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ORIGINAL ARTICLE

Possibility of Using Quantitative Assessment with the Cube Copying Test for Evaluation of Visuo-spatial Function in Patients with Alzheimer's Disease

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Objectives: The aim of this study was to investigate the clinical usefulness of the Cube Copying Test (CCT) for quantitative assessment of visuo-spatial function in patients with Alzheimer's disease (AD). **Methods:** The CCT, Raven's Colored Progressive Matrices (RCPM), and other neuropsychological tests were administered to 152 AD outpatients. For the quantitative assessment of CCT, we scored the points of connection (POC) and the number of plane-drawing errors (PDE) and categorized the pattern classification (PAC). We also measured Functional Assessment Staging (FAST) to assess the severity of AD. The relationships among CCT, RCPM, and FAST were then analyzed. **Results:** The mean POC and PDE scores were 2.7 and 3.6, respectively, and the median PAC score was 6.0. PDE and PAC showed a linear relationship, but POC and PDE, and POC and PAC did not. Each component of CCT showed a significant correlation with RCPM scores. PDE and PAC had closer correlations with RCPM scores than POC did. The PDE and PAC results were significantly different among most of the FAST stages. **Conclusions:** Quantitative assessment using CCT may be effective for the quick determination of the visuo-spatial function in AD patients.

Key Words: Alzheimer's disease; Cube Copying Test (CCT); Raven's Colored Progressive Matrices (RCPM); visuo-spatial function

INTRODUCTION

From the early phases of Alzheimer's disease (AD), visuo-spatial impairments such as topographical disorientation and constructional disability are seen in addition to progressive memory loss as the core symptoms of AD.[1–6] These abilities deteriorate gradually according to the progression of symptoms.[7] Topographical disorientation in AD patients has several relevant outcomes such as patients becoming lost, despite, in some cases, recognition of landmarks.[1]

Many examinations, such as Raven's Progressive Matrices (RPM),[8] the Rey-Osterrieth Complex Figure,[9] and the Clock Drawing Test,[10] are useful for clinically assessing the visuo-spatial functions of dementia patients. In RPM, which is one of the most frequently used nonverbal visual neuropsychological tests, detection of the correct response involves identifying sameness, symmetry, and analogy, and requires the ability to analyze form, color, and linear slope.[11,12] Raven's Colored Progressive Matrices (RCPM),[8] one of the components of RPM, is a test for elderly people and children. The RCPM results are correlated with the cog-

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nitive function of dementia patients.[13] RCPM includes the subtests Set-A, Set-A_B, and Set-B. Set-A mainly identifies figural problems and is associated with simple visuo-spatial functions, whereas Set-B requires an analytic technique for answering correctly.[14,15] RCPM is a clinically useful test, but it takes 15–20 min to complete. The Cube Copying Test (CCT), which requires the examinee to copy a picture of the Necker Cube, is a very simple and easy copying test. It can be done in a few seconds, and no preparation is needed except for the availability of a piece of paper and a pencil. This test is easily repeated. Unlike other copying tests, the various methods of assessing CCT are not solely subjective but also involve quantitative scoring and/or categorized scoring.[15–18] However, no systematically gathered data for dementia patients undergoing scoring methods of CCT are available.

In this study, we discuss the clinical usefulness and detailed scoring methods of CCT in AD patients and compare the CCT results with those of RCPM. Additionally, we consider differences in the ability to copy cubes on CCT according to the severity of AD.

MATERIALS AND METHODS

Ethics

The Ethics Committee of the National Center for Geriatrics and Gerontology approved this study (No. 1247). Written informed consent was obtained from all subjects before they were enrolled in the study.

Participants

The participants in this study were 807 outpatients who came to our hospital between January and December 2013 with the chief complaint of cognitive decline. For all participants, we obtained their demographic and clinical backgrounds, including age, sex, years of education, and duration of disease. We diagnosed 276 patients with AD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.[19] AD patients who also had another type of dementia and/or other problems that contributed to cognitive decline were excluded. Also, patients who did not complete the CCT because they could not understand the instructions at all due to aphasia or could not draw at all due to apraxia were excluded. Finally, 152 AD patients met these criteria. **Figure 1** summarizes the flow of exclusions of potential participants, and **Table 1 gives** detailed background clinical data and the results of neuropsychological tests of the AD participants. Of the 152 participants, 39 were men and 113 were women, and the average age was 77.6 ± 7.1 years old.

