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Cognitive function in Japanese elderly with type 2 diabetes mellitus

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Abstract

The current study was conducted to investigate the cognitive function in Japanese elderly with type 2 diabetes mellitus (DM). Participants included 69 diabetic and 27 nondiabetic subjects (60 to 85 years old). The cognitive functional tests conducted were the Mini-Mental State Examination (MMSE), Word Lists Recall (immediate, delayed), Digit Symbol Test (Wechsler Adult Intelligence Scale—Revised [WAIS-R]), and the Stroop Color Word Test. Hemoglobin A1c (HbA1c) was measured as the index of glycemic control, and information about recent hypoglycemic episodes was gathered by using questionnaires. Student's t test showed that DM subjects had significantly lower scores in the MMSE ($P<.01$) and Digit Symbol Test ($P<.05$) than non-DM subjects. The scores of the Digit Symbol Test in diabetes subjects had a significant negative relationship with HbA1c ($r=-.433$; $P<.001$), and insulin-use had a significant relationship with the scores of the MMSE and Digit Symbol Test. Subjects in the DM group were further divided by insulin use. Comparison of insulin-treated DM subjects, non-insulin-treated DM subjects, and nondiabetic subjects by analysis of variance followed by Bonferroni's post hoc test showed that insulin-treated DM subjects had significantly lower scores in the MMSE and Digit Symbol Tests than both non-insulin-treated DM subjects ($P<.05$) and nondiabetic subjects ($P<.01$). Our study suggests that Japanese elderly DM subjects, especially those with insulin treatment, have poor cognitive function.

Keywords: Digit Symbol Test; MMSE; HbA1c; Insulin; Hypoglycemia

1. Introduction

Cognitive function in elderly diabetes mellitus (DM) subjects has been of interest for more than 80 years and has been explored in several studies; however, the outcomes of these studies have not been entirely conclusive (Strachan, Deary, Ewing, & Frier, 1997). Although most studies have concluded that cognitive performance is worse in elderly DM subjects (Gradman, Laws, Thompson, & Reaven, 1993; Miles & Root, 1922; Perlmuter et al., 1984; Reaven, Thompson, Nahum, & Haskins, 1990), some studies have reported that cognitive function in type 2 DM subjects is comparable to that in non-DM subjects (Atiea, Moses, & Sinclair, 1995; Mattlar, Falck, Ronnemaa, & Hyyppa, 1985). These studies have been performed mainly in Western countries. Because cognitive functional tests are based on language communication, studies should be performed using subjects with different genetic and cultural backgrounds in different languages.

Among the factors involved in the mechanism of cognitive impairment in DM subjects, glycemic control may be one of the most important (Gradman et al., 1993; Meneilly, Cheung, Tessier, Yakura, & Tuokko, 1993). Few studies have investigated the relationship between glycemic control and cognitive function in DM patients. However, one study reported that glycemic control, as measured by hemoglobin A1c (HbA1c) levels, showed a significant negative correlation with cognitive function in DM patients (Reaven et al., 1990). Another reported that oral hypoglycemic medication improved some domains of cognitive ability (attention/concentration, new learning, and problem solving) (Gradman

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et al., 1993). To maintain glycemic control, a combination of several kinds of treatments—including diet regulation, oral medication, and/or insulin treatment—is needed for DM patients. Large prospective studies have shown that persons with DM are at an increased risk of developing dementia, including Alzheimer's disease, particularly when treated with insulin (Ott et al., 1996, 1999). However, the effects of various treatments on cognitive function in DM patients have not been well investigated. For example, there has been only one study—that of Jagusch, Cramon, Renner, & Hepp, 1992—on the effect of treatment in nondemented DM patients; the results showed that insulin-treated subjects had slower simple reaction times. Recently we investigated the effect of treatment on the brain atrophy in elderly DM subjects, and found that the insulin-treated group had the most severe atrophy (Ushida et al., 2001).

Given this situation, the present study was initiated with the following three goals. First, we compared the domains of cognitive functional tests in elderly Japanese subjects (age >60 years) with type 2 DM with a group of elderly non-DM subjects (age >60 years). Second, we wanted to determine whether there was any correlation between the measures of cognitive function and the degree of glycemic control in patients with type 2 DM. Third, we investigated the effect of DM treatment on the performance of cognitive function tests.

2. Subjects and methods

2.1. Subjects

There were 69 subjects with type 2 DM and 27 non-DM subjects. All subjects were outpatients at Nagoya University Hospital in Aichi, Japan, at Gifu Prefectural Tajimi Hospital in Gifu, Japan, at Chiaki Hospital in Aichi, Japan, or at Aoki Kinen Hospital in Mie, Japan. They ranged in age from 60 to 85 years old. All subjects with diagnosis of dementia, depressive disorders by the clinical criteria defined by DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994), respectively, or any other diseases known to affect cognitive function, or subjects who had cerebral infarctions of more than 1 cm in diameter as visualized by brain CT or MRI, and/or had neurological sings or symptoms, and/or clinical histories of stroke including transient ischemic attacks were excluded. No subjects had audio–visual deficiencies sufficient to impair their performance in the cognitive functional assessments. All participants were independent in terms of performing their daily activities.

