001.
†CA, PE and TE were included in factor 1 in a previous study.
‡Reference 10.
§Reference 23.
¶Reference 9.
CA, categories achieved; DMS, difficulties of maintaining set; n/a, data not available; ns, not significant; PANSS, positive and negative syndrome scale; PEM, perseverative errors in Milner; PEN, perseverative errors in Nelson; TE, total errors; WCST, Wisconsin Card Sorting Test.

possibility of type I errors due to multiple comparisons. Factors 1 and 2 in our study resembled those in previous studies.[19–21] Therefore, the KWCST measures cognitive function similarly to the traditional WCST.

We compared the Spearman's rank correlation coefficients with the Pearson's product moment correlation coefficients between the five indicators of WCST (table 2 and supplementary table S1). Correlations between CA, PEM, PEN and TE and a correlation between CA and DMS were statistically significant ($p<0.001$). In this point, both correlation coefficients showed the same direction. Therefore, using Pearson's correlation matrix, instead of Spearman's correlation matrix, in principal component analysis may be justified in our study.

Main analysis

We identified clinical and sociodemographic factors (age, education years and PANSS negative scale score) affecting WCST factor 1 score. We also identified a clinical and sociodemographic factor (duration of illness) affecting WCST factor 2 score. This is an important new finding. Comparing the three main previous studies [9 10 23] with the current study, we summarised shared and different findings, shown in table 4.

The shared findings were that age and PANSS negative scale score were related to WCST scores (table 4).[9 10 23]

Two findings differed from previous studies (table 4).[9 10 23] First, we found a new relationship between education years and WCST scores. Second, we found no relationship between age of onset and WCST scores. Differences in the results between previous studies [9 10 23] and our study may be explained by differences of ethnicity, distribution of age and education years, types of statistical analysis used, and the version of WCST. These differences suggest that future studies about WCST should be conducted with attention to these conditions.

CPZ equivalent doses did not affect the WCST scores in this study. This result was in the same direction as one meta-analysis (n=4524) though recent studies had suggested the possibility of an effect.[31 39 40] Future studies will be necessary to clarify whether CPZ equivalent doses affect WCST scores under other conditions.

PANSS positive scale score did not affect the WCST scores but the PANSS negative scale score did. A recent meta-analysis (n=6519) suggested that negative symptoms related to cognitive performance in patients with schizophrenia whereas positive symptoms did not.[41] This suggests that the relationships between PANSS positive and negative scale scores and WCST scores in this study may be reasonable.

Subanalysis

We found that factor 1 score and factor 1 score's main components (CA, PEM, PEN and TE) related to age and education years (see online supplementary table S5 (web-only file)).

The effect of duration of illness on WCST factor 2 score, which was mainly influenced by DMS, is the novel finding of the main analysis. However, DMS is not significantly associated with the duration of illness in the subanalysis (see online supplementary table S5 (web-only file)). This

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discrepancy between the main analysis and subanalysis may be derived from the difference between DMS and factor 2 (factor 2 included not only DMS, but also CA, PEM, PEN and TE).

Limitations

There are several limitations in this study. First, other clinical and sociodemographic factors that were not investigated in the current study could affect WCST scores. Candidates for such clinical and sociodemographic factors are IQ,[42] participants' dominant arm, experience with using a computer, doses of drugs affecting cognitive performance (anticholinergics, benzodiazepines, etc), sleep,[43] eating and risk factors of arteriosclerosis (body mass index, blood pressure, etc).[44] It may be useful to include these factors in future studies. Second, the WCST indicators (CA, PEM, PEN, TE and DMS scores) in our study did not cover all WCST indicators; we selected the major five indicators. We might find other factors by principal component analysis or new relationships between new WCST factors and clinical and sociodemographic factors if we included other clinical indicators. Third, instead of using Spearman's correlation matrix in the principal component analysis, which might be more appropriate method in terms of the non-normal distribution of five WCST indicators, we used Pearson's correlation matrix. Fourth, we dichotomised continuous variables (WCST factor scores) in the multiple logistic regression analysis. Therefore, careful interpretation of the results may be needed, considering the statistical weak points.[45]