For an AD severity scale, we used Functional Assessment Staging (FAST).[20] FAST is an observational behavior scale that is classified into seven groups by staging the level of activities of daily living (ADL). FAST 1 is defined as no cognitive dysfunction, FAST 2 as aging deterioration, FAST 3 as borderline area (MCI or early AD), FAST 4 as mild AD, FAST 5 as moderate AD, FAST 6 as moderately severe AD, and FAST 7 as severe AD. The participants were classified into four groups based on their FAST stage: FAST 3 (n=14), FAST 4 (n=120), FAST 5 (n=14), and FAST 6 (n=4). No patients were classified as FAST 1, 2, or 7.

The Cube Copying Test

The participants were asked to perform the CCT. Two attempts at copying were allowed, with no time limit. If participants drew the cube twice, we scored the first cube drawing.

Scoring Methods of CCT

To assess cube copying, we adopted one of the scoring methods of Maeshima et al.[15] and one of the categorized scoring methods of Shimada et al.[17] Because the reliability and suitability of both assessments have already been reported,[21] a dementia specialist scored the CCT using these two methods.

Maeshima et al.[15] reported quantitative scoring assessments of CCT. For quantitative assessment of construction ability, points of connection (POC) and the number of plane-drawing errors (PDE) were evaluated by the method (see Appendix 1). A POC was defined as a point at which three lines met to form a vertex (lines less than 3 mm distant from the point were considered to be accurate). Subjects could score up to eight points, because eight points of connection exist in a cube. For PDE, each plane, defined by two pairs of parallel lines, was evaluated in terms of the number of lines and the extent to which they were parallel. No plane-orientation errors were scored if the cube was copied accurately (PDE=0).

Next, the categorized scoring assessment of CCT reported by Shimada et al.[17] was performed. In the current study, we name this method “pattern classification” (PAC) for descriptive purposes (see Appendix 2). It has eight original criteria: Patterns 0–7. Pattern 7 means a perfect copy. Pattern 0 is lines only. Patterns 0–2 were assessed as being two-dimensional. The remaining patterns, 3–6, were assessed as being three-dimensional (3D).

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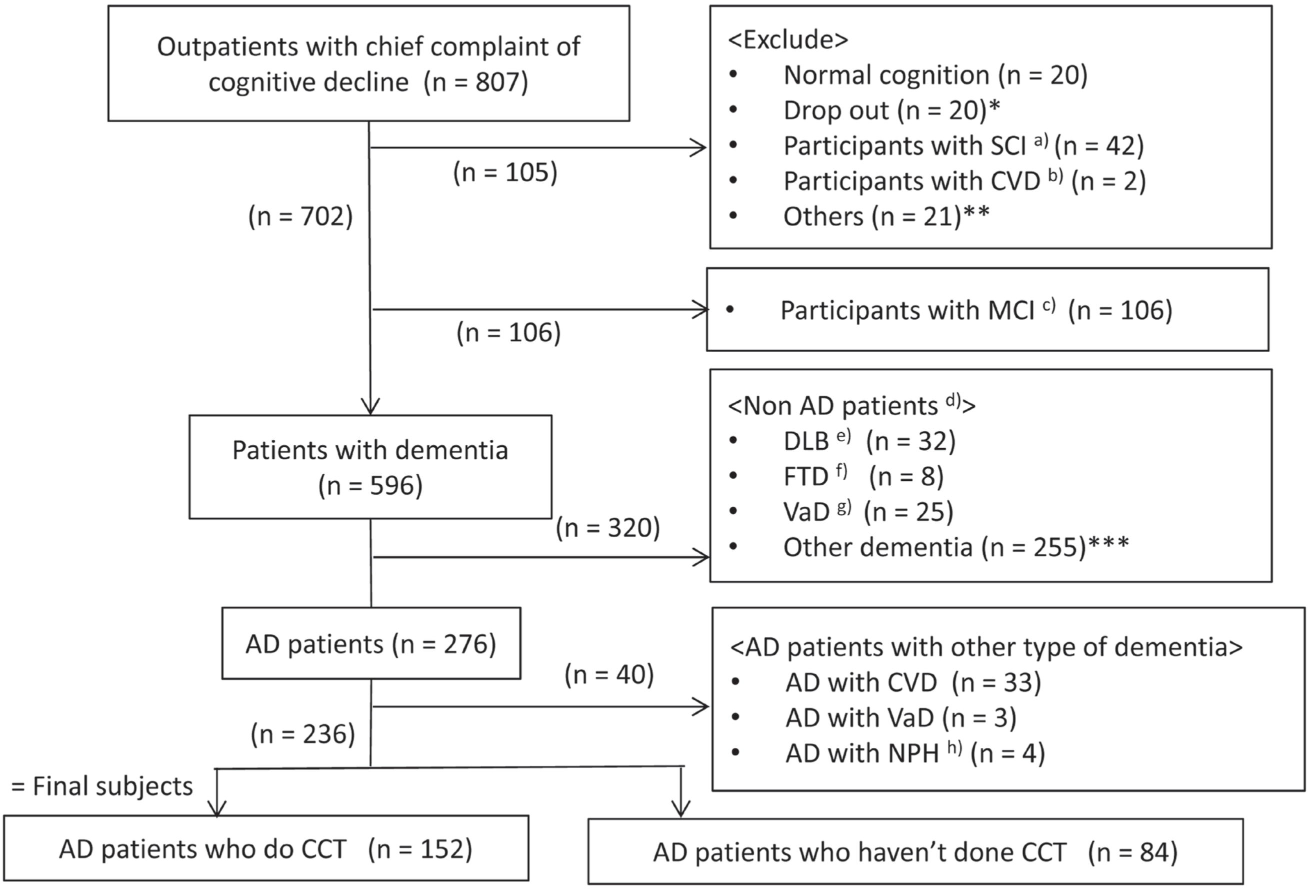

