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Validation of the Addenbrooke's Cognitive Examination for Detecting Early Alzheimer's Disease and Mild Vascular Dementia in a German Population

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Key Words
Alzheimer's disease · Vascular dementia · German population · Addenbrooke's Cognitive Examination · Mini-Mental State Examination

Abstract
We assessed the diagnostic accuracy of the German version of the Addenbrooke's Cognitive Examination (ACE) in identifying early Alzheimer's disease (AD) and mild vascular dementia (VaD) in comparison with the conventional Mini-Mental State Examination (MMSE). The study refers to 50 patients with mild dementia of AD, 26 patients with mild dementia of vascular etiology and to 54 cognitively normal subjects. The ACE and MMSE were validated against an expert diagnosis based on a comprehensive diagnostic workup. Statistical analysis was performed using the receiver operator characteristics method. The optimal cut-off score for the ACE for detecting dementia in patients with early AD was 85/86, which had a sensitivity of 93% and a specificity of 86%. The optimal cut-off for the ACE for the identification of dementia in patients with mild VaD was also 85/86 and it had a sensitivity of 93% and a specificity of 100%. The κ values imply a substantial agreement between the diagnoses made by the ACE and the MMSE. The German version of the ACE is a short and practical but accurate test battery for the identification of AD and VaD, assessing a broad range of cognitive functions and providing a wide profile of cognitive functions/dysfunctions.

Introduction

As a result of the rapidly aging population, the incidence of age-related cognitive disorders substantially and dramatically increases and constitutes a challenge to social, financial and health policy-makers. It is of great importance to make an early diagnosis of dementia in order to institute appropriate medical and social interventions. Alzheimer's disease (AD) and vascular dementia (VaD) are the most common types of dementia [1, 2]. The diagnosis of dementia is based on the clinical assessment of cognitive impairments and their impact on the activities of daily living. Screening and diagnostic tests, providing an objective measure of the cognitive performance, contribute to the detection of dementia and support diagnosis. Ideally the tests for screening dementia should be sensitive and specific enough to identify cognitive deficits, quick to administer, easy to score and they should sample a broad range of cognitive capacities and difficulty levels [3, 4].

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The Addenbrooke's Cognitive Examination (ACE) is a brief, 15- to 20-min bedside or clinic-based schedule test battery originally designed to detect dementia and to classify different kinds of dementia, particularly AD and frontotemporal dementia (FTD), without the use of specialized test equipment [5]. It incorporates the Mini-Mental State Examination (MMSE), expands memory, language and visuospatial components and adds tests of verbal fluency. The memory component evaluates episodic and semantic memory. In addition to the recall of three items from the MMSE, there is a 'name and address learning and delayed recall test'. The language component comprises naming of 12 line drawings of medium and low familiarity, comprehension of sentences, repeating words and phrases, reading regular and irregular words and writing a sentence. Frontal executive function is tested by verbal fluency in two tasks: letter fluency (generating words beginning with letter P in 1 min) and category fluency (generating names of animals in 1 min). Letter fluency relies upon phonologic processing and category fluency on semantic memory in addition to other executive processes. Visuospatial testing includes copying overlapping pentagons (from the MMSE) and a wire cube and drawing a clock face. Adding the three-dimensional wire cube copying and the clock face drawing test provides a greater scope for detecting impaired constructional abilities [6]. A maximum score of 100 is weighted as follows: orientation (10), attention (8), memory (35), verbal fluency (14), language (28) and visuospatial ability (5) [6].

