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The Usefulness of Cube Copying for Evaluating Treatment of Alzheimer's Disease

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Aims: Cube copying measures visuospatial ability, which is often impaired in Alzheimer's disease (AD). Cube copying was examined as an evaluation of cholinesterase inhibitor (ChEI) treatment in AD. *Methods:* Eighty-five ChEI-treated AD patients were included. Cube drawings made at prebaseline, baseline, 6 months, and 12 months were assessed. Cube drawings from 56 healthy individuals were also examined. *Results:* The healthy individuals remained stable in cube copying, whereas untreated AD patients deteriorated during a median period of 6 months. When treatment was given, the deterioration was interrupted. After 12 months, Mini-Mental State Examination (MMSE) had deteriorated compared with baseline whereas cube copying was unchanged. *Conclusions:* The results indicate that cube copying can be used to evaluate ChEI treatment. It might also show a more long-lasting response to treatment than MMSE. Cube copying only measures a narrow cognitive function and can preferably be used with MMSE, which evaluates visuospatial ability poorly.

Keywords: Alzheimer's disease; cube copying; cholinesterase inhibitors; treatment outcome; box copying; Necker cube

Alzheimer's disease (AD) is the most common of all dementia diagnoses, and it has been estimated by the American National Institute of Health that 8.5 million people will be affected by the year 2030 in the United States alone.[1] So far, no preventive drugs have been discovered, but a well-controlled blood pressure and an active life, both mentally and socially, are known to delay or lower the risk of AD.[2]

Since 1997, the second generation of cholinesterase inhibitors (ChEIs) has been used to treat patients with AD. In a Cochrane review from 2006, it was concluded that all 3 ChEIs on the market produce improvements in behavior, activities of daily living (ADL), and cognitive function.[3] One of the cognitive functions that has improved due to ChEI treatment is visuospatial ability.[4] The positive effects of ChEI have not been great, and the best results were achieved within 6 months. Many of the patients also reported mild adverse events such as nausea, vomiting, and diarrhoea.[3]

It is important to have reliable follow-ups due to the moderately positive effects of the treatment, the adverse events, and the high medical costs. According to the National Institute for Health and Clinical Excellence, the treatment should be reviewed every 6 months by the Mini-Mental State Examination (MMSE) score and global, functional, and behavioral assessments.[5] As a result, the treatment of AD is quite expensive, not only regarding medication but also regarding time and personnel in outpatient clinics.

A common finding in patients with AD is impairment in visuospatial abilities, as demonstrated in different tests.[6-9] The cube-copying task, which mainly measures visuospatial ability and to a lesser

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extent constructional praxis, has been shown to be deteriorated in AD.[10-13] In the cube-copying task, the patient copies a cube on a piece of paper. The simplicity of the test has made it a popular evaluation tool among clinicians.

Although widely used, no previous study has examined the cube-copying task as an evaluation tool of treated AD patients, but several studies state that cube copying needs more research.[12,14,15] On the basis of the positive effect ChEI has on visuospatial ability, we hypothesize that cube-copying performance will deteriorate in a nontreated AD patient and improve when treatment is given. The aim of this study will, therefore, be to examine if cube copying can be used as a tool for measuring the treatment effect of ChEI.

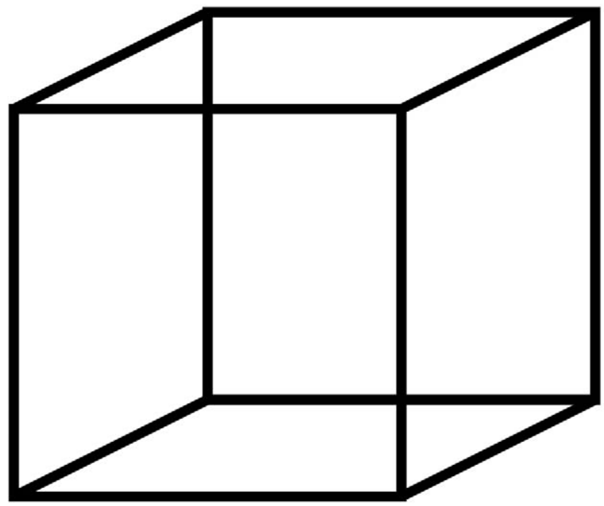

Figure 1. The original cube, often referred to as the Necker cube.