Fig. 1. Flow chart of participants.
*People who stop coming to the hospital before the examination
**Epilepsy (n = 4), delirium (n = 1), cognitive decline due to alcohol (n = 3), depression and other mental disorders (n = 12), head injury (n = 1)
*** Dementia that cannot be diagnosed (n = 244), NPH (n = 9), PSP [i] (n = 1), PDD [j] (n = 1)
a) SCI: Subjective cognitive impairment , b) CVD: Cerebrovascular disease, c) MCI: Mild Cognitive Impairment, d) AD: Alzheimer's disease, e) DLB: Dementia of Lewy bodies, f) FTD: Frontotemporal dementia, g) VaD: Vascular dementia, h) NPH: , i) PSP: Progressive supranuclear palsy, j) PDD: Parkinson's disease with dementia

Neuropsychological Tests and Other Evaluation Tools

The following neuropsychological tests were administered to patients during a single session. Neuropsychological tests included the Mini-Mental State Examination (MMSE),[22] the Frontal Assessment Battery (FAB),[23] the Word Fluency Test (WFT),[24] the Digit Span Test (forward, backward), and RCPM.[8] The MMSE was conducted to assess the generalized cognitive function. RCPM was used to examine visual perception and consisted of three sub-tests, i.e., Set-A, Set-A_B, and Set-B. Each test has a score of 12 points, and the total maximum score is 36 points. The WFT is a test in which participants have to say as many words as possible from a given category (e.g., vegetables) in 1 min.

We also performed the Alzheimer's Disease Assessment Scale − cognitive subscale Japanese version (ADAS-Jcog). The ADAS[25] was designed to measure the severity of the most important symptoms of AD. One of the subscales, ADAS-cog, is one of the most frequently used tests to measure cognition. The maximum total score of ADAS-Jcog is 70 points. A higher score means more severe AD.[25] Additionally, to assess ADL, the Barthel Index[26] was used.

Statistical Analyses

Spearman's rank correlation coefficient was used to assess relationships among variables. In this study, we used

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Table 1. Background data and neuropsychological test results of 152 patients with Alzheimer's disease

	AD participants (n=152)
Age (years): mean ± SD (range)	77.6 ± 7.1 (60−95)
Sex: number of participants	
Male	39
Female	113
Education (years): mean ± SD (range)	10.6 ± 2.6 (4−18)
Duration (months): mean ± SD (range)	25.7 ± 23.8 (2−216)
Barthel index: mean ± SD (range)	95.6 ± 9.3 (50−100)
MMSE total score (/30): mean ± SD (range)	19.7 ± 4.3 (7−28)
FAB (/18): mean ± SD (range)	9.5 ± 3.1 (0−16)
WFT (words): mean ± SD (range)	2.7 ± 2.0 (0−5)
Digit Span: mean ± SD (range)	
Forward	5.2 ± 1.2 (3−9)
Backward	3.1 ± 1.2 (0−6)
ADAS-Jcog: mean ± SD (range)	17.5 ± 6.4 (5.7−40.7)
FAST: number of participants	
FAST 3	14
FAST 4	120
FAST 5	14
FAST 6	4

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; WFT, Word Fluency Test; ADAS-Jcog, Alzheimer's Disease Assessment Scale − cognitive subscale Japanese version; FAST, Functional Assessment Staging.

non-parametric statistical methods, because the assumptions about the underlying population were questionable. We used the Kruskal-Wallis Test to assess the significance of the differences between the groups classified by FAST. A P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of the Statistical Package for Social Sciences software (version 18.0 for Windows; SPSS Inc.).