The validation studies of the ACE reflected its usefulness as a guide to assist the clinician in the detection of dementia and in the differential diagnosis of the different causes of the dementia syndrome. According to the results of the validation study of the English version, which included 115 patients with dementia of different etiologies (AD, VaD, FTD, dementia with Lewy bodies, corticobasal degeneration or other miscellaneous organic syndromes) and 127 age- and education-matched controls, a cut-off of 88 points has a high sensitivity (93%) at a specificity of 71%. A cut-off score of 83 points has an optimal sensitivity (82%) and specificity (96%) [5]. Based on a study with 97 patients with AD, VaD, FTD, dementia with Lewy bodies dementia, mixed dementia, corticobasal degeneration and supranuclear palsy, and with 61 nondemented participants, the validation of the French version of the ACE in the field of detecting mild dementia revealed a sensitivity of 86.6% with a specificity of 70.5% when the cut-off score is 83 points. A cut-off score of 88 points has a sensitivity of 97.9% at a specificity of 59% [7]. Furthermore, the ACE has been proposed as a simple and effective instrument to differentiate FTD from AD. According to Mathuranath et al. [5], the verbal language/orientation memory ratio, which compares language and memory scores in the ACE, determines whether FTD or AD is more likely. Bier et al. [8], who validated the French version of the ACE, concluded however that the ACE is not effective in discriminating FTD when used as originally proposed.

Most of the screening and diagnostic tests for dementia that are available in German have been criticized for several shortcomings. For example, the 7-min screening battery solely assesses disturbances of memory [9] and is too complicated to score and to interpret [10]. Others such as the DemTect [9] fail to assess visuospatial ability, though the performance of patients in visuospatial tasks does have a strong relationship to functional abilities [11]. The MMSE is currently the most widely used single measure of cognitive function. Several studies have demonstrated the usefulness of the MMSE for distinguishing persons with dementia from cognitively normal people and it has been shown to have an acceptable reliability in identifying dementia [12–15]. Reviews of the MMSE have cited however several weaknesses including its small number of items; the quite restricted difficulty of its tasks; the narrow range of cognitive abilities assessed; ceiling effects and the limited range of possible scores of individual items [4].

The aim of the present study was to investigate the ability of the German version of the ACE to detect patients with early AD and mild VaD, being the two most common etiologies of dementia. The ACE and MMSE were validated against the clinical diagnosis based on a comprehensive diagnostic workup. We selected an optimal cut-off value for the German version of the ACE and we compared the usefulness of the ACE and the MMSE in identifying early AD and mild VaD.

Method, Study Sample and Design

Independently of one another, two members of our group translated the ACE into German with some adaptations concerning the name and address learning and delayed recall test, semantic memory test, word and sentence repetition and reading tests. The modification did not alter the number of words in the name and address learning test. The semantic memory test needed cultural adaptation. The translators discussed thoroughly the differences between the two versions and developed a final consensus version, providing the most comprehensive form of questions. Like the original one, it can be administered in 15–20 min. Thereafter, a bilingual expert not familiar with the original ACE made

at the University of Cambridge, UK, a back translation into English. The new version was very similar to the original one except for the adapted points.

The study was carried out at a university unit for neuropsychiatric disorders of the University of Rostock. The examination of the participants included a history from the patient and from an informant; medical, neurological and psychiatric examination; laboratory screening and brain imaging (CT or MRI) and the administration of the MMSE, assessing five areas of cognition (orientation, attention, episodic memory, visuospatial capacity, language). The further neuropsychological examination was based on a flexible battery, whose component tests varied according to the aims of the neuropsychological assessment of each individual clinical case, which were defined by the clinicians. The tests, that carried out, examined verbal fluency (category-fluency test), verbal (verbal learning test VLT or recalling of 10 learnt words) and non-verbal memory (non-verbal learning test NVLT, or recalling of five learnt line drawings), visual short-term memory and implicit visual-spatial learning (Corsi Block-Tapping Test), constructive abilities (Ray-Osterrieth Complex Figure), attention (test battery for the examination of attention – TAP) and abstract reasoning (similarities and differences). The diagnosis of dementia was made according to the criteria of the ICD-10 classification of mental and behavioral disorders [16]. The diagnosis of AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for the diagnosis of AD [17]. The diagnosis of VaD followed the criteria of the National Institute of Neurological Disorders and Stroke, Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [18]. For the assessment of the overall severity of dementia, we used the ICD-10 criteria (table 1). However, to ensure that patients with significant functional impairments, who might already have crossed the threshold to moderate dementia, were not included, patients with a score below 15 points on the MMSE were excluded from the study. This score on the MMSE has been found to discriminate mild from moderate dementia [19]. MMSE staging has been proven to be a good choice for tracking the earlier stages of dementia [19].