Materials and Methods

The Population and the Sample Selection

The subjects in this study were enrolled from the Swedish Alzheimer Treatment Study (SATS).[16] The SATS is a national, longitudinal study in routine clinical settings. Ten clinical memory units gather patients who meet the criteria for AD according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association guidelines.[17] In the SATS, patients are treated with ChEI (rivastigmin, donepezil, or galantamin) and are followed with cognitive, global, and ADL assessments.

The participants in this study were chosen from the patients in the SATS located in the town of Malmö, Sweden. All patients treated with donepezil were chosen because this was the first ChEI on the market and consequently all the data had been collected. This selection generated a pool of 120 patients. All the subjects lived in their homes and suffered from mild to moderate dementia according to the American Psychological Association's *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised).[18]

To compare cube copying with treatment results, there had to be 1 cube drawing made at baseline and 1 cube drawing at a later point in time (in this case at the 6-month or 12-month follow-up). Thirty-three patients had only 1 cube drawing and were therefore excluded. In 2 cases, the patient file was not available. Thus, 85 participants were finally included in this study. All patients started their treatment with 5 mg donepezil. After 6 months, the mean dose was 6.0 ± 2.0 and after 12 months 6.6 ± 2.5.

The Necker Cube

The drawing of the copied cube was collected from the Alzheimer's Disease Assessment Scale–cognition test, in which cube copying is a subtest.[19] The original cube can be found in the constructional praxis part of the test and consists of lines that are 4.3-cm long (Figure 1). In the cube-copying task, the patient is asked to make a copy of the figure below the original, with no time limit.

The drawings were assembled from examinations made at baseline and after 6 and/or 12 months. This resulted in either 2 or 3 drawings from each patient. To further examine the treatment effect on cube copying, prebaseline cube drawings were collected from old, archived medical files. These drawings, together with the baseline drawings, were thus made before the ChEI treatment was started.

To include a prebaseline drawing, it had to be dated at least 3 months and not more than 16 months before baseline. If more than 1 drawing was found, only the oldest was included. Where a cube drawing was found, the oldest MMSE score between 3 and 16 months before baseline also was collected. Because cube copying was not a standard test outside of the SATS, only 36 cube drawings and 29 MMSE results were found among the 85

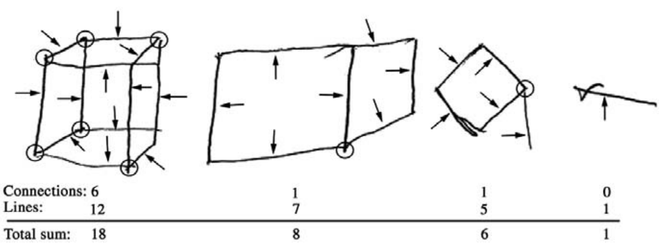

Figure 2. Four cube drawings made by different patients and the assessment based on Maeshima et al.[12]

patients. The cube drawings were found at a median of 6 months (range 3-16) before baseline, and the MMSE scores were found at a median of 7 months before baseline (range 4-13).

The assessment of the cube drawings was based on the cube assessment of Maeshima et al.[12] In this assessment, both connections and lines in the cube are evaluated. A point of connection is defined as a point where 3 lines meet to form a vertex. Lines less than 3 mm off the point are considered to be accurate. Because a cube consists of 8 connections, the patient could score a maximum of 8 points. Then the number of parallel lines is counted. Twelve lines can be found in a cube, and the patient could therefore score 12 points.

Maeshima et al[12] have not specified a degree of angle to define parallel lines. Therefore, all lines in a patient's drawing that could be considered to represent a line in a cube were counted. In Maeshima's method, incorrect lines and correct corners were counted, but in this study, correct lines and corners were counted to generate a combined score of correct connections and lines with a maximum of 20 points (Figure 2).

