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Early detection of Alzheimer's disease using the Cambridge Cognitive Examination (CAMCOG)

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ABSTRACT

Background. Dementia screening instruments, such as the Cambridge Cognitive Examination (CAMCOG), measure a variety of cognitive functions. However, memory impairment generally is the first sign of Alzheimer's disease (AD). It seems logical, therefore, to use only memory-related items for the early detection of AD. We divided the CAMCOG into a memory section and a non-memory section, and tested the hypothesis that the memory section predicts AD better than the non-memory section. We also provide normative data for both sections.

Methods. Normal subjects ($N = 169$) and patients with incident AD (i.e. satisfying AD criteria between 1 and 3 years from baseline; $N = 25$) were participants in the Amsterdam Study of the Elderly (AMSTEL), a population-based longitudinal study on cognitive decline and dementia. Patients with prevalent AD (i.e. satisfying AD criteria at baseline; $N = 155$) were either recruited in a memory clinic or came from AMSTEL. Normal subjects were cognitively intact at baseline and remained so for at least 3 years. The CAMCOG was administered to all subjects. AD was diagnosed by DSM-III-R criteria.

Results. Logistic regression analysis showed that the memory section was related to prevalent AD, whereas in multivariate analysis the non-memory section was not (after correction for the memory score and demographic characteristics). A similar analysis showed that the memory section predicted incident AD, as did a higher score on the non-memory section. The MMSE did not predict incident AD better than age alone.

Conclusion. For the early detection of AD it is best to use the memory and non-memory sections separately instead of the total CAMCOG score.

INTRODUCTION

The clinical diagnosis of dementia, and more specifically of Alzheimer's disease (AD), is based on a syndromal approach. The major diagnostic systems currently in use such as DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1992) require the presence of memory disorders together with one or more other cognitive or psychiatric symptoms. Onset is insidious, decline is progressive, and other causes of decline should be ruled out before the diagnosis of AD may be made. The memory disorder is mandatory, while the other symptoms are optional provided that at least one is present. Thus, if one wants to detect AD, it seems logical to use a cognitive test covering the domains where symptoms are to be expected. However, from clinical experience and epidemiological studies we know that AD is almost always preluded by memory disorders (Christensen *et al.* 1991; Flicker *et al.* 1991; Masur *et al.* 1994; Newman *et al.* 1994; Linn *et*

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al. 1995; Grober & Kawas, 1997; Howieson *et al*. 1997). This is, of course, precisely the reason why symptoms of amnesia play such a central role in the diagnostic definitions. Viewed from this point it is doubtful whether a broad-ranged cognitive test is a good choice to detect early stages of AD. Perhaps it is wiser to focus on the amnesic symptoms and to use only memory-related tasks as detectors.

The Cambridge Cognitive Examination (CAMCOG) is one of the diagnostic instruments that are widely used in clinical settings and in epidemiological research on dementia. It is part of the Cambridge Examination of Mental Disorders of the Elderly (CAMDEX; Roth *et al*. 1986, 1988), which consists of a structured interview with the patient and an informant, a physical examination, and the CAMCOG. In this paper we will concentrate on the CAMCOG. It is our aim to show how the instrument may be used more efficiently to detect early AD and prodromal stages of AD.

The CAMCOG is a broad ranged psychometric test consisting of a variety of items leading to a single total test score. The CAMCOG has 60 items that were grouped by its authors into eight subscales measuring: (1) orientation in time and place; (2) language comprehension and expression; (3) remote and recent memory and learning; (4) attention; (5) ideational and ideomotor praxis; (6) calculation; (7) abstract thinking; and (8) visual and tactile perception. The maximum obtainable total score is 107, and a cut-off value of 79/80 is recommended to distinguish between individuals with dementia and normal subjects (Roth *et al*. 1986, 1988).

In the present study we tested the hypothesis that the memory-related tasks of the CAMCOG are a more sensitive detector of AD and its prodromal stages than the non-memory related tasks. Therefore, we divided the CAMCOG into a 'memory section' and a 'non-memory section' and examined the predictive validity of both sections in elderly subjects. To this end, we combined data from two studies, one clinic-based and one population-based study. We also provide psychometric and normative data by which clinicians and researchers may interpret the memory and non-memory sections of the CAMCOG separately.