An ethical committee approved the study protocol and all patients gave their written informed consent prior to the investigation. After the provision of informed consent, the cognitive functional tests were administered individually to each subject. HbA1c was measured as a marker of glycemic control. DM patients were asked if they had had any hypoglycemic episodes during the recent month over the last month by questionnaire. At the day of the assessment subjects had breakfast as usual and the assessment was performed before noon. The doctors checked the physical conditions of the subjects before the assessment and confirmed that they were not hypoglycemic. Hypertension was diagnosed as follows: prescription of antihypertensive medicine, systolic blood pressure (SBP) of 160 mm Hg or higher, and/or diastolic blood pressure (DBP) of 95 mm Hg or higher. The diagnosis of hyperlipidemia was based on the *Japan atherosclerosis society guidelines for diagnosis and treatment of atherosclerotic cardiovascular disease* (Japan Atherosclerosis Society, 2002). Regarding complications of

Table 1
Characteristics of participants by diabetes status

Variable	DM subjects	Non-DM subjects	*P* value
N	69	27	–
Age	71.6 ± 5.6	73.4 ± 6.6	0.164
Gender (% female)	70.4	52.2	0.107
Education (years)	10.4 ± 2.7	11.4 ± 3.0	0.167
Hypertension (%)	52.5	50.0	0.845
Hyperlipidemia (%)	36.5	60.0	0.074
HbA1c (%)	8.0 ± 1.0	5.7 ± 0.4	*P*<.01

Data are the mean ± S.D. unless otherwise indicated.
Student's unpaired *t*–test (age, education, HbA1c) and Kruskal–Wallis analysis (other variables).

Table 2
Performance on measures of cognitive function by diabetes status

Measure	DM subjects	Non-DM subjects	*P* value
MMSE	27.1 ± 2.2	28.3 ± 1.7	*P*<.05
Word List (immediate)	5.7 ± 1.7	6.2 ± 1.7	0.254
(delayed)	7.1 ± 2.2	6.7 ± 2.0	0.364
WAIS-R Digit Symbol	36.3 ± 10.9	43.0 ± 12.1	*P*<.05
Stroop Color Word Test	19.2 ± 12.8	15.0 ± 6.7	0.113

Data are the means ± S.D., unless otherwise indicated.
A higher score indicates better performance, except in the case of the Stroop Color Word Test.
Student's unpaired *t*–test.
WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Table 3
Correlation coefficients between scores of cognitive tests and diabetic characteristics

Variables	MMSE	WAIS-R
WAIS-R Digit Symbol	0.456**	–
Diabetes duration	0.078	−0.155
HbA1c	−0.205	−0.433**
Neuropathy	−0.075	0.005
Nephropathy	−0.008	−0.021
Retinopathy	−0.095	0.015
Hypoglycemia	−0.265	−0.229
Insulin-treatment	−0.379**	−0.304*

Pearson's correlation coefficients analysis (MMSE, WAIS-R digit symbol, Diabetes duration HbA1c) and Spearman's correlation coefficients analysis (other variables).
* *P*<.05.
** *P*<.01.

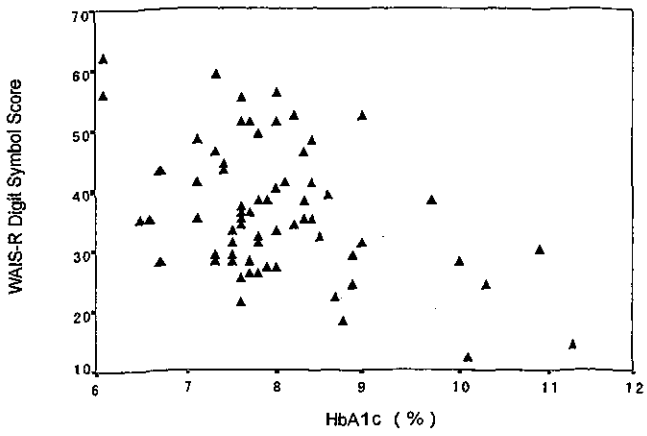

Fig. 1. Relationship between glycosylated hemoglobin (HbA1c) concentration and score of WAIS-R Digit Symbol on DM subjects (N = 69 r = −0.433, $P<0.001$).

DM, neuropathy was diagnosed as elevated vibratory perception thresholds or symptomatic neuropathy including parethesia; retinopathy was diagnosed as simple retinopathy and more advanced; and nephropathy was diagnosed as microalbuminuria (30 mg/g ≦ albumin-to-creatine ratio < 200 mg/g) and more advanced.

2.2. Assessment of cognitive function

Cognitive function was assessed by structured performance tests that were selected to represent a broad range of cognitive domains, including those measured in previous studies in type 2 DM. Strachan et al. (1997) summarized psychological tests used among the previous studies into six broad categories. In considering total administration time and elderly subjects' burden to complete the test battery, we decided to investigate four of these categories, and selected the following standardized psychological tests for measurement of each. (1) Mental Status: the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHigh, 1978) was used to evaluate this category. The MMSE assesses orientation, registration, attention, calculation, language, and recall with a score range from 0 to 30. (2) Verbal Memory: the Word List (a subtest of the Alzheimer's Disease Assessment Scale [ADAS] (Mohs, Rosen, & Davis, 1983)) was used. This test asks subjects to read aloud and remember 10 concrete words printed on individual cards. The subjects' immediate recall is evaluated directly after reading the words, and the delayed recall is assessed at 30 min after reading the words. The score range is 0–10. (3) Complex Psychomotor Skill: the Digit Symbol Test (a subtest of the Wechsler Adult Intelligence Scale—Revised [WAIS-R]; Shinagawa, Kobayashi, Fujita, & Maekawa, 1990) was used. This test consists of a sample line with nine pairs of numbers and meaningless symbols. Subjects are asked to fill in the blanks with the correctly paired symbols in 90 s. The score range is 0–93. (4) Attention: the Stroop Color Word Test (Stroop, 1935; Japanese version) employs a card with 24 colored dots and a card with 24 names of colors printed in different colored ink, e.g., the word "yellow" printed in blue ink. Subjects are asked to name the color of the dots as quickly as possible, and then to name the color of the ink that a color word was printed in as quickly as possible. Seconds to completion are recorded and the difference between the time required to read the word card and that required to read the dots card is calculated. Well-trained psychological testers administered all four tests in the same order for all subjects.