The cube drawings were further assessed by categorizing the AD patients into 2 groups, one in which 3-dimensionality (3D) could be found and one in which the drawings were 1-dimensional or 2-dimensional. Three-dimensionality is an easily identifiable characteristic in a cube drawing. It has been used in previous studies as part of quantifying the cube-copying assessment, but the correlation with evaluation instruments has not been investigated.[15,20]

Control Population

All cube drawings assessed in this study so far were thus made by AD patients. To compare these with cube copying in healthy individuals, a control population was examined. It consisted of 62 healthy individuals with the inclusion criteria "intact ADL function and no memory complaints" and exclusion criteria "physical or mental disease that could affect the cognitive status."[21] They were recruited through advertisements and examined at the Clinical Memory Research Unit in Malmö, Sweden. The control study was conducted between 2002 and 2005, and it was a study separated from the SATS. Of the 62 healthy individuals, 56 had a recorded cube and MMSE score at the starting point and 3 years later and were thus examined in this study. The cube drawings were scored by the researchers of that study the same way they were in this study.

The Other Evaluation Instruments

In the SATS, several evaluation instruments were used. To assess cognition, the MMSE was used.[22] The ADL status was assessed with the Physical Self-Maintenance Scale,[23] which rates the basic ADL of the patient (ie, getting dressed, managing personal hygiene), and Instrumental Activities of Daily Living (IADL),[23] which measures the ability to manage daily chores involving objects (ie, cooking, phoning). The IADL score was converted to a quotient to compensate for different individual maximum scores, as certain items were not applicable for some patients. The overall, global impression of the patient was measured with Clinical Global Impression of Change (CGIC),[24] wherein the doctor initially grades the severity of the dementia based on the overall impression of the patient and thereafter grades the change in the dementia severity since baseline.

Procedures

To examine the relation between cube copying and the other evaluation instruments, the cube score at baseline, 6 months, and 12 months was correlated to the other evaluation instruments, except the CGIC values at 6 and 12 months because these state a relative change and not a static value. The 3D feature of cube copying was also analyzed in relation to the other evaluation instruments and to cube score.

To examine cube copying as an evaluation of AD treatment, the prebaseline and postbaseline changes were compared to see possible effects of treatment. The change in MMSE and cube score in the control population compared with the AD patients was also examined.

Statistical Analysis

All data in this study were derived from ordinal scales (eg, MMSE, cube score, IADL), and therefore, nonparametric statistical methods were used. Correlations were analyzed with Spearman's rank correlation coefficients. Changes of the same variable over time were examined with the Wilcoxon test (2 related samples). Differences between independent variables were tested with the Mann–Whitney *U* test (2 independent samples). Data were not found for all evaluation instruments at each specific point in time, and pairwise exclusion of cases was applied. Dichotomized values were compared using the χ^2 test, except for the change in 3D ability, which was analyzed with the McNemar test (2 related samples) test. *P* values were 2-sided and unadjusted for multiple comparisons. A *P* value of less than .05 was considered to indicate statistical significance. All statistical analyses were performed with the use of the Statistical Package for Social Sciences software (version 12.0.1 for Windows; SPSS Inc, Chicago, IL).

Results

Descriptive Data

Table 1 shows background data from the selected and the excluded patient samples as well the control population at baseline. The selected AD sample had a higher mean MMSE score than the excluded sample. The control population was a little younger and had, as expected, higher MMSE and cube score than the selected AD sample.

The 36 AD patients who had a prebaseline cube drawing did not differ significantly from the 49 AD patients in any characteristic (Table 2). Moreover, neither of the 2 groups differed significantly in MMSE and cube scores at the 6-month and 12-month follow-up (data not shown).

Table 1. Demographics and Significant Differences Compared to the Selected AD Sample

Characteristic	Selected AD Sample (N = 85)	Excluded AD Sample (N = 35)	Control Population (N = 56)
Age[a]	76 (52-88)	77 (61-87)	72.5 (60-94)[c]
Gender (% women)	68	80	64
Baseline MMSE[b]	23.0 ± 3.9	18.6 ± 6.1[d]	29.3 ± 0.9[d]
Baseline cube score[b]	14.2 ± 5.4	NA	18.3 ± 2.3[d]

Abbreviations: AD, Alzheimer's disease; MMSE, Mini-Mental State Examination, NA, not applicable.
[a]Data presented as median (range).
[b]Data presented as mean ± standard deviation.
[c]$P < .05$.
[d]$P < .001$.

Table 2. Comparison Between the AD Patients Who Had a Prebaseline Cube Score and Those Who Did Not

Characteristic	AD Patients With a Prebaseline Cube Score (N = 36)	AD Patients With No Prebaseline Cube Score (N = 49)
Age[a]	77 (52-87)	76 (58-88)
Gender (% women)	69	67
Baseline MMSE[b]	22.4 ± 4.1	23.5 ± 3.8
Baseline cube score[b]	14.2 ± 5.4	14.2 ± 5.4

Abbreviations: AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.
[a]Data presented as median (range). No significant differences were found for any characterisics.
[b]Data presented as mean ± standard deviation. No significant differences were found for any characterisics.