CONCLUSION

This study is the first study that investigated clinical and sociodemographic factors affecting WCST factor scores calculated by principal component analysis in patients with schizophrenia. The study was conducted in a relatively large Japanese population. We showed distribution of measured five WCST indicators in patients with schizophrenia and confirmed two WCST factors by principal component analysis. Age, education years, PANSS negative scale score and duration of illness affected WCST scores in patients with schizophrenia. The interaction between the duration of illness and a factor of the WCST needs further confirmation in future studies because there was a discrepancy between the results of the main analysis and the subanalysis in this study.

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Contributors MB, TKo and NO conceived and designed the experiments. MB, TKo, TKi, KK and YA performed the experiments. MB, TKo, BA, TO, NK, TI and NO analysed the data. MB, TKo and YA contributed reagents/materials/analysis tools. MB, TKo, TO, BA and NO wrote the paper.

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Competing interests None.

Ethics approval This study was approved under the guidelines for epidemiological studies by the Nagoya University Graduate School of Medicine and Nagoya University Hospital Ethics Review Committee and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before the start of the study.

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Wisconsin Card Sorting Test scores and clinical and sociodemographic correlates in Schizophrenia: multiple logistic regression analysis

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The pilot study of a Neuropsychological Educational Approach to Cognitive Remediation for patients with schizophrenia in Japan

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ABSTRACT

The main aim of this study is to demonstrate the feasibility and efficacy of a Neuropsychological Educational Approach to Cognitive Remediation (NEAR) in Japan. This multi-site study used a quasi-experimental design. Fifty-one patients with schizophrenia or schizoaffective disorder participated. The NEAR program consisted of two 1-h computer sessions per week and an additional group meeting session lasting 30 to 60 min once a week. The subjects completed 6 months of NEAR sessions before being assessed. Moreover, taking into consideration the possible practice effect, we assessed 21 control patients twice with an interval of 6 months. We assessed cognitive function by using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J). Consequently, the NEAR group showed significant improvement in overall cognitive function, and in comparison with the control group, these findings were generally similar except for motor speed. Although the present study has its limitations, it demonstrates that the NEAR is feasible in Japan as well as it is in Western countries.

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1. Introduction

It is widely accepted that cognitive dysfunction in schizophrenia plays a major role in determining social function (Green et al., 2000). Although there have been numerous reports that indicate the effectiveness of atypical antipsychotics (AAPs) on cognitive function, the size of the effect of AAPs is generally about 0.2–0.5 standard deviations (S.D.) (Woodward et al., 2005; Keefe et al., 2007), while the extent of cognitive dysfunction in schizophrenia is about 1–1.5 S.D. below the level of healthy populations (Bilder et al., 2000; Heinrichs, 2004). To bridge this gap, other treatment methods, such as cognitive remediation, have been considered in Western countries.

In Japan, the "Services and Supports for Persons with Disabilities Act" was established in 2006. Although disabled persons' employment, deinstitutionalization, and socialization were promoted by this law, there are actually many people with psychiatric illnesses, including patients with schizophrenia, who still suffer from social dysfunction. With the aim of alleviating the many difficulties that patients encounter in their lives, cognitive remediation therapy for patients with schizophrenia has gradually been launched in Japan (Nemoto et al., 2009).

We have become interested in one of the cognitive remediation therapies, namely, a Neuropsychological Educational Approach to Cognitive Remediation (NEAR) (Medalia and Freilich, 2008; Medalia et al., 2009), which is theoretically based on neuropsychology, educational psychology, learning theory, and cognitive psychology. After participating in 1-week clinician training for NEAR, we started implementing NEAR in Japan. NEAR is an evidence-based approach to cognitive remediation specifically developed for use with psychiatric patients. NEAR is a group-based treatment that provides a positive learning experience to each and every client, to promote independent learning, and to promote optimal cognitive function in everyday life. Sessions are structured in a way to enhance intrinsic motivation and learning. The main aim of this study is to demonstrate the feasibility and efficacy of NEAR in Japan by assessing its effectiveness on cognitive function using neuropsychological indices as a primary endpoint.