Table 4
Characteristics and performance on measures of cognitive function by diabetes subgroup

Variable	Insulin-treated diabetes	Noninsulin diabetes	Nondiabetic subjects	*P* value
N	13	56	27	
Age	72.8 ± 6.3	71.3 ± 5.4	73.4 ± 6.6	0.261
Education (year)	10.5 ± 2.6	10.4 ± 2.7	11.4 ± 3.0	0.386
MMSE	25.4 ± 2.0[††]	27.5 ± 2.0[¶]	28.3 ± 1.7[§]	$P<.01$
Word List (immediate)	5.2 ± 1.5	5.9 ± 1.7	6.2 ± 1.7	0.205
(delayed)	6.8 ± 1.3	7.2 ± 2.3	6.7 ± 2.0	0.567
WAIS-R Digit Symbol	29.2 ± 8.1[††]	37.9 ± 10.8[¶]	43.0 ± 12.1[§]	$P<.01$
Stroop Color Word Test	17.8 ± 7.6	19.5 ± 13.8	15.0 ± 6.7	0.252
HbA1c (%)	8.7 ± 1.5[†]	7.9 ± 0.8[¶¶]	5.7 ± 0.4[§§]	$P<.01$
Hypertension (%)	53.2	50.0	50.0	0.845
Hyperlipidemia (%)	36.4	36.6	60.0	0.074

Data are the mean ± S.D., unless otherwise indicated.
A higher score indicates better performance, except in the case of the Stroop Color Word Test.
ANOVA. Bonferroni's post-hoc test showed following;
[†] Significant difference with noninsulin diabetes ($P<.05$) and nondiabetic subjects ($P<.01$).
[††] Significant difference with noninsulin diabetes ($P<.05$) and nondiabetic subjects ($P<.05$).
[¶] Significant difference with insulin-treated diabetes ($P<.05$).
[¶¶] Significant difference with insulin-treated diabetes ($P<.05$) and nondiabetic subjects ($P<.05$).
[§] Significant difference with insulin-treated diabetes ($P<.01$).
[§§] Significant difference with insulin-treated diabetes ($P<.05$) and noninsulin subjects ($P<.05$).

2.3. Statistical analysis

All data are presented as the means ± S.D. Comparisons between two groups were made by using Student's t–test or the Kruskal–Wallis analysis. Pearson's correlation coefficients and Spearman's correlation coefficients were calculated for parametric and nonparametric variables, respectively. For the Spearman's correlation coefficients, nonparametric variables were coded as follows. The existence of DM complication or hypoglycemic episode was scored as 1, and the absence of these parameters was scored as 0. The use of insulin was scored as 1, and the nonuse as 0. Comparisons among three groups were made by using analysis of variance (ANOVA) followed by Bonferroni's post hoc test. In all analyses, values of $P<.05$ were considered to indicate statistical significance. All analysiswas performed with SPSS software for Windows (SPSS Inc., 2001).

3. Results

The characteristics of the subjects included in the current study are shown in Table 1. There were no significant differences between DM patients and non-DM subjects in any area except HbA1c ($P<.01$). Table 2 shows the means and S.D. for four measures of cognitive function in DM and control subjects. The DM group performed significantly worse in the MMSE ($P<.05$) and Digit Symbol Test ($P<.05$), and tended to perform more poorly in other tests, although these differences were not significant. The results of the correlation analysis between cognitive tests scores and diabetic characteristics are shown in Table 3. The scores of the Digit Symbol Test in DM subjects had a significant negative correlation with HbA1c ($r=-.433$, $P<.001$, Fig. 1). The insulin-use for DM treatment was also significantly correlated to the Digit Symbol Test ($r=-.304$, $P<.05$). Further, we divided the DM group into two subgroups: an insulin-treated and a non-insulin-treated group. The history of insulin treatment ranged from 1 to 30 years (mean = 10.85; S.D. = 11.10). The frequencies of daily insulin injection were scored as follows: once = 3, twice = 6, three times = 3, four times = 1. ANOVA showed that both the MMSE and Digit Symbol Test scores were significantly different among the three groups ($P<.01$, $P<.01$, respectively, Table 4). Bonferroni's post hoc test showed that the scores of the MMSE and Digit Symbol Test in the insulin-treated DM group was significantly lower than those in the non-insulin-treated DM ($P<.05$), and non-DM ($P<.01$) subjects. Insulin-treated DM subjects had significantly higher HbA1c. The prevalence of DM complications and hypoglycemic episodes by DM treatment were compared and are shown in Table 5. The frequency of hypoglycemic episodes was from three times a year to once a month. No subjects experienced hypoglycemic coma or hospitalization from hypoglycemia-related events. Only prevalence of retinopathy was significantly different between insulin-treated and non-insulin-treated DM subjects.

Table 5
The characteristics and presence of diabetic complication and hypoglycemia by diabetic treatment groups

Variable	Insulin-treated DM	Noninsulin DM	P value
Diabetes Duration (year)	19.2 ± 12.6	13.7 ± 11.2	.164
Neuropathy (%)	66.7	59.2	.637
Retinopathy (%)	63.6	31.2	$P<.05$
Nephropathy (%)	58.3	31.2	.084
Hypoglycemia (%)	36.4	11.4	.060

Data are [the] mean ± S.D., unless otherwise indicated.
Student's t–test. (diabetes history), Kruskal–Wallis analysis (other variables).