The Changes of the Evaluation Instruments in the Control Population and in the AD Patients

The cube score of the control population remained unchanged, with a mean value of 18.3 ± 2.3 at the starting point and 18.3 ± 3.2 after 3 years (Figure 3A). The MMSE also remained unchanged, with a mean value of 29.3 ± 0.84 at the starting point and 29.3 ± 0.86 after 3 years (Figure 3B).

In the AD population, there was a decline during the pretreatment period both in cube score at $P < .05$ (Figure 3A, Table 3) and in MMSE score at $P < .05$ (Figure 3B, Table 3) When ChEI treatment was given, this decline was interrupted during the first 6 months. However, after 12 months of treatment, the MMSE score had again declined compared with the baseline at $P < .0005$ (Figure 3B, Table 3). In contrast, the mean cube score had not declined after 12 months. Instead, the mean score had increased compared with the baseline, although not statistically significant (Figure 3A, Table 3).

Similarly to the cube score changes, the 3D ability deteriorated significantly from prebaseline to baseline, where 11 of 36 patients lost 3D in the cube drawing and only 1 gained it. After 12 months, 3D ability also showed a nonsignificant increase (Table 3).

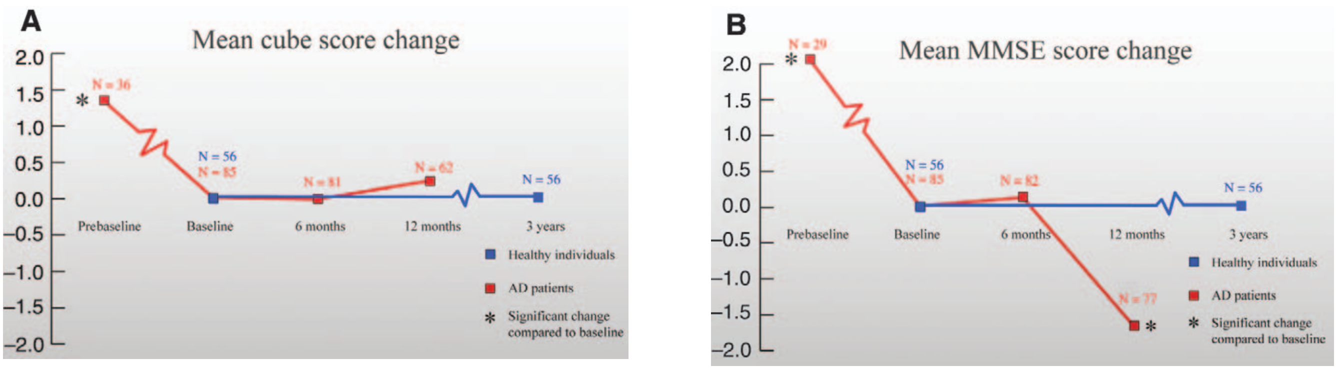

Figure 3. The paired change in (A) mean cube and (B) MMSE score (the mean intra-individual change) compared with baseline. Note that the MMSE is measured on a 0-30 point scale and the cube score on a 0-20 point scale, which make changes in cube score relatively greater than the changes of the MMSE score.

Table 3. Evaluation Instruments at the Different Time Points in Patients With AD and the Significant Differences Compared With Baseline Values

Evaluation Instrument	Prebaseline (N = 29-36)	Baseline (N = 83-85)	6 Months (N = 78-82)	12 Months (N = 57-77)
MMSE[a,b]	24.2 ± 3.4[f]	23.0 ± 3.9	23.1 ± 4.1	21.4 ± 4.7[h]
IADL quotient[c,d]	NA	0.47 (0.33-0.63)	0.47 (0.33-0.63)	0.50 (0.37-0.74)[h]
PSMS[d,e]	NA	7 (6-8)	7 (6-8)	7 (6-9)[g]
Cube score[b,i]	15.5 ± 4.7[f]	14.2 ± 5.4	14.1 ± 5.4	15.0 ± 5.7
3D[j]	97%[f]	72%	72%	78%