2. Methods

This multi-site study used a quasi-experimental design. All participants were recruited from five psychiatric hospitals in the western region of Japan called the 'San-in' district and exposed to NEAR in each hospital. All participants were recruited on the basis of consecutive referrals.

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Table 1
Baseline demographic variables.

	NEAR group	Control group
Number of patients		
Sch: Schizophrenia	Sch: 48	Sch: 21
SchAf: Schizoaffective disorder	SchAf: 3	SchAf: 1
Gender	Male: 31, Female: 20	Male: 14, Female: 8
Mean age	36.1 ± 10.6 y.o.	41.1 ± 12.4 y.o.
Years of education	13.5 ± 2.5 years	12.5 ± 2.6 years
Duration of illness	13.8 ± 9.8 years	16.1 ± 10.8 years
Age at onset of illness	22.3 ± 6.6 y.o.	22.6 ± 6.3 y.o.
Total number of hospitalizations	2.8 ± 3.1 times	4.6 ± 5.2 times
Total months of hospitalization	19.4 ± 29.4 Months	39.3 ± 65.8 months
Mean dosage of antipsychotics (Chlorpromazine equivalent dose)	634.5 ± 364.9 mg/day	699.2 ± 569.2 mg/day
Treatment settings (Outpatient or inpatient) *	Outpatients: 42 Inpatients: 9	Outpatients: 12 Inpatients: 10
NEAR attendance rate	0.90 ± 0.11	
BACS-J z score; Verbal memory**	−1.09 ± 0.92	−2.00 ± 1.05
BACS-J z score; Working memory	−0.95 ± 0.95	−1.30 ± 1.08
BACS-J z score; Speed	−1.60 ± 1.37	−2.25 ± 1.74
BACS-J z score; Verbal fluency	−0.47 ± 1.00	−0.71 ± 0.89
BACS-J z score; Attention and speed of information processing	−1.24 ± 0.88	−1.56 ± 0.77
BACS-J z score; Executive function	−0.57 ± 1.42	−1.56 ± 2.15
[EX]**	−0.79 ± 0.59	−1.10 ± 0.59
BACS-J composite score**	−1.65 ± 1.27	−2.61 ± 1.51

* $p<0.05$ Fisher's exact test.
** $p<0.05$ Student's t test.
[EX] = −log[2 − (Executive function BACS-J z score)].

2.1. Subjects (Table 1)

After a complete explanation of the study, informed consent was obtained from the participants. The protocol of this study was approved by the Ethics Committee of Tottori University. Inclusion criteria were outpatients or inpatients (a) with a diagnosis of schizophrenia or schizoaffective disorder made by two experienced psychiatrists according to DSM-IV-TR criteria, (b) between 13 and 65 years old, (c) able to sit for a 1-hour session, (d) willing to participate in the study, and (e) being recommended by their doctors. Exclusion criteria were patients (a) with active substance or alcohol abuse or having left a detoxification program within the last month, or (b) with traumatic head injury within the past 3 years.

Sixty-two patients were referred to the program, and 11 dropped out at the midway point (the dropout rate was 17.4%). Among these 11 patients, five patients dropped out owing to a lack of motivation and five patients dropped out because of relapse of psychotic symptoms. One patient found a job and left the program. Six of the patients who withdrew left the program within the first half of the 6-month trial. Finally, 51 patients with schizophrenia or schizoaffective disorder completed the NEAR program. The NEAR program consisted of two 1-h computer sessions per week and an additional group meeting session lasting 30 to 60 min once a week. The subjects completed approximately 6 months before the program's efficacy was assessed.