RESULTS

CCT Results (POC, PDE, PAC)

The measured POC and PDE values showed a nearly normal distribution, but the PAC results did not. The mean ± standard deviation of POC and PDE were 2.7 ± 1.9 and 3.6 ± 2.4, respectively. The median (quartile range) of the PAC score was 6.0 (6.0–3.5).

Relationship Between the Results of CCT Components

Patients who had a low PDE score had a wide variation of POC scores (e.g., patients with PDE=0 scored POC=2–7, and those with PDE=1 scored POC=0–7). The relationship between POC and PAC was very similar. In contrast, PDE and PAC showed a linear relationship (ρ=−0.864) (**Fig. 2**).

Total RCPM Scores and Subtest Scores

The mean ± standard deviation of the total RCPM score of all participants was 22.4 ± 5.6. The scores for the subtests (Set-A, Set-A_B, and Set-B) were 8.6 ± 2.2, 8.0 ± 2.4, and 6.2 ± 2.0, respectively.

Correlations Between CCT Results (POC, PDE, PAC) and the RCPM Results

The results of each component of the CCT were mainly significantly correlated with the scores of the RCPM (**Table 2**). The PDE and PAC results were highly correlated with the RCPM results, but the POC results were less highly correlated with those of RCPM. Moreover, the PAC results were highly correlated with the total RCPM score, the score of Set-A, and the score of Set-A_B, but less so with the score of Set-B. The PDE results showed the same pattern. In contrast, the POC results had similar and consistently lower correlations with all the RCPM subtest results (**Table 2**).

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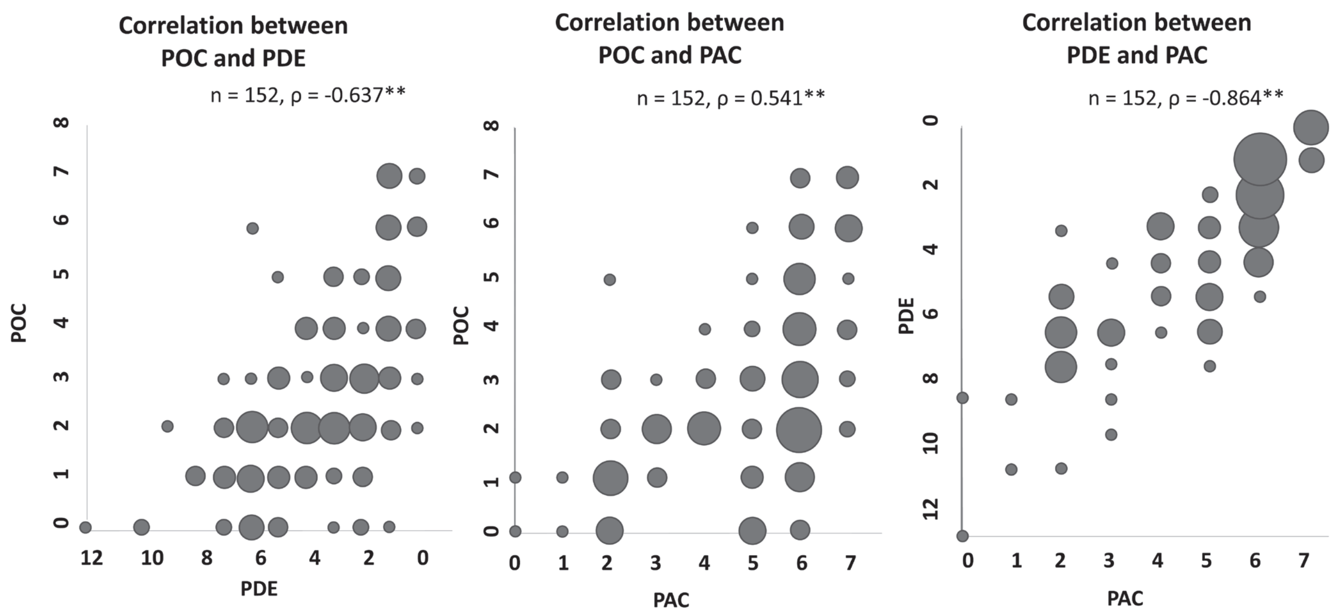