The present study refers to 50 patients with early AD, to 26 patients with mild VaD and to 54 cognitively normal subjects. The participants were 50 years old or older, German-speaking and had adequate vision and hearing, although many wore glasses and some required a hearing aid. The 54 cognitively normal subjects were spouses and friends of patients of our center or patients with clinically and neuropsychologically normal cognitive performance, who were independent in activities of daily living. Subjects with serious medical, psychiatric or neurological disorders that could affect cognitive functioning were excluded (e.g. major depression, schizophrenia, seizure disorder, head injury). Patients with mixed dementia, which was diagnosed when the clinical team believed that both AD and VaD made contributions to the dementia, were excluded from the study. Epidemiological data and MMSE scores are summarized in table 2. The ACE was completed during the neuropsychological examination of the patients. The components of the ACE that are identical to those of the MMSE were not administered twice. The study protocol was approved by the Ethics Committee of the University of Rostock.

Table 1. Definition of mild dementia according to ICD-10 criteria

A degree of memory loss sufficient to interfere with everyday activities, though not so severe as to be incompatible with independent living. The main function affected is the learning of new material. For example, the individual has difficulty in registering, storing and recalling elements in daily living, such as where belongings have been put, social arrangements, or information recently imparted by family members.
The decline in cognitive abilities, characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information, causes impaired performance in daily living, but not to a degree making the individual dependent on others. More complicated daily tasks or recreational activities cannot be undertaken.
The overall severity of the dementia is best expressed as the level of decline in memory or other cognitive abilities, whichever is the more severe (e.g. mild decline in memory and moderate decline in cognitive abilities indicate a dementia of moderate severity).

Data Analysis

Statistical analysis was performed using the statistical package for the Social Sciences (SPSS) Version 12 for Windows (SPSS Inc., Chicago, Ill., USA). Differences with regard to demographic variables, baseline MMSE scores and component and composite scores on the ACE among cognitively normal participants and patients with AD and VAD were tested using one-way analysis of variance. Pairwise comparisons were performed using the Scheffé's test. If differences in demographic variables attained statistical significance, the correlation coefficient between the participants' performance in the ACE and the demographic variable was calculated and an analysis of covariance was carried out. To determine the usefulness of the ACE and MMSE for the diagnosis of AD and VaD, a receiver operator curve (ROC) was applied to the sample. The area under the ROC curve (AUC) was used to compare the accuracy of the two tests in differentiating between patients and controls. The ROC was also used to select an optimal cut-off value, below which an individual has a very high chance of having dementia.

Results

There were no statistically significant differences in gender and years of education among AD patients, VaD patients and cognitively normal participants. Patients were significantly older than the group of the cognitively normal subjects (see table 2). As expected, the patients showed impaired performance on the ACE compared to the healthy controls (analysis of variance: d.f. = 2.127, $F = 69.84$, $p < 0.001$ (mean ± SD); AD patients: 69.3 ±

Table 2. Description of study sample

Group variable	Cognitively normal participants	VaD patients	AD patients	Inferential statistics
Number	54	26	50	
Age mean ± SD (range)	65.76 ± 9.49 (52–84)	72.23 ± 7.38 (52–85)	72.6 ± 8.1 (50–86)	One-way ANOVA d.f. = 2.127; F = 9.705; p < 0.001
Gender: female, %	48	50	46	$\chi^2 = 0.117$; d.f. = 2; p = 0.943
Education, years mean ± SD	10.18 ± 2.68	8.96 ± 2.20	9.86 ± 2.42	One-way ANOVA d.f. = 2.127; F = 2.122; p = 0.124
MMSE score mean ± SD	28.96 ± 1.36	23.31 ± 3.00	23.8 ± 3.86	One-way ANOVA d.f. = 2.127; F = 54.705; p < 0.001

Table 3. Component and composite mean (SD) scores on the ACE of cognitively normal, VaD and AD groups (mean score ± SD)