Abbreviations: AD, Alzheimer's disease; MMSE, Mini-Mental State Examination, IADL, Instrumental Activities of Daily Living; NA, not applicable; PSMS, Physical Self-Maintenance Scale; 3D, 3-dimensionality; ADL, activities of daily living.
[a]MMSE (0-30 points).
[b]Data presented as mean value ± standard deviation.
[c]Quotient of IADL (0-1 point, larger quotient = worse ADL ability).
[d]Data presented as median value (25th-75th percentiles).
[e]PSMS (6-30 points, higher score = worse ADL ability).
[f]$P < .05$.
[g]$P < .005$.
[h]$P < .0005$.
[i]0-20 points.
[j]Percentage of patients with 3D in the cube drawing.

It should be noted that 12 of the 85 AD patients at baseline received a maximum cube score. This results in a certain ceiling effect, where the patient cannot show any improvements in cube copying.

Correlations and Comparisons

The correlations between the cube score and the other evaluation instruments are presented in Table 4. The correlations with MMSE were significant at all 3 time points. The cube score also correlated significantly with the ADL assessments at 6 months and at 12 months. The global assessment, CGIC, showed the highest correlation with cube score. The cube score did not differ significantly between men and women and was not significantly correlated with age.

When comparing the 3D and non-3D groups, the MMSE scores differed in mean values at all time points ($P < .01$). The differences in mean MMSE values were only 2.0 to 3.5 points. The other evaluation instruments showed a slightly better mean value in the 3D group, but none of the differences were significant. When compared with the cube score, the non-3D group had a lower mean score at all time points compared with the 3D group ($P < .00000001$) with almost no overlapping (Figure 4).

Table 4. Correlations Between Cube Score and the Evaluation Instruments

	Cube Score		
Evaluation Instrument	Baseline	6 Months	12 Months
MMSE	0.43[a]	0.24[b]	0.25[b]
IADL quotient	−0.17	−0.24[b]	−0.36[a]
PSMS	−0.13	−0.29[b]	−0.31[b]
CGIC	−0.44[a]	NA	NA

Abbreviations: MMSE, Mini-Mental State Examination, IADL, Instrumental Activities of Daily Living; PSMS, Physical Self-Maintenance Scale; CGIC, Clinical Global Impression of Change; NA, not applicable.
[a]$P < .01$.
[b]$P < .05$.

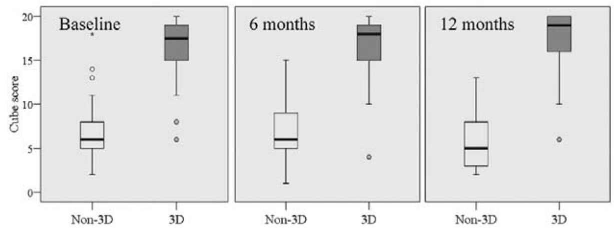

Figure 4. Cube score in the 3D and non-3D group ($P < .00000001$ at baseline, at 6 months, and at 12 months).

Discussion

In this study, the cube-copying ability as an evaluation method for ChEI-treated AD patients was examined. The results show that cube copying deteriorated significantly in untreated AD patients but not when they were given ChEI treatment. This was shown both in cube score change and change in 3D ability. In healthy individuals, cube-copying performance remained stable over 3 years.

Correlations Between the Cube Score and the Other Evaluation Instruments

The majority of the other evaluation instruments used in this study correlated significantly with the cube score. The correlation with the MMSE and ADL assessments confirms what has been shown in earlier studies.[12,13] The correlation with the global dementia rating, CGIC, suggests that cube copying can give an indication of the dementia severity. It should, however, be noted that the significant correlations of the cube score are not strong overall. This is in agreement with the fact that visuospatial assessment, which is mainly what the cube measures, is only 1 component of many that are measured by the other evaluation instruments.

Three-Dimensionality

The significant differences in mean MMSE scores between the 3D and non-3D groups were too small to be clinically relevant. When the 3D and non-3D groups were compared with the cube score, as expected, 3D separated the cube score into 2 groups with almost no overlapping. The identification of 3D in a cube drawing can thus be used to easily indicate a high or low cube score. What further emphasized the practical use of the 3D assessment is the fact that it followed the change in cube score over time, with a significant decline to baseline and a nonsignificant increase after 12 months of treatment. In clinical practice, a comment about 3D can therefore be used in medical records as a simple substitute for the more complicated evaluation of lines and corners. However, 3D was not a sensitive tool in early AD because the majority of the AD patients succeeded in copying the cube into a 3D figure.