Fig. 2. Correlations between the three methods of assessing the Cube Copying Test (POC, PDE, PAC). In the relationship between POC and PDE, patients with a low PDE score had a wide variation of POC scores. The relationship between POC and PAC was very similar. In contrast, PDE and PAC showed a linear relationship.
In the relationship between POC and PDE, the patients who got a low PDE score had a wide variation of POC scores. The relationship between POC and PAC were observed to be very similar. On the other hand, PDE and PAC showed the linear relationship between them.
Spearman's rank correlation coefficient (** P < 0.01)
CCT: Cube Copying Test, POC: Points of Connection, PDE: Plane-drawing Errors, PAC: Pattern Classification

Table 2. Correlation between the results of each CCT scoring method and the neuropsychological test results and background data

		POC	PDE	PAC
Age (years)	(ρ)	–0.263**	0.246**	–0.182*
Sex	(ρ)	0.314**	–0.308**	0.311**
Education (years)	(ρ)	0.314**	–0.308**	0.311**
Duration (months)	(ρ)	–0.070	–0.081	0.064
MMSE Total score	(ρ)	0.15	–0.32**	0.27**
FAB	(ρ)	0.15	–0.26**	0.22**
WFT (words)	(ρ)	–0.06	–0.03	–0.10
Digit Span Test				
Forward	(ρ)	0.12	–0.14	0.17*
Backward	(ρ)	0.28**	–0.31**	0.29**
RCPM				
Total	(ρ)	0.26**	–0.48**	0.45**
Set-A	(ρ)	0.26**	–0.45**	0.42**
Set-A_B	(ρ)	0.27**	–0.42**	0.43**
Set-B	(ρ)	0.23**	–0.36**	0.33**

Spearman's rank correlation coefficient (ρ).
RCPM, Raven's Colored Progressive Matrices; POC, points of connection; PDE, plane-drawing errors; PAC, pattern classification.
*P <0.05, ** P <0.01.

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Table 3. Comparison between the groups classified by FAST

	FAST 3 (n=14)	FAST 4 (n=120)	FAST 5 (n=14)	FAST 6 (n=4)	P-value[a]
Age (years): mean ± SD	71.6 ± 6.6	78.0 ± 6.8	82.5 ± 6.3	71.6 ± 6.6	0.001
Sex: number of participants					0.465
Male	4	28	6	1	
Female	10	92	8	3	
Education (years): mean ± SD	10.9 ± 1.9	10.7 ± 2.7	9.1 ± 2.1	9.3 ± 1.5	0.058
Duration (months): median ± SD	16.6 ± 12.4	25.6 ± 24.5	34.4 ± 25.1	31.8 ± 22.0	0.154
Barthel index: mean ± SD	100 ± 0.0	96.8 ± 7.0	83.6 ± 16.9	85.0 ± 13.5	0.000
MMSE total score (/30): mean ± SD	21.1 ± 4.0	20.1 ± 3.9	16.9 ± 4.6	12.8 ± 4.0	0.003
FAB (/18): mean ± SD	9.6 ± 3.3	9.7 ± 3.1	7.9 ± 2.4	5.3 ± 1.5	0.003
WFT (words): mean ± SD	3.0 ± 2.2	2.8 ± 2.0	1.9 ± 1.9	2.0 ± 2.2	0.252
Digit Span Test: mean ± SD					
Forward	5.5 ± 1.6	5.2 ± 1.2	4.3 ± 1.5	4.3 ± 1.3	0.097
Backward	3.4 ± 0.7	3.2 ± 1.1	2.2 ± 1.6	1.5 ± 1.0	0.002
ADAS-Jcog: mean ± SD	15.0 ± 6.0	17.0 ± 5.9	19.9 ± 5.3	31.1 ± 9.7	0.008
CCT: mean ± SD					
POC	3.9 ± 2.1	2.6 ± 1.8	2.3 ± 1.8	1.0 ± 1.4	0.031
PDE	2.1 ± 2.1	3.5 ± 2.2	4.1 ± 2.3	8.8 ± 1.8	0.001
PAC	5.9 ± 1.1	4.9 ± 1.7	4.2 ± 1.9	1.8 ± 1.3	0.002
RCPM: mean ± SD					
Total (/36)	26.3 ± 4.2	22.5 ± 5.8	19.6 ± 4.6	13.3 ± 2.2	0.000
Set-A (/12)	9.7 ± 2.4	8.7 ± 2.1	7.6 ± 2.5	6.3 ± 1.0	0.005
Set-A_B (/12)	9.7 ± 1.6	8.0 ± 2.4	7.1 ± 2.0	4.5 ± 1.9	0.001
Set-B (/12)	6.9 ± 2.0	6.3 ± 2.0	4.6 ± 1.6	3.3 ± 1.5	0.006