Moreover, we assessed 22 control patients twice with an interval of 6 months, taking into consideration a possible practice effect, which may have affected the scores of neuropsychological tests. They did not receive any cognitive training program including NEAR. As for the clinical backgrounds, the treatment settings were significantly different between the two groups, with more inpatients being included in the control group than in the NEAR participant group.

In each computer session, patients engaged with some educational computer software that was related to various domains of cognitive function, including attention, memory, and executive function, taking into account the profiles of the patients' cognitive impairments. The software available in Japan is not identical to that in Western countries; however, it appeared to cover the relevant cognitive domains (Table 2).

The main aim of the group meeting sessions was to contextualize the computer training into the patients' everyday activities. The process should lead to enhancing motivation and generalization of cognitive skills to real-life activities.

One of our co-authors is certified as a supervisor of NEAR and she supervised NEAR sessions periodically. In order to use consistent methods across sites, all clinicians participated in 1-week clinician training, and they attended trimonthly meetings.

Although the medications were changed throughout the whole period as little as possible, there were 16 patients whose medications needed to be changed because of clinical decisions. However, the change in the medication status of these 16 patients was only related to daily dosage levels.

2.2. Assessments

We assessed cognitive function using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) (Keefe et al., 2004; Kaneda et al., 2007). Z scores were calculated for each subcomponent score using means and standard deviations based on the dataset of 340 healthy control Japanese populations; however, it must be noted that age, sex, and socio-economic status of the healthy controls were not necessarily matched to those of the patients in the present study. Composite scores were calculated by averaging all z scores of the six subcomponents (verbal memory, working memory, motor speed, verbal fluency, attention and speed of information processing, and executive functions), and then re-normed based upon the standard deviations (SD) of the average of those scores in the normative sample (SD = 0.6).

2.3. Statistical analysis

Two-tailed paired t-tests were performed for the assessment of change between the two measurements of BACS-J data, which were administered before (baseline) and after (post-treatment) the NEAR sessions. Each subcomponent score was normally distributed except for the executive function score. Through a logarithmic transformation of the executive function score, the curve was modified to a normal distribution, described by [EX] = −log[2 − (Executive function BACS-J z score)]. Therefore, we used [EX] instead of "executive function BACS-J z score" for analysis.

Except for the treatment settings, baseline verbal memory, baseline [EX], and baseline composite scores, neither socio-demographic nor clinical variables differed significantly between the two groups (Table 1). Therefore, repeated measures analyses

Table 2
Sample educational computer software used in the computer sessions.

Task	Software	Activity	Target cognitive domain
The mail room	Monsters Inc.: Scream Team Training	Sort all the mail into the proper mailboxes before the clock hits 9 a.m.	Attention, speed
Lunch room	Monsters Inc.: Scream Team Training	Select food items and daily specials to serve to each monster in accordance with the figure presented on the lunch-order ticket.	Attention, speed
Moonfish	Finding Nemo: Nemo's Underwater World of Fun	Repeat the shape patterns made by the moonfish.	Working memory
Spark! Mejikara	Let's refresh your brain	Memorize the illustrations that appear one after another on the screen, and recollect them in order.	Working memory
Hustle memory	Let's refresh your brain	Memorize the character's clothes that are put on within 10 s.	Visual learning and memory
Frippletration	Thinkin' Things 2	Visual and auditory memory matching game.	Visual/auditory learning and memory
Stocktopus	Thinkin' Things 3	Repeat trading items to get the items you need for your portfolio.	Working memory, executive function,
Build it	Factory Deluxe	Build up the presented goal product by selecting and using appropriate tools.	Executive function
The puzzles	Logical Journey Of The Zoombinis	Solve puzzles with various rules using as clues physical features of hair, eyes, nose, and feet of little creatures called Zoombinis.	Executive function

"Thinkin' Things 2", "Thinkin' Things 3", and "Factory Deluxe" were English versions; however, English ability was not necessary to accomplish the tasks. Other software programs were Japanese versions.