4. Discussion

In the current study we investigated cognitive function in the Japanese elderly with type 2 DM. Recently many studies—primarily from Western countries—have reported cognitive functional deficits in elderly DM subjects, and the term "diabetic encephalopathy" is seeing increasing use (Biessels, der Heide, Kamal, Bleys, & Gispen, 2002). Nonetheless, there have been few reports showing cognitive deficits in Japanese subjects with DM. Our results suggest that DM-related cognitive impairment does exist in Japanese subjects, and that such impairment is not dependent on cultural or genetic background.

In the present study the insulin-treated subjects had the worst cognitive function. Three possible mechanisms could be hypothesized for the poor cognitive function in insulin-treated subjects. In the present study, subjects receiving insulin-treatment had significantly higher HbA1c, and the scores of the Digit Symbol test were negatively correlated with HbA1c; therefore, the effects of hyperglycemia should be given primary consideration. Secondly, hypoglycemia-related neuronal damage may have been involved, since insulin-treated elderly DM subjects reportedly have more risks for hypoglycemia (Schorr, Ray, Daugherty, & Griffin, 1997). However, several studies have shown that subjects with impaired glucose tolerance who receive no drug treatment and are at minimum risk for hypoglycemia also sometimes show cognitive impairment (Convit, Wolf, Tarshish, & de Leon, 2003; Vanhanen et al., 1988). This suggests that hypoglycemia may not be a major factor for cognitive functional deficits. Our study failed to show a significant correlation between hypoglycemia and the scores of cognitive functional tests. Thirdly, direct effects of insulin on the neuronal system may have played a role in the poor cognitive function of insulin-treated subjects. Recently, insulin and its receptor have been shown to be present in the brain and appear to play a modulatory role in synaptic transmission (Schwartz, Figlewicz, Baskin, Woods, & Porte, 1992). Ott et al. (1996, 1999) reported that insulin-treated subjects are at greater risk for dementia. In the present study,

however, analysis of the correlation coefficient between fasting serum insulin levels in non-insulin-treated DM subjects and the performance on cognitive functional tests failed to show any significant differences ($P = .092–0.645$, data not shown).

As discussed above, hyperglycemia may be a major factor for cognitive impairment in elderly DM subjects. However, in the current study, microangiopathies, including neuropathy, were very weakly related to the scores of the MMSE and Digit Symbol test. The duration of DM also showed no significant relationship with the scores of the cognitive functional tests. These findings suggest that cognitive impairment in DM subjects is induced by mechanisms other than microangiopathy. The scores of the Digit Symbol test had a significant negative association with HbA1c, which reflects the status of glycemic control in a relatively short period of time. Interestingly, several studies have shown that improvement in glycemic control had beneficial effects on cognitive function in elderly DM subjects (Gradman et al., 1993; Meneilly et al., 1993). This would suggest that the cognitive function in DM subjects is affected at least partially by the blood glucose levels for a relatively short period of time. Further longitudinal studies with a larger number of subjects will be needed to follow the cognitive function in elderly DM subjects, as well as investigations into the mechanism by which hyperglycemia affects cognitive function.

5. Conclusion

In conclusion, we demonstrated that Japanese elderly with DM had mild cognitive impairment. Hyperglycemia may be a major factor for this cognitive impairment; however, further studies with increased number of subjects and longitudinal studies will be needed to clarify this relation.

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The Clock Drawing Test as a Valid Screening Method for Mild Cognitive Impairment

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Key Words
Clock drawing · Early diagnosis of dementia · Screening test · Cutoff point · Cahn's scoring protocol

Abstract
To validate the Clock Drawing Test (CDT) as a screening method for detecting mild cognitive impairment (MCI) and to find the appropriate scoring protocol and its cutoff point, we compared the sensitivity and specificity of three CDT protocols. Subjects included 219 outpatients with memory complaints, who were attending the geriatric memory clinic. Cahn's protocol, with a cutoff point of 7, was more successful at differentiating clinically diagnosed MCI subjects from normal elderly individuals, with higher sensitivity (74.7%) and specificity (75.6%), than were the other protocols. The CDT, as a handy screening method, may be useful for clinicians to reliably identify subjects with MCI, and it may contribute to early detection of dementia.

Introduction

Early detection of dementia is an issue of growing concern because of improved clinical outcomes expected as a result of early therapeutic interventions or preventive approaches [1]. In terms of care, the diagnosis of cognitive deficits at an early stage, when the patient is still competent enough to make important decisions, can give the patients and their caregivers the opportunity to prepare for situations expected to occur as the symptoms progress (e.g. making environmental arrangements or educating the family), and also facilitate autonomic future planning (e.g. writing a living will, assigning durable power to an attorney or composing advanced directives) [2]. The term 'mild cognitive impairment' (MCI) was originally used to describe a transitional state between normal condition and Alzheimer's disease (AD) [3] and was first defined by Petersen et al. [4]. Recently, a revised and extended definition of MCI has been proposed that covers a broader range of cognitive impairment. It categorizes MCI into the following three subtypes: purely amnestic syndrome, impairment of a single nonmemory domain of cognition, and slight cognitive impairment in multiple domains of cognition [5]. It has also been suggested that enlarging the definition would allow the screening of more subjects at

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risk of dementia [6]. Although many detailed neuropsychological tests evaluating executive functions are available as screening instruments to quantify the degree of cognitive impairment, most of them are impractical for general physicians to administer in their clinical settings [2, 7]. To our knowledge, none of these neuropsychometric tests can contribute to the accurate diagnosis of MCI with reliable sensitivity and specificity.