[a]Kruskal-Wallis test.
*P<0.05, ** P<0.01.
CCT, Cube Copying Test.

Comparison Between FAST Stages

The scores of each neuropsychological test gradually worsened as the FAST stage increased (**Table 3**). The patients' sex, years of education, and duration of disease showed no significant differences across the FAST stages. However, a significant difference was found for age, but the mean age did not monotonously increase according to disease progression. Furthermore, PDE and PAC showed significant differences between FAST stages except between FAST 4 and FAST 5 [FAST 3 to 4: P (PDE/PAC)=0.030/0.007, FAST 4 to 5: P (PDE/PAC)=0.389/0.250, FAST 5 to 6: P (PDE/PAC)=0.033/0.017, FAST 3 to 5: P (PDE/PAC)=0.024/0.012, FAST 3 to 6: P (PDE/PAC)=0.010/0.003, FAST 4 to 6: P (PDE/PAC)=0.030/0.013, respectively]. On the other hand, POC showed significant differences only between FAST 3 and 5 and between FAST 3 and 6 (FAST 3 to 5: P=0.047, FAST 3 to 6: P=0.015).

DISCUSSION

Recently, symptoms of AD patients, such as wandering and becoming lost, have attracted attention as serious social problems.[27] Visuo-spatial function is impaired from the early phase of AD.[2] It is known that the focus of route finding is associated with the function of the retrosplenial cortex and the medial parietal lobe.[28] Furthermore, the entorhinal cortex and its connected regions are also known as the place cell–heading direction cell–grid cell (PHG) system, which is a network in the brain providing navigators with knowledge of their current location and a representation of environmental scenes.[29,30] These neural structures overlap

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the regions that are damaged in the initial stages of AD.[31] However, the mechanistic details of symptoms such as wandering and becoming lost are not yet known. Maksimenko et al.[32] reported that the precuneus and parahippocampal gyrus were active while deciding the orientation of the Necker cube under a priming condition. Therefore, in AD, low scores on the CCT and impaired route finding may have the same neural basis. The CCT is a very simple neuropsychological test that can evaluate visuo-spatial functions in a short time. It is also employed as a part of ADAS, but in ADAS, the CCT is only assessed as "It could be drawn correctly or not". Similarly, few studies have focused on the degree of accuracy and the details of the shapes of the copied cube. Therefore, we examined the CCT in detail in 152 AD patients and analyzed the association of lines, points of connections, and the formation of copied figures. Additionally, we evaluated the correlations between the CCT results and those of other neuropsychological tests, including RCPM, based on the severity of dementia. A previous report showed that visuo-spatial function declines with age and is lower in those with a lower educational level.[17] Our CCT results (POC, PDE, PAC) showed a significant correlation with age and education, and the results were similar to those of previous studies. In contrast, we found no correlation between the CCT results and the duration of disease. Most of the patients' chief complaints were regarding memory loss; moreover, the duration of illness, which mainly indicates the period from the appearance of memory loss, may not be directly related to impaired visuospatial cognitive dysfunction.

Correlations Between CCT and RCPM Results

The relationships between the three components of the CCT (POC, PDE, PAC) were analyzed, and PDE and PAC showed a linear relationship. In contrast, the correlations between POC and PDE and between POC and PAC were significant, but the relationships were not clearly linear. PAC reflects the pattern classification of the 3D structure, and PDE reflects the accuracy of the spatial arrangement of each line. If lines are distorted and are in erroneous positions, the cubic shape is not accurate. Consequently, PDE and PAC are considered to estimate relatively pure visuo-spatial functions. This may be the reason for the high correlation coefficients for PDE/PAC and RCPM. In contrast, POC enumerates errors in connecting points and does not solely represent simple shape distortion and the absence of lines. POC may be related to visuo-spatial attention, and it is considered that the differences in the characteristics of POC, PDE, and PAC contributed to the strength of the correlations with RCPM.