METHOD

Subjects and diagnostic procedures

Data of subjects from two studies were pooled. The first was a clinic-based study on the utility of diagnostic procedures in a memory clinic (Teunisse *et al*. 1997; Walstra *et al*. 1997). This study included 200 consecutive patients who were referred by their general practitioner because a dementia syndrome was suspected. Inclusion criteria were: age of $\geqslant 65$ and availability of a caregiver, who was able to give sufficient information on the everyday functioning of the patient. Exclusion criteria were: any previous medical examinations for dementia and the presence of co-morbidity, which might substantially shorten the life expectancy of the patient. All subjects were examined using the Dutch version of the CAMDEX (Derix *et al*. 1992). Patients who were demented according to DSM-III-R criteria received standard laboratory tests (ESR, total blood count, serum electrolytes, calcium, urea, creatinine, glucose, bilirubin, liver enzymes, cholesterol, triglycerides, TSH, vitamin B1, B6 and B12, folate, VDRL, TPHA and urinalysis), chest X-ray, ECG, EEG and CT of the brain. Additional investigations were performed when indicated. A final diagnosis was made according to DSM-III-R criteria after all test results were reviewed. Administration of the CAMDEX was repeated after a median interval of six months (184 days; interquartile range 168–253 days). The diagnosis made at baseline was checked. In the present analyses only patients were included who received a DSM-III-R diagnosis of Alzheimer's disease ($N = 120$).

The second source of subjects was the population-based Amsterdam Study of the Elderly (AMSTEL), which focused on cognitive decline and dementia. The design and sampling of this study have been described in detail elsewhere (Launder *et al*. 1993; Jonker *et al*. 1998). Briefly, a random age-stratified sample ($N = 4051$, age range 65–84 years) was selected from 30 general practices in Amsterdam. This sample was screened using the Mini-Mental State Examination (MMSE; Folstein *et al*. 1975). A subsample was composed based on the MMSE scores: all subjects with low MMSE scores ($\leqslant 21$), 45% of subjects with borderline scores

(22–26) and 7% of subjects with good MMSE scores (27–30). These persons were invited to participate in a longitudinal part of the study. A total of 511 subjects agreed to participate (of $N = 787$ who were invited; response rate 65%). They were examined at baseline and then annually for 3 years by a physician and a research nurse using the Dutch version of the CAMDEX.

For the present analyses three subsets of subjects were used: (1) subjects from the AMSTEL study who according to CAMDEX criteria were normal at baseline and remained normal during the three follow-up examinations (normal controls; $N = 169$); (2) subjects from the AMSTEL study who were normal at baseline or might have had some cognitive symptoms without being demented at baseline, but subsequently developed Alzheimer's disease during the course of the study (cases of incident AD; $N = 25$); and (3) subjects from both studies who received a DSM-III-R diagnosis of Alzheimer's disease at baseline (cases of prevalent AD, $N = 35$ from AMSTEL, and the above described 120 subjects from the memory clinic). All subjects from both studies who had a non-Alzheimer type of dementia or who were primarily suffering of a psychiatric condition during any of the baseline or follow-up examinations were excluded. Subjects who at any moment were diagnosed as having 'minimal dementia' were also excluded from the normal group. Thus, our data set contains patients with either prevalent or incident AD, as well as subjects who were normal at baseline and remained normal during the subsequent 3 years.

Statistical analyses

The score on the memory section was calculated by summing the scores of the Orientation and Memory subscales; the non-memory section score was calculated as the sum of the remaining subscales. The item 'recognition of a person or his/her function' (item 185) was not administered. It was always scored as correct (1 point). Missing values on the CAMCOG subscales were corrected by estimating the score on the scale in question as the rounded average corresponding (in subjects without missing values) with the sum of the valid item scores.

As preliminary steps the reliabilities (Cronbach's alpha) of the two CAMCOG sections were calculated in the normal control group as well as in the AD patients from the memory clinic. We also calculated the annual decline of the CAMCOG scores in the three groups of subjects (prevalent AD, incident AD, normal). Since the follow-up intervals differed considerably in both studies, the score declines were calculated as the score at follow-up minus the score at baseline, multiplied by 365 and divided by the length of the follow-up interval in days. Furthermore, we looked at the correlations of the memory and non-memory section scores with age and education in the normal control group, because these variables may bias the instrument as a dementia screener.