Group subtest	Cognitively normal participants	VaD patients	AD patients
Orientation	9.91 ± 0.35	7.77 ± 1.90	7.70 ± 2.23
Attention	8.13 ± 1.39	6.81 ± 1.42	6.96 ± 1.48
Memory	29.96 ± 3.18	22.62 ± 5.63	20.28 ± 7.12
Verbal fluency	10.09 ± 1.99	5.27 ± 2.39	6.50 ± 3.49
Language	27.76 ± 0.58	25.77 ± 1.96	25.54 ± 2.87
Visuospatial	4.43 ± 0.98	2.46 ± 1.42	2.46 ± 1.42
ACE (composite score)	90.04 ± 3.64	70.46 ± 10.49	69.30 ± 13.12

13.1 vs. controls: 90 ± 3.6 Scheffé's test $p < 0.001$; VaD patients: 70.5 ± 10.5 vs. controls: 90 ± 3.6 Scheffé's test $p < 0.001$). It is of note that the investigation of Pearson's correlation coefficient did not elicit a significant effect of age ($r = 0.101$, $p = 0.466$) and years of education ($r = 0.144$, $p = 0.299$) on performance on the ACE in the control group. Because the overall correlation between the ACE score and age was statistically significant ($r = -0.298$, $p = 0.001$), we controlled the group difference in the ACE for the influence of age differences. In the analysis of covariance the effect of the clinical diagnosis regarding performance in the ACE score remained highly significant ($F = 57.88$, $p < 0.001$). Table 3 summarizes the mean (± SD) individual component and composite scores on the ACE for the AD, VaD and cognitively normal groups. The VaD and AD groups had significantly lower scores than the group of cognitively normal participants on all components (Scheffé's test $p < 0.05$). The differences in scores on the ACE subtests between the VaD and AD groups did not reach statistical significance (Scheffé's test $p > 0.88$). Only the mean score of the VaD group in verbal fluency tended to be lower than that of the AD group (Scheffé's test $p = 0.184$), and the performance of the AD patients on memory subtest was lower than that of the VaD patients (Scheffé's test $p = 0.241$), though both differences failed to attain statistical significance.

The results of the ROC analyses displayed in figure 1 show that both instruments discriminated very well between AD patients and controls. The optimal cut-off score for the ACE was determined as 85/86 and for the MMSE as 27/28. 93% of the patients (sensitivity) and 86% of the cognitively normal subjects (specificity) were correctly identified by the ACE. The sensitivity of the MMSE was 96% and the specificity 66%. The AUC of the ACE was 0.960 and of the MMSE 0.941 (table 4). The diagnoses according to the ACE and to the MMSE are presented on a two-way contingency table (table 5). The κ value was 0.73, implying a substantial agreement between the two instruments in the detection of early AD (table 5).

Moreover, both instruments distinguished well between VaD patients and controls, as the ROC analyses displayed in figure 2 illustrate. At the optimal cut-off

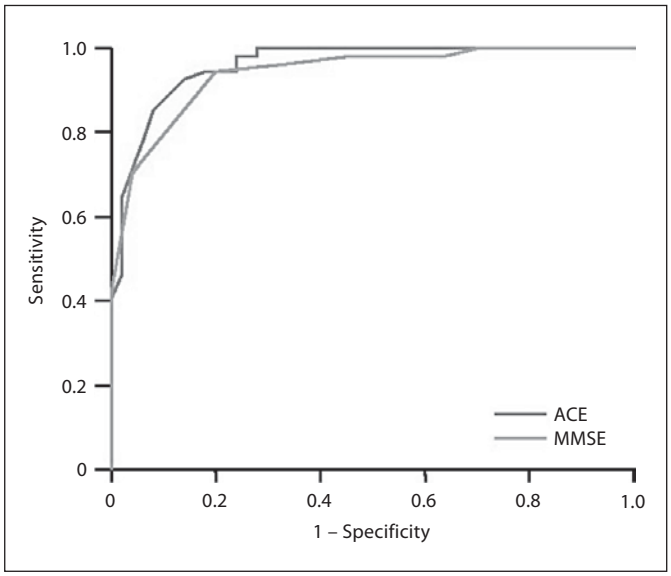

Fig. 1. ACE and MMSE ROC curves for the detection of patients with AD.