Analysis of the relationship between POC/PDE/PAC and RCPM showed a stronger correlation between POC/PDE/PAC and the score of Set-A rather than Set-B of RCPM. Set-A mainly reflects pure visuo-cognitive functions, and Set-B requires a more analytical technique.[12–14] Therefore, evaluation of CCT using POC/PDE/PAC reflects the details of visuo-cognitive functions. Additionally, CCT may assess some analytical abilities. Moreover, PDE and PAC were correlated with MMSE and FAB, and POC/PDE/PAC were correlated with the backward Digit Span Test. Therefore, an association between the results of CCT and frontal lobe function, including working memory and attention, may be present. An association between dementia and frontal lobe function, including working memory, has been previously reported.[33] Consequently, the CCT may be useful for estimation of these cognitive functions. Further studies that evaluate CCT in more detail will be required.

Relationship Between POC/PDE/PAC and the Severity of AD

The participants were classified according to the severity of AD based on their FAST stage. The POC/PDE/PAC results gradually declined with increasing AD severity. Because patients' sex, years of education, and duration of disease were not significantly different among the severity groups, the association between the POC/PDE/PAC results and the severity of AD may not be influenced by such background factors. In contrast, a significant relationship with age was seen between the FAST stages; however, the average age of the FAST 6 group was younger than that of the FAST 5 group, suggesting that reasons other than age may explain the decline in CCT results. The PAC results suggested that, on average, FAST 3 patients could copy a nearly perfect cube, FAST 4 patients could draw a 3D figure but could not draw a cube or a figure in perspective, and FAST 6 patients could not draw a 3D figure, which suggested that they could not recognize 3D structures. This last finding may influence impairment of activities associated with visuo-spatial functions such as putting on clothes and tying a necktie or shoelaces. Visuo-spatial function is closely connected to instrumental ADL and ADL of AD patients. Therefore, briefly evaluating the visuo-spatial function in patients with AD by analyzing CCT results in detail may be of great value.

Limitations and Future Research

One limitation of this study is that CCT allows assessment of only one aspect of visuo-constructional function. Furthermore, this was a retrospective and cross-sectional study.

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We did not perform a longitudinal study of how the results of CCT change with the progression of disease. Additionally, in this study, we did not consider any association with neuroradiological findings. Therefore, a longitudinal study is needed in which the changes in CCT are measured with the progression of disease and the associations with other neuropsychological tests are evaluated. Furthermore, we believe that looking at the relationship between other neuropsychological tests and imaging findings will contribute to the elucidation of the pathophysiology of dementia.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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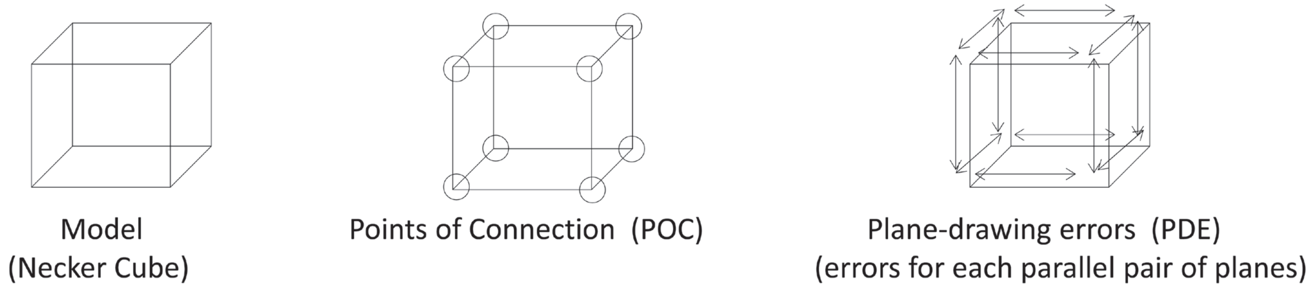
APPENDICES



Appendix 1. Evaluation using Maeshima's method (Maeshima et al., Brain Inj 2004;18:889–898) for impairment of constructional ability using a cube copying test.
Maeshima's method evaluates the points of connection (POC) and plane-drawing errors (PDE) by using a Necker cube. POC was defined as a point at which three lines met to form a vertex (lines less than 3 mm distant from the point were considered to be accurate). Subjects could score up to eight points, because eight POC exist in a cube. Each plane, defined by two pairs of parallel lines, was evaluated in terms of the number of lines and the extent to which they were parallel. No plane-drawing errors were scored if the cube was copied accurately.