The Clock Drawing Test (CDT) has been arousing the interest of clinicians and researchers as a convenient screening instrument for dementia, either by itself or as a part of a brief neuropsychological test battery. The CDT takes less than 2 min to administer, and it is easy to comprehend the instructions, making it suitable for elderly patients who may not be able to maintain concentration [8]. Previous replication studies, which applied various scoring systems, demonstrated that the CDT is a reliable method for the detection of dementia [9–12]. The CDT is relatively less affected by the level of education, language, and cultural background than are the other cognitive tests such as the Mini-Mental State Examination (MMSE) [13, 14]. The protocols of the CDT in published studies are various. They differ not only in the instructions (with or without predrawn circle, different time setting) but also in their scoring criteria. To obtain acceptable reliability for screening MCI among a target population, the cutoff points of the CDT applied in previous studies must be reexamined, since they may not be appropriate in populations with lower prevalence rates of dementia [9]. To date, there has been a dearth of studies examining the utility of the CDT in detecting cognitive deficits in their early stages, in particular MCI. Previous studies yielded conflicting results with limitations in terms of the criteria used for group assignment, the sample size, and the optimal cutoff points for different types of cognitive status [15, 16]. Besides, most previous studies emphasized the use of quantitative analyses of the CDT results, leaving detailed qualitative analyses of the results somewhat neglected. Despite the existence of reports regarding qualitative analyses of the CDT results in AD and vascular dementia (VD) patients, those focusing on MCI subjects are still lacking [17, 18]. The purpose of this study was to warrant the validity of the CDT as a screening method for detecting MCI by determining an appropriate scoring protocol with an optimal cutoff point and qualitative features.

Table 1. The neuropsychological test battery

Function	Test
Global cognitive function	MMSE
Orientation	MMSE-1, 2
Memory	MMSE-5
	Verbal recall (ADAS, paragraphs)
Verbal fluency	Initial letter
	Category
Visuospatial praxis	CDT, MMSE-11
	ADAS-7
Psychomotor speed	Digit symbol
Attention	Stroop test
	Digit Span

ADAS = The Alzheimer's disease assessment scale; ADAS-7 = constructional ability.

Methods

Participants

Subjects were recruited from outpatients at the geriatric memory clinic in the Nagoya University Hospital. A total of 219 subjects (male: 75, female: 144) aged 60 years and older who had either subjective memory complaints or memory loss reported by their informants participated in this study. Informed consent was obtained from all the participants or their primary caregivers after complete description of the study. The age of the participants ranged from 60 to 93 years (mean = 75.1 years, SD = 6.7 years). Years of education ranged from 3 to 24 years (mean = 10.2 years, SD = 2.8 years). None of the participants had a history of neurological or psychiatric disorders, and none had been diagnosed as having reversible causes of cognitive impairment. Routine physical examinations and neurological examinations had been carried out in all subjects. Subjects with receptive aphasias or visual impairment and those who had abnormal thyroid functions or serum vitamin B_{12} or folate levels in laboratory studies were excluded from the study. Magnetic resonance imaging of the brain was performed on all subjects. The Geriatric Depression Scale (GDS)-15 was applied as a screening test for excluding subjects with possible depression at a cutoff point of 8 [19]. Subjects were administered a neuropsychological test battery including the CDT, as shown in table 1 [20–22]. General cognitive impairment was assessed by the MMSE with a score <24 [23]. Information derived from a series of diagnostic evaluations, except for the CDT in the neuropsychological test battery, was reviewed by a team of experienced geriatricians at a case conference, and all the participants were categorized into five groups: normal elderly (NE), MCI, AD/senile dementia of Alzheimer's type (AD/SDAT) and mixed dementia, VD, and unclassified demented. The distribution of subjects by diagnostic category and sex is shown in table 2. Consensus diagnosis was made at the conference, using the Diagnostic and Statistical Manual of Mental Disorders Revised Third Edition (DSM-III-R) for dementia [24] as well as the National Institute of Neurological and

Table 2. Participant characteristics

	Whole sample	Nondemented		Demented		
		NE	MCI	SDAT[1]	VD	others
n; M/F	219; 75/144	41; 10/31	48; 21/27	102; 33/69	14; 6/8	14; 5/9
Age	75.1 (6.7)	72.7 (6.3)	74.7 (6.2)	76.0 (6.7)	76.9 (6.0)	74.9 (8.3)
Education	10.2 (2.8)	10.2 (1.8)	11.5 (3.7)	9.7 (2.4)	10.3 (3.0)	8.5 (2.5)
MMSE	24.4 (5.0)	28.4 (1.8)	27.2 (2.1)	22.2 (5.1)	20.5 (5.8)	20.6 (3.7)
CDT (Sunderland)	7.1 (2.4)	9.2 (1.1)	7.8 (2.1)	6.3 (2.3)	5.6 (2.5)	5.4 (2.3)
CDT (Rouleau)	7.0 (2.3)	8.7 (1.0)	8.0 (1.2)	6.3 (2.5)	5.6 (2.2)	5.6 (2.2)
CDT (Cahn)	6.1 (2.8)	8.4 (1.4)	7.1 (2.0)	5.2 (2.8)	4.1 (2.5)	4.1 (2.4)

Figures indicate means, with SD in parentheses.
[1] SDAT includes SDAT, AD and mixed dementia.

Communicative Disorders and Stroke and the Alzheimer's Disease and Related Association Work Group (NINCDS-ADRDA) criteria for probable AD to determine patients with AD/SDAT [25], and using the National Institute of Neurological and Communicative Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neuroscience Work Group (NINCDS-AIREN) criteria for probable VD to determine VD patients [26]. Mixed dementia was diagnosed as probable mixed dementia, when there was a clinical indication that dementia was likely to be attributable to both conditions. In this study, patients with mixed dementia were incorporated into the AD/SDAT group as stated above. The diagnosis of MCI was made according to the following criteria: (1) not demented, (2) subjective memory complaint, (3) normal general cognitive functioning assessed by the MMSE (score, ≥24), (4) objective memory impairment and/or impairment in other cognitive domains as evidenced by scores >1.5 SD below the age-appropriate mean score of at least one or more neuropsychological tests examined, (5) autonomy in the basic activities of daily living [7, 27].