The hypothesis of a differential sensitivity of the two CAMCOG sections as detectors of AD was tested by logistic regression analyses and by analysis of receiver operating characteristics (ROC). The dependent variable in the logistic regression analyses was the diagnosis (prevalent or incident AD *versus* normal), whereas the independent variables were the section scores, age, years of education, and gender. ROC analyses were performed to compare the areas under curve of the CAMCOG sections (Hanley & McNeil, 1983). We also compared the section scores with the total CAMCOG score, the MMSE score and age of the subjects.

RESULTS

The demographic characteristics of the subjects, their test scores at baseline, and the annual decline scores of the CAMCOG sections are shown in Table 1. Both the prevalent and the incident AD groups contained more women, were older and slightly less educated than the normal group. The annual cognitive decline was greatest in the incident AD group.

The reliabilities of the memory and non-memory sections were satisfactory and of comparable magnitude in the prevalent AD group (0·86 and 0·87, respectively; Cronbach's alpha). In the control group the reliabilities were considerably less (0·56 and 0·68, respectively). The correlations of the test scores with age and level of education were lower for the memory section than for the non-memory section and CAMCOG total score (memory section, −0·11

Table 1. *Demographic characteristics and baseline test scores of the subjects who were normal at baseline and remained normal during the following three years (controls; N = 169, from AMSTEL); subjects who were not demented at baseline, but developed Alzheimer's disease during the course of the study (incident AD; N = 25 from AMSTEL); and patients who had Alzheimer's disease at baseline (prevalent AD; N = 35 from AMSTEL; N = 120 from memory clinic)*

	Controls Mean (S.D.)	Incident AD Mean (S.D.)	Prevalent AD Mean (S.D.)
Female (%)	51·5	76·0	63·9
Age	72·7 (5·3)	79·0 (4·6)	78·5 (5·7)
Education (years)	8·0 (2·4)	7·1 (1·8)	7·6 (2·3)
MMSE score	27·2 (2·5)	23·5 (3·8)	16·9 (5·5)
CAMCOG scores*			
Memory section	31·9 (2·6)	21·9 (6·1)	15·0 (7·5)
Non-memory section	60·1 (5·8)	52·6 (7·5)	44·9 (10·7)
CAMCOG total score	91·7 (8·1)	75·4 (12·3)	60·2 (16·3)
Annual decline	(*N* = 162)	(*N* = 24)	(*N* = 116)
Memory section	0·4 (2·6)	−2·4 (4·9)	−1·8 (6·0)
Non-memory section	−1·8 (5·2)	−7·4 (4·9)	−5·5 (10·9)
CAMCOG total score	−0·3 (6·4)	−9·8 (7·2)	−7·5 (3·8)

* Memory section, sum of orientation and memory subscales; non-memory section, sum of remaining subscales; mean scores of both subsections do not add up to the total score due to missing values (1·0% missing scores in controls; 2·7% in incident AD; 4·1% in prevalent AD).

Table 2. *Results of a logistic regression analysis (method enter) with dementia status as the dependent variable, and baseline CAMCOG memory score, baseline CAMCOG non-memory score, and demographic characteristics as independent variables*

Variable	B	S.E.	Signif.	*R*
(*a*) Control *versus* AD at baseline; *N* = 164 and 143, respectively				
Age	0·079	0·029	0·007	0·11
Gender	−2·571	0·790	0·001	−0·14
Years of education	0·123	0·138	0·37	0·00
Memory section	−0·711	0·126	0·0001	−0·27
Non-memory section	0·024	0·052	0·65	0·00
Constant	14·432	3·488		
(*b*) Control *versus* incident AD; *N* = 164 and 23, respectively				
Age	0·248	0·088	0·005	0·21
Gender	−0·461	0·832	0·58	0·00
Years of education	−0·287	0·220	0·19	0·00
Memory section	−0·785	0·194	0·0001	−0·32
Non-memory section	0·197	0·087	0·02	0·15
Constant	−6·726	6·939		

B, regression weight; S.E., standard error; signif., level of significance; *R*, partial correlation between the variable concerned and dementia status, after correction for the remaining variables in the model.

with age and 0·19 with education; non-memory section, −0·16 and 0·40; total score, −0·20 and 0·37, respectively; Pearson correlations in the normal group).