Another interesting aspect of 3D is that the Necker actually is a 2-dimensional figure that, through visual illusion, is perceived as a 3D figure. The nature of the perceived cube is not static; one can, for example, see the cube from slightly above or slightly below. In the case of AD, one could speculate if the deterioration in cube copying is not only due to impaired ability to perceive 3D but also due to a disturbing shift of perspective or the appearing and reappearing of 3D.

At prebaseline, 97% of the 36 AD patients copied a 3D figure, and at baseline, 12 of 85 AD patients scored 20 of 20 cube points. The cause of this high performance in cube score could be a result of disregarding the parallelism of lines in the cube drawings, which gives a higher cube score. Perhaps a more clinical, subjective assessment might be more sensitive, as a cube drawing does not have to be perfectly copied to receive maximum cube score or to contain 3D. Overall, these results suggest that cube copying can be fairly intact in mild AD.

Does Cube Copying Measure Treatment Effect?

When the change in mean cube score was compared in the control population and the prebaseline (untreated) AD patients, the healthy individuals had a stable mean cube score during a 3-year period, whereas the untreated AD group declined significantly during a median period of 6 months. From this result, we conclude that the change in cube score is altered in untreated AD patients. As treatment was given to the AD patients, the decline in cube score was interrupted (which is shown in Figure 3A). We interpret this as an indication that cube copying measures treatment effect.

The mean MMSE score also showed a significant decline prebaseline, which was interrupted when treatment was given. The fact that this well-acknowledged evaluation instrument followed the same pattern as the cube score further strengthens the assumption that cube copying measures treatment effect.

After 12 months of treatment, the mean MMSE score had again declined significantly with compared with the baseline score. The mean cube score, on the other hand, had not declined after 12 months. The differences between the MMSE score and the cube score suggest that cube copying might show a more long-lasting response to ChEI treatment. A speculative explanation for this could be that cube copying measures a cognitive function that has a longer lasting effect of ChEI treatment than the combined cognitive functions measured by the MMSE score. Another explanation for the difference between cube and MMSE scores could be that cube copying has less reliability than the MMSE. However, both these assumptions need to be investigated in future studies.

The small mean changes of MMSE and cube scores that are showed in Figure 3A and B might seem weak as illustrations of treatment effect, but they really should be reviewed in comparison with the progression of untreated AD patients. As cube copying has never been evaluated over time in AD, there are no previous data for this test, but a large meta-analysis concluded that the MMSE score declined with an average of 3.3 points per year in untreated AD patients.[25]

Practical Use of Cube Copying

Although cube copying seems to evaluate ChEI and show a longer lasting treatment effect, it should not be used on its own, due to its narrow cognitive evaluation, but as a complement.

The MMSE mainly evaluates verbal cognition, with a visuospatial assessment of only 1 of 30 points. The visuospatial ability is assessed by having the patient copy 2 overlapping pentagons. Most clinicians do not consider a change of only 1 point in the MMSE score an actual change. Furthermore, a pentagon is a 2-dimensional figure that can be copied correctly in more severe dementia than the cube.[14] Improvements in less demented patients are thus more difficult to observe with pentagon drawings. Hence, the change in visuospatial ability is poorly measured by the MMSE. Cube copying is therefore recommended as a complement to the MMSE.

Shortcomings

Because fewer AD patients were found at prebaseline and their values were from different time points before baseline, the prebaseline results have weaker evidence than the results from baseline, 6 months, and 12 months. A prospective study establishing the decline in cube copying prior to ChEI treatment during a defined period of time would be more conclusive. Also, studies regarding the reliability of cube copying are needed.

The number of AD patients who had done the MMSE and the cube-copying task varied between the different time points. It was especially so not only for the prebaseline values but also for the 12-month values. However, this was compensated for by using paired (or 2 related samples) analyses with pairwise exclusion of patients when comparing changes over time. Analyses were also performed to verify that the 36 AD patients with prebaseline cube scores did not differ from the other AD patients in MMSE score, cube score, age, or gender at any point in time.