Measurements

The subjects were given a blank piece of paper and asked to follow a two-step instruction: 'First, draw a 10-cm diameter clock face with all numbers on it. Second, put hands on the clock to make it read 10:10.' The CDT was scored by a psychologist according to the rating scales of Sunderland et al. [28], Rouleau et al. [29] and Cahn et al. [30]. These three sets of scoring criteria were chosen because they are characterized by concrete scoring instructions with presentations of actual error types, unlike other scoring methods, which contain vague or equivocal expressions in their scoring criteria. The psychologist who was the CDT rater of the present study was not given any information about the participant, including performance on other cognitive tests or clinical diagnosis.

The scoring methods used in the present study are as follows. (1) The CDT by Sunderland et al. [28] (Appendix 1): this method is based on the assumption that the representation of the hands is the first and solely affected item (score 6–10 points), and additional errors in the representation of numbers and the clock face occur later (score 1–5 points), so that a 10-point scale is used, with higher numbers indicating better performance. (2) The CDT by Rouleau et al. [29] (Appendix 2): three components of the drawing (integrity of the clock face, 0–2 points; presence and sequencing of the numbers, 0–4 points, and presence and sequencing of the hands, 0–4 points) are independently assessed. The scoring method supplies 0–10 points, with higher numbers indicating better performance. (3) The CDT by Cahn et al. [30] (Appendix 3): this is considered to be a modified version of the method by Rouleau et al. [29]. The difference in the Cahn scoring method is that while Rouleau's scoring method is regarded as a quantitative scoring of 0–10 points, the administrator notes the presence of qualitative errors shown in Appendix 3 and adds the error numbers up as a qualitative score with a maximum number of 8. The global CDT score is calculated by subtracting the qualitative score from the quantitative score. A 10-point scale is used, with higher numbers indicating better performance.

Statistical Analysis

All statistical analyses were performed using SPSS 11.0J. for Windows. Differences in age and years of education among the diagnostic groups were tested using the Kruskal-Wallis test. To examine the relationships between the CDTs and other variables (age, years of education, GDS, MMSE score), correlations and their p values were calculated using the Spearman rank order correlation coefficients. Distributions of Cahn's qualitative errors were examined using χ^2 analyses and Ryan's procedure for multiple comparisons.

Results

The five diagnostic groups shown in table 2 did not differ in terms of age (p = 0.0811). As for the educational years, except for the unclassified demented group, the four definite diagnostic groups did not differ (p = 0.0183). Distributions of the MCI subtypes are shown in table 3. The three groups (amnestic, single nonmemory and multiple domains) did not differ in age and years of education (p = 0.8623, 0.3575, respectively).

Table 3. MCI characteristics

	MCI		
	amnestic	single nonmemory	multiple domains
n; M/F	10; 2/8	10; 4/6	28; 15/13
Age	74.6 (7.2)	74.0 (7.2)	75.0 (5.6)
Education	11.5 (3.0)	9.0 (3.5)	12.4 (3.0)
MMSE	26.8 (2.8)	28.9 (1.2)	26.9 (2.0)
CDT (Sunderland)	9.4 (0.5)	7.3 (1.8)	7.4 (2.3)
CDT (Rouleau)	9.3 (0.7)	7.5 (1.1)	7.7 (1.2)
CDT (Cahn)	9.3 (0.7)	6.1 (2.0)	6.7 (1.8)

Figures indicate means, with SD in parentheses.

Table 4. Correlation matrix

	Sunderland	Rouleau	Cahn
Age	0.146	0.182	0.180
Education, years	0.210	0.220	0.201
GDS	0.281	0.312	0.312
MMSE	0.459 *	0.492*	0.490*
Sunderland		0.836*	0.857*
Rouleau			0.979*

* $p < 0.001$.

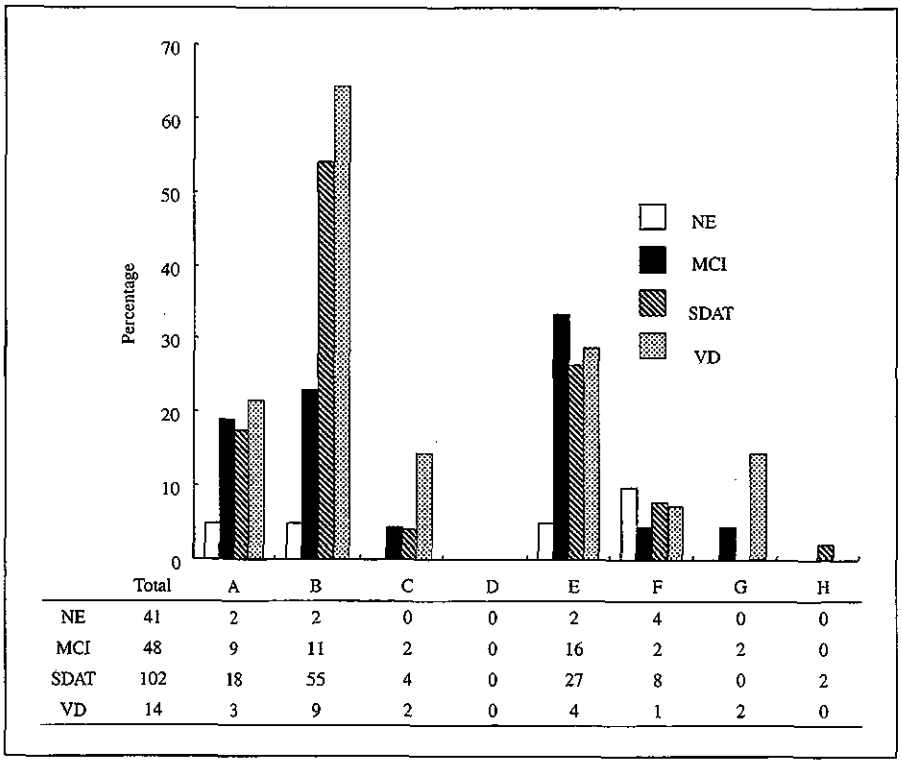
Correlations between the three CDT scores and other variables are presented in table 4. None of the CDTs correlated significantly with age, years of education, or the GDS score. However, all the CDTs correlated significantly with the MMSE score. Within the three CDTs, the scores correlated significantly with each other. In particular, the Cahn and Rouleau scores correlated with the highest correlation coefficient ($r = 0.979$, $p < 0.0001$).