The results of a logistic regression with normal cognition *versus* baseline AD as the dependent variable, and age, gender, education and the memory and non-memory sections as independent variables are shown in Table 2(*a*) (*N* = 164 and *N* = 143, respectively, had complete data). Higher age, male sex and lower scores on the memory section were related to dementia: 93·5% of subjects were correctly classified. Table 2(*b*) shows the results of a logistic regression with normal cognition *versus* incident AD (*N* = 164 and *N* = 23, respectively, had complete data) as the dependent variable, and the memory and non-memory scores and demographic characteristics as the independent variables. Again, higher age and lower scores on

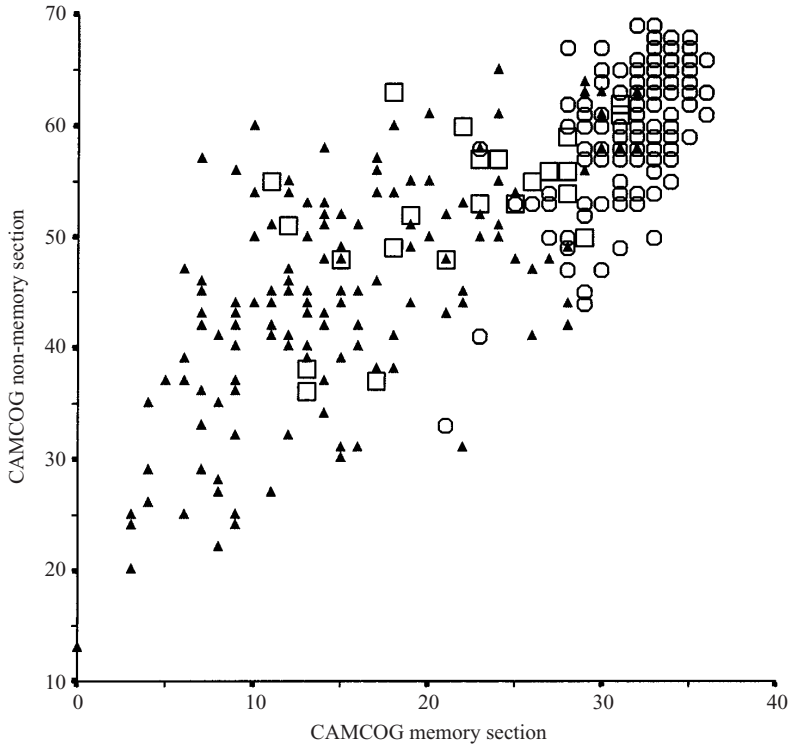

FIG. 1. Scatterplot of CAMCOG memory and non-memory section scores at baseline in the prevalent AD (▲), incident AD (□) and control (○) groups.

the memory section were predictive of incident dementia, but in this analysis a higher score on the non-memory section was also predictive. There was no significant interaction between the memory and non-memory sections: 94% of subjects were correctly classified. Fig. 1 shows a scatterplot of the memory *versus* non-memory section scores in the three groups.

Fig. 2 shows the receiver operating characteristics curves of the CAMCOG total score, and of its memory and non-memory sections with respect to the distinction between healthy controls and prevalent and incident Alzheimer's disease, respectively. As can be seen from Fig. 2, the memory section performs better than the non-memory section both with respect to the distinction between prevalent AD cases and normal controls (Fig. 2(*a*): AUCs 0·98 S.E. = 0·01 and 0·90 S.E. = 0·02, respectively; $P < 0{\cdot}001$), and with respect to the distinction between cases of incident AD and normal controls (Fig. 2(*b*): AUCs 0·95 S.E. = 0·03 and 0·81 S.E. = 0·06; $P = 0{\cdot}02$). The memory section performs slightly (but not significantly) better than the total CAMCOG score. Also, the memory section predicts incident dementia better ($P = 0{\cdot}01$) than the MMSE score (AUC 0·80 S.E. = 0·05). The AUCs of MMSE and age are equal in the case of incident AD, indicating that the MMSE score cannot predict incident AD any better than age.