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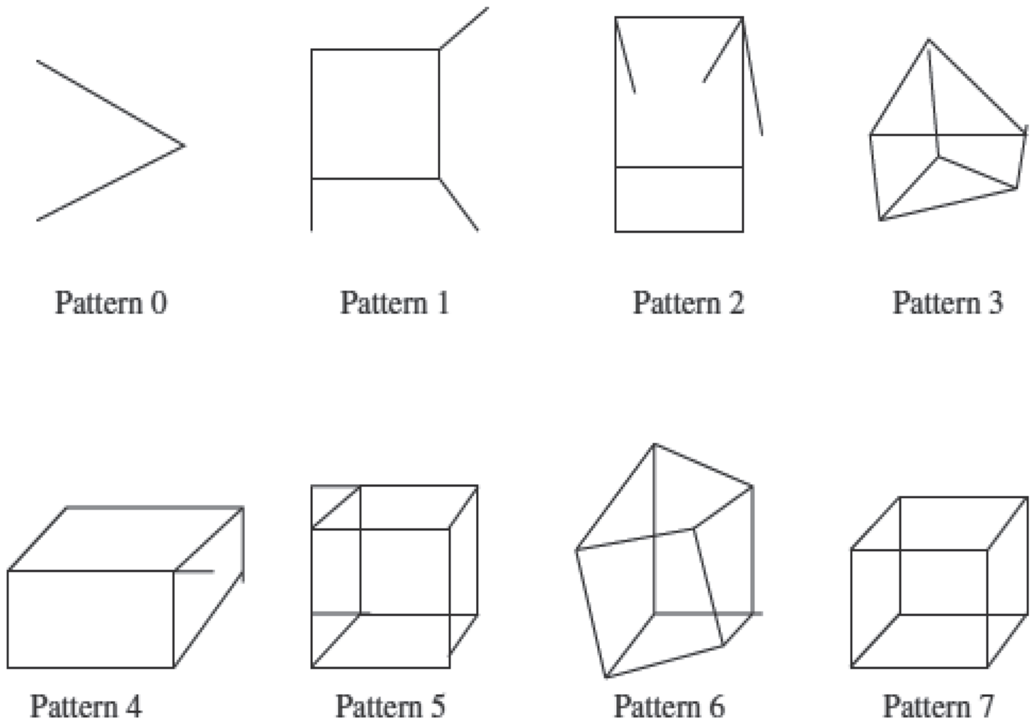

Appendix 2. Evaluation using Shimada's method (Shimada et al., Psychogeriatrics 2006;6:4–9) for impairment of constructional ability using a cube copying test.
Shimada's method (pattern classification: PAC) has eight original criteria that are used for assessing the participants' ability to copy the Necker cube. 1. Pattern 0, lines only: participants could not copy any quadrilaterals and drew only lines. 2. Pattern 1, one quadrilateral (plus lines): participants copied only one quadrilateral, with or without some lines running from the quadrilateral. 3. Pattern 2, two or more quadrilaterals (plus lines): Participants copied two or more quadrilaterals with or without some lines. However, the drawing could not be judged to be a three-dimensional (3D) figure (Hochberg and Brooks, Am J Psychol 1960;73:337–354). 4. Pattern 3, 3D but not a cube: Participants succeeded in constructing a 3D figure but failed to make it a cube. 5. Pattern 4, cube (plus lines): Participants succeeded in drawing a cube but fell short of the Necker cube. 6. Pattern 5, distorted model: Although the figure consisted of 12 or more lines and could be judged to be the Necker cube, the relationship between these line segments was different from that of the model, based on at least one of the following criteria: (i) each side of the figure could not be judged to be a quadrilateral, or the figure had more than six sides; and (ii) the two overlapping squares of the Necker cube were transposed from the left-lower–right-upper pattern to the left-upper–right-lower pattern, or the two squares did not overlap each other. 7. Pattern 6, almost the same as the model: Participants were able to copy a figure almost correctly, only some angles were incorrect. 8. Pattern 7, the same as the model.
These are examples of the eight patterns of drawing according to our original criteria.

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