Conclusions

We found that cube copying seems to evaluate the effect of ChEI treatment in AD. Our results also suggest that cube copying might show a more long-lasting response to treatment. Furthermore, this study has shown that the identification of 3D in a cube drawing provides an easy measurement of the cube score and that the 3D ability can be used to evaluate changes in cube copying.

Based on the results of this study, we suggest that cube copying is used in the follow-up of ChEI-treated AD patients, preferably together with the MMSE.

References

1. National Institutes of Health. *Progress Report on Alzheimer's Disease*. Washington, DC: US Department of Health and Human Services; 1999.
2. Scalco MZ, van Reekum R. Prevention of Alzheimer disease. Encouraging evidence. *Can Fam Physician*. 2006;52:200-207.
3. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006;(1):CD005593. doi:101002/14651858.
4. Emre M, Aarsland D, Albanese A, et al: Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med*. 2004;351:2509-2518.
5. National Institute for Health and Clinical Excellence. *Dementia: Supporting People With Dementia and Their Carers in Health and Social Care*. London, UK: National Institute for Health and Clinical Excellence.
6. Graham N, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. *J Neurol Neurosurg Psychiatry*. 2004;75:61-71.
7. Filley C, Kelly J, Heaton R. Neuropsychologic features of early- and late-onset Alzheimer's disease. *Arch Neurol*. 1986;43:574-576.
8. Binetti G, Cappa S, Magni E, Padovani A, Bianchetti A, Trabucchi M. Visual and spatial perception in the early phase of Alzheimer's disease. *Neuropsychology*. 1998;12: 29-33.
9. Guerin F, Belleville S, Ska B. Characterization of visuoconstructional disabilities in patients with probable dementia of Alzheimer's type. *J Clin Exp Neuropsychol*. 2002;24:1-17.
10. Kirk A, Kertesz A. On drawing impairment in Alzheimer's disease. *Arch Neurol*. 1991;48:73-77.
11. Kato M, Sano Y, Uno A. Constructive deficits in brain damaged patients: effects of the localized and /or diffuse cerebral lesions. *Higher Brain Funct Res*. 1988;8:305-319.
12. Maeshima S, Osawa A, Maeshima E, et al. Usefulness of a cube-copying test in outpatients with dementia. *Brain Inj*. 2004;18:889-898.
13. Maeshima S, Itakura T, Nakagawa M, Nakai K, Komai N. Visuospatial impairment and activities of daily living in patient's with Parkinson's disease: a quantitative assessment of the cube-copying task. *Am J Phys Med Rehabil*. 1997;76:383-388.
14. Ericsson K, Forssell L, Holmén K, Viitanen M, Winblad B. Copying and handwriting ability in the screening of cognitive dysfunction in old age. *Arch Gerontol Geriatr*. 1996;22:103-121.
15. Shimada Y, Meguro K, Kasai M, et al. Necker cube copying ability in normal elderly and Alzheimer's disease. A community-based study: the Tajiri project. *Psychogeriatrics*. 2006;6:4-9.
16. Wallin A, Andreasen N, Eriksson S, et al. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. *Dement Geriatr Cogn Disord*. 2007;23:150-160.
17. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. rev. Washington DC: American Psychiatric Association; 1987.
19. Rosen W, Mohs R, Davis K. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356-1364.
20. Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in older adults by clock drawing, box copying and narrative writing. *Dement Geriatr Cogn Disord*. 2007;23:74-81.
21. Stomrud E, Hansson O, Blennow K, Minthon L, Londos E. Cerebrospinal fluid biomarkers predict decline in subjective cognitive function over 3 years in healthy elderly. *Dement Geriatr Cogn Disord*. 2007;24:118-124.
22. Folstein MF, Folstein SE, McHugh PF. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12: 182-198.
23. Green C, Mohs R, Schmeidler J, Aryan M, Davis K. Functional decline in Alzheimer's disease: a longitudinal study. *J Am Geriatr Soc*. 1993;41:654-661.
24. Schneider LS, Olin JT. Clinical global impressions in Alzheimer's clinical trials. *Int Psychogeriatr*. 1996;8:2 77-290.
25. Han L, Cole M, Bellavance F, McCusker J, Primeau F. Tracking cognitive decline in Alzheimer's disease using the Mini-Mental State Examination: a meta-analysis. *Int Psychogeriatr*. 2000;12:231-247.