We calculated the sensitivities and specificities with different CDT cutoff points to examine the discriminatory power of the CDTs for differentiating MCI and demented subjects from NE (table 5). The analyses demonstrated that Cahn's protocol had the highest discriminatory power at a cutoff point of 7, with a sensitivity of 74.7% and specificity of 75.6%.

Observed error types in the four definite diagnostic categories using Cahn's criteria for qualitative analysis are presented in figure 1. The four definite diagnostic groups did not differ in terms of age and years of education. The letters 'A' to 'H' represent Cahn's qualitative error types, which are described in Appendix 3. Regarding the distribution of error types in each group, only a few errors were noted in the NE group according to Cahn's criteria. In the MCI group, E (planning deficit) was the most frequent (16 of 48 cases), followed by B (conceptual deficit) and A (stimulus-bound response; 11 and 9 of 48 cases, respectively). In the AD group (SDAT/AD/MIXED), B was the most frequent (55 of 102 cases, 53.9%), followed by E (27 of 102 cases, 26.5%) and A (18 of 102 cases, 17.6%). In

Table 5. Sensitivities and specificities (%)

Cutoff point	Sunderland		Rouleau		Cahn	
	sensitivity	specificity	sensitivity	specificity	sensitivity	specificity
10	100.0	0.0	100.0	0.0	100.0	0.0
9	93.8	48.8	96.1	17.1	96.1	17.1
8	66.0	90.2	78.1	65.9	82.6	65.9
7	61.2	95.1	56.7	92.7	74.7	75.6
6	42.7	95.1	36.5	95.1	60.1	92.7
5	38.2	95.1	24.7	97.6	44.4	95.1
4	26.4	100.0	18.5	100.0	33.7	97.6
3	10.0	100.0	11.8	100.0	23.0	100.0
2	5.1	100.0	0.8	100.0	14.6	100.0
1	1.1	100.0	0.5	100.0	10.6	100.0



	Total	A	B	C	D	E	F	G	H
NE	41	2	2	0	0	2	4	0	0
MCI	48	9	11	2	0	16	2	2	0
SDAT	102	18	55	4	0	27	8	0	2
VD	14	3	9	2	0	4	1	2	0

Fig. 1. Comparison of error types among the four diagnostic groups: NE, MCI, SDAT, (represents SDAT, AD and mixed dementia), and VD. The horizontal scale (A–H) represents Cahn's qualitative error types: A = Stimulus-bound response; B = conceptual deficit; C = perseveration; D = neglect of hemispace; E = planning deficit; F = nonspecific spatial error; G = numbers written on the outside of the clock, and H = numbers written counterclockwise. The bottom table is the matrix showing participants' actual *number of errors* in the four diagnostic groups.

the VD group, B was the most frequent (9 of 14 cases), followed by E and A (4 and 3 of 14 cases, respectively). The χ^2 analysis comparing the frequency of Cahn's error types made by the four diagnostic groups revealed that there was a significant effect of diagnosis in all error types ($p < 0.0001$).

Discussion

While various CDT scales are available for detecting dementia, few studies have examined the adequate scoring protocol and optimal cutoff point for screening MCI. With the aim of detecting dementia at an early stage, particularly MCI, the present study compares the three scoring methods, all of which were found to be independent of years of education and depression scale, which is in keeping with the findings by Shulman et al. [8]. In addition, the CDT scores determined using the three scoring methods correlated with MMSE scores with high statistical significance, as confirmed in previous studies [12, 31, 32]. In most of the former studies, the cutoff points of CDTs were provided with the aim of distinguishing a demented state or AD from normal cognition. Recently, Powlishta et al. [16], choosing 6 different scoring criteria of the CDT for comparing subjects without altering the cutoff points determined for dementia in each original CDT criterion, have reported that the CDT was a poor screening method for very mild dementia. The sensitivity and specificity for detecting MCI by the CDT obtained in the current study were satisfactory. The discrepancy between the results of the study by Powlishta et al. [16] and those of the current study may be due to different cutoff points. Comparison of sensitivities and specificities among the three CDT protocols revealed that the Cahn scale had the best discriminatory power at the cutoff point of 7. Thus, the results may indicate that Cahn's protocol is the most suitable method for screening MCI in general practice. As shown in table 3, the analyses based on MCI subtypes suggest that subjects with amnestic MCI cannot be screened by the cutoff point we consider optimal for differentiating MCI subjects from normal individuals. This may simply imply that MCI subjects without deficits in the cognitive domain do not lose scores on the CDT, but we need further investigation to warrant this notion, given the limited number of participants included in this study. However, as we acknowledge the significance of including MCI subtypes other than the amnestic type, we believe that the

present findings would provide useful information for clinicians for screening subjects at risk of dementia in earlier stages.