Table 3 shows the score distributions in cumulative percentages of the memory and non-memory sections in normal subjects stratified into those who had only primary education (6 years or less), and those who had at least some secondary education (7 years or more). Memory section cut-points of 25/26 and 27/28 for people with primary and secondary education, respectively, are recommended to discriminate optimally between memory impaired and normal subjects. This implies a cut-point around the fifth centile. At these points the specificity of the memory section is 96%, whereas the sensitivity of the section is 76% for incident AD and 91% for prevalent AD. For

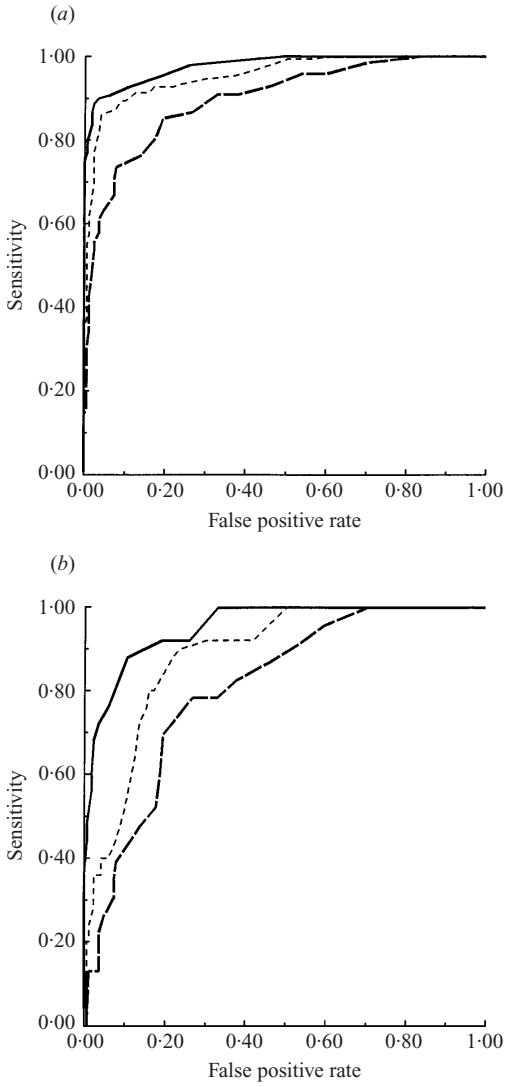

FIG. 2. Receiver operating characteristics curves of the CAMCOG total score (-----), and of its memory (——) and non-memory (— — —) sections at baseline with respect to the distinction between healthy controls ($N = 169$) and: (*a*) prevalent Alzheimer's disease ($N = 155$); (*b*) incident Alzheimer's disease ($N = 25$).

example, suppose a patient who had several years of secondary education scores 27 points on the memory section and 66 points on the non-memory section. According to Table 3 his memory score is in the 4th centile while his non-memory score is around the 85th centile. Thus, we would conclude that he is memory impaired. His CAMCOG total score is 93, which is far above the conventional cut-point (79/80).

DISCUSSION

The memory section of the CAMCOG is a better detector of Alzheimer's disease than the non-memory section. This differential sensitivity of both sections is especially found in persons who are in the early stages of the disease and therefore do not yet satisfy the diagnostic criteria of AD, but will do so within 1 to 3 years (incident AD see Fig. 2(*b*)). Similar forms of mild cognitive impairment and isolated memory loss have been found by others to signify a high risk of progression to AD (Bowen *et al.* 1997; Petersen *et al.* 1997, 1999). This is probably explained by the fact that the score on the memory subscale strongly correlates with hippocampal volume (O'Brien *et al.* 1997*a*, *b*), which decreases early in the degenerative process of AD (Jack, Jr. *et al.* 1997, 1999; Fox *et al.* 1998; Soininen & Scheltens, 1998).