We also examined the error types in MCI subjects using Cahn's qualitative criteria and compared them with the results in the NE and subjects with dementia. In what follows, impairment underlying each type of frequent error is disclosed [11, 17, 30]:

(A) stimulus-bound response: disturbance of inhibition in executive control functioning, an aspect of the frontal cortical function;

(B) conceptual deficit: loss of semantic memory usually evoked by the word 'clock';

(C) perseveration: an aspect of frontal dysfunction, and

(E) planning deficit: suggested to be associated with visuospatial constructional/frontosubcortical dysfuntion.

As shown in figure 1, error type E (planning deficit) could be a distinctive feature of MCI, which is represented by imprecise gaps before 12, 3, 6, or 9 of the numbers arranged in the clock face, or by clock hands drawn not from the center of the clock face. This type of error is considered to represent the inability to form a strategy for drawing a clock, presumably due to frontosubcortical dysfunction. The frequency of conceptual deficit in the MCI group was significantly lower than that in the SDAT/AD/MIXED and VD group. The conceptual deficit reflects a loss or deficit in accessing knowledge of the attributes, features, and meaning of a clock, and this category includes misrepresentation of the clock itself and the time on the clock [30]. Eleven out of 41 MCI subjects made this type of error; the difference in frequency between the MCI and the other groups' subjects did reach statistical significance. The SDAT/AD/MIXED and VD groups made this type of error with a frequency of 50% or above, which was statistically higher than that in the MCI and NE group, and that in the MCI being again higher than that in the NE group. Further investigations with increased number of subjects may clarify detailed characteristics of the clock drawing in MCI or its subgroups.

Between SDAT and VD subjects, no significant difference in error types was identified. This might be because of the relatively small number of patients in the VD subgroup in the current study, which may thus have influenced the statistical analysis. The previous study showed that the frequency of spatial and/or planning deficit was significantly higher in patients with mild VD than mild AD, and in patients with moderate VD, the frequency of graphic difficulties was significantly higher than in moderate AD [17]. These assumptions derived from the observations in this study may help to guide and benefit from future studies with larger numbers of subjects.

Although the CDT cannot be used solely for clinical diagnoses, the CDT, as a simple screening method, provides objective and graphic documentation of cognitive deficits that can be shared by a wide range of clinicians. In conclusion, among the three scales examined in this study, the Cahn scoring method at a cutoff point of 7 is the most likely indicator for MCI. Petersen et al. [7] recommended the CDT using Cahn's protocol as an optional instrument for brief cognitive assessment, as an addition to a general cognitive screening test, e.g. MMSE. We believe that the results obtained in the current study provide important evidence of the validity of the CDT as one of the useful screening method for discriminating MCI from normal cognition.

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Appendix 1
Sunderland's protocol: a priori criteria for evaluating clock drawings

10–6	Drawing of clock face with circle and numbers is generally intact
10	Hands are in correct position
9	Slight errors in placement of the hands
8	More noticeable errors in the placement of hour and minute hands
7	Placement of hands is significantly off course
6	Inappropriate use of clock hands
5–1	Drawing of clock face with circle and numbers is not intact
5	Crowding of numbers at one end of the clock or reversal of numbers
4	Further distortion of numbers sequence; integrity of clock face is now gone
3	Numbers and clock face no longer obviously connected in the drawing; hands are not present
2	Drawing reveals some evidence of instructions being received but only a vague representation of a clock
1	Either no attempt or an uninterpretable effort is made

10 = Best, and 1 = worst.

Appendix 2
Rouleau's protocol: the score is calculated by a sum of three components (I, II, III)

I Integrity of the clock face (maximum: 2 points)
- 2 Present without gross distortion
- 1 Incomplete or some distortion
- 0 Absent or totally inappropriate

II Presence and sequencing of the numbers (maximum: 4 points)
- 4 All present in the right order and at most minimal error in the spatial arrangement
- 3 All present but errors in spatial arrangement
- 2 Numbers missing or added but no gross distortions of the remaining numbers; numbers placed in counterclockwise direction or all present but gross distortion in spatial layout (i.e. hemineglect, numbers outside the clock)
- 1 Missing or added numbers and gross distortions
- 0 Absence or poor representation of numbers

III Presence and placement of the hands (maximum: 4 points)
- 4 Hands are in correct position and the size difference is respected
- 3 Slight errors in the placement of the hands or no representation of size difference between the hands
- 2 Major errors in the placement of the hands
- 1 Only one hand or poor representation of two hands
- 0 No hands or perseveration on hands

Appendix 3
Cahn's protocol: the global score is calculated by subtracting qualitative score (II) from quantitative score (I)

I Quantitative CDT score = maximum 10 points: assesses the presence and correctness of the clock; the clock face (0–2 points), the placement of the hands (0–4 points) and the placement of the numbers (0–4 points)

II Qualitative CDT score = maximum 8 points: summary of the following errors
- 1 Stimulus-bound response: the tendency of the drawing to be dominated or guided by a single stimulus
- 2 Conceptual deficit: this error type reflects a loss or deficit in accessing knowledge of the attributes, features and meaning of a clock
- 3 Perseveration: the continuation or the recurrence of activity without an appropriate stimulus
- 4 Neglect of left hemispace: all attributes of the clock are written on the right half of the clock face
- 5 Plannning deficit: this error type is represented by gaps before 12, 3, 6 or 9
- 6 Nonspecific spatial error: a deficit in the spatial layout of numbers, without any specific pattern in spatial disorganization
- 7 Numbers written on the outside of the clock: numbers written either around the perimeter of the circle or the circle itself
- 8 Numbers written counterclockwise: arrangement of the numbers with '12' at the top of the clock face and then continuing around in a counterclockwise fashion

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