Contrary to the early detection of AD, the subsequent cognitive decline of AD patients is better documented by the non-memory section of the CAMCOG. In cases with prevalent AD the decline on the non-memory section was 5·5 points per year, which is about half a standard deviation of the baseline score distribution (Table 1). Incident cases even declined a full standard deviation per year on the non-memory section. The corresponding decline on the memory section was much less notable. This fast decline of the non-memory score, which follows the decline of memory functioning, is probably explained by involvement of other cortical structures at a later moment in the disease process. At that stage of the disease, memory functions are already at a very low level, and apparently deteriorate at a slower rate. This reasoning is based at the statistical assumptions that the CAMCOG sections behave like interval scales and are free of floor effects. The latter assumption is valid (see Table 1), but the former remains to be proved. However, a similar succession of declining functions has been reported using other neuropsychological test batteries (Welsh *et al.* 1991; Locascio *et al.* 1995).

The memory section alone had a sensitivity of 76% for incident AD when specificity was set at 96%. The finding that a high score on the non-memory section also has some predictive power for incident AD is somewhat counter-intuitive.

Table 3. *Normative data (cumulative percentages) of the CAMCOG memory section for two levels of education (primary and secondary education;* N = 74 *and* 95, *respectively). Recommended cut-points of the memory section:* 25/26 *for people with primary education only;* 27/28 *for people with at least some secondary education*

Memory section			Non-memory section		
Score	Primary	Secondary	Score	Primary	Secondary
23	3	1	43	3	1
24	3	1	45	4	1
25	4	1	47	7	1
26	7	1	49	10	1
27	8	4	51	13	3
28	16	6	53	27	4
29	26	14	55	33	9
30	37	18	57	44	14
31	45	24	59	63	19
32	62	39	61	76	37
33	82	64	63	83	61
34	93	88	65	91	78
35	99	95	67	97	97
36	100	100	69	100	100

It indicates that a weak memory function does not predict AD in persons who have limited cognitive abilities in general. A low memory score in the context of a relatively good general cognition, on the contrary, strongly predicts early stages of AD (see Fig. 1). The normative data of the memory and non-memory sections that were presented in Table 3 may assist the clinician in interpreting the CAMCOG results more efficiently.

The memory section appeared to correlate only slightly with age and education. This is an advantage because it implies that the memory score can hardly be sensitive to educational and age bias. Especially the educational bias is a notorious problem of dementia screening instruments (e.g. Kittner *et al.* 1986; Uhlmann & Larson, 1991; Tombaugh & McIntyre, 1992; Schmand *et al.* 1995). This relative insensitivity to bias renders the memory section even more attractive as a stand alone measure. The MMSE, on the other hand, appeared to be incapable of predicting incident dementia; it was no more informative than the age of the subject alone.

The reliabilities of the memory and non-memory sections are of comparable magnitude, and they are sufficiently high to permit the clinician to draw conclusions on individual patients. This is not the case for all of the eight subscales as originally conceived by Roth *et al.* (1986, 1988). The shortest of these subscales, such as the perception subscale, are insufficiently reliable to be considered on their own (Lindeboom *et al.* 1993). The fact that the reliabilities are higher in patient groups than in control groups is probably due to the larger variance in the patients (see Table 1).

We conclude with a cautionary note. Busy clinicians might be tempted by this paper to use only the memory parts of the CAMCOG and to skip the rest of the items. We do not recommend this for several reasons. First, as our results on incident dementia indicated, it is important to consider the memory score in the broader context of other cognitive functions. To obtain this context it is necessary to test more than memory alone. Secondly, the order of items is fixed in such a way that intervals of a certain duration are guaranteed, after which delayed recall is tested. If one skips items, the duration of these intervals changes, which may invalidate the memory measurements. Finally, and perhaps most importantly, the goal of the CAMCOG (and of the CAMDEX) is not merely to detect AD but to screen for a range of dementias and psychiatric disorders. Thus, the complete CAMCOG may provide much more useful information than is strictly necessary for the early detection of AD. Disorders such as frontotemporal dementia and primary progressive aphasia will probably show the reverse pattern and may be detected more readily by the non-memory section. The complete CAMCOG may also aid in the differential diagnostics of

vascular dementia, Lewy body disease and stroke (Kwa *et al*. 1996; Walker *et al*. 1997; de Koning *et al*. 1998; Ballard *et al*. 1999). To skip the non-memory section is to throw out the baby with the bathwater.

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