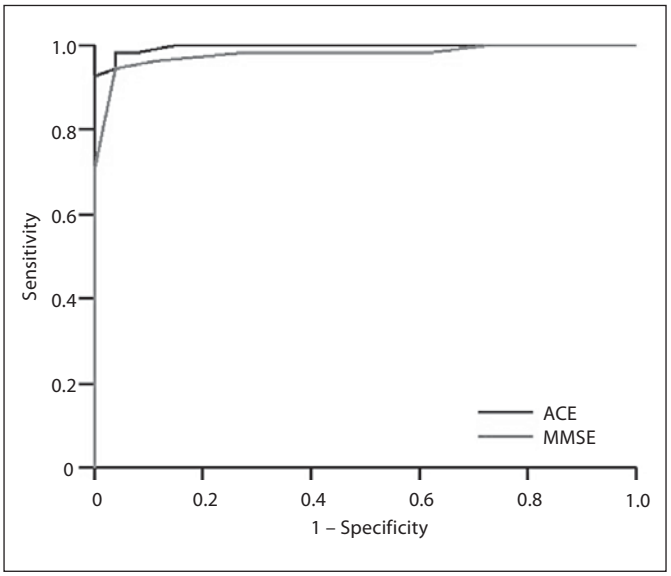

Fig. 2. ACE and MMSE ROC curves for the detection of patients with VaD.

Table 4. Optimal cut-off scores of the two tests for detecting AD

	ACE	MMSE
Optimal cut-off score	85/86	27/28
Sensitivity	0.93	0.96
Specificity	0.86	0.66
Area under the curve	0.960	0.941
p value	<0.001	<0.001

Table 5. Detecting AD: two-way contingency table of the diagnoses according to MMSE and ACE

	ACE diagnosis		All
	no dementia	dementia	
MMSE diagnosis			
No dementia	52	9	61
Dementia	5	38	43
All	57	47	104

Table 6. Optimal cut-off scores of the two tests for detecting VaD

	ACE	MMSE
Optimal cut-off score	85/86	27/28
Sensitivity	0.93	0.94
Specificity	1.00	0.80
Area under the curve	0.996	0.978
p value	<0.001	<0.001

Table 7. Detecting VaD: two-way contingency table of the diagnoses according to MMSE and ACE

	ACE diagnosis		All
	no dementia	dementia	
MMSE diagnosis			
No dementia	47	5	52
Dementia	3	25	28
All	50	30	80

score of 85/86, 93% of the patients were correctly identified by the ACE and 100% of the cognitively normal participants were correctly classified. The optimal cut-off score for the MMSE was 27/28. The sensitivity was 94% and the specificity 80%. The AUC of the ACE was 0.996 and of the MMSE 0.978 (table 6). The diagnoses according to the ACE and to the MMSE are shown in table 7. The agreement between the two tests in identifying dementia was substantial (κ value 0.78).

Discussion

This study was performed to evaluate the accuracy of the German version of the ACE in detecting early AD and mild VaD, being the two most common causes of dementia. We compared its validity with the validity of the MMSE, being a short test with widespread international usage. We compared the diagnostic accuracy of the tests not only with regard to sensitivity and specificity, but also to AUC [20, 21]. Although the assessment of diagnostic accuracy using sensitivity and specificity is commonly used, it is adequate only when the decision criterion such as the cut-off score is agreed upon an invariant. Moreover, the decision criterion is susceptible to differences in the characteristics of the study sample. In contrast, the AUC is independent of the decision criterion and less contaminated by the extraneous factors that affect the response, although it is neither perfectly reliable nor perfectly valid, since it is not free from the influences of the version or administration procedure of an instrument. Thus the AUC provides a better measure of predictive accuracy than the measurement's sensitivity and specificity [22].

According to our findings, the German ACE has an excellent accuracy in differentiating between patients with early AD and cognitively healthy participants and between mild VaD and controls. The ACE has a good sensitivity and specificity in detecting dementia. The AUC values of the ACE for identifying early AD and for detecting VaD were 0.960 and 0.996 respectively. Both values refer to an excellent accuracy [23].

The ACE assesses a broad range of cognitive abilities and provides a wide profile of cognitive functions/dysfunctions. It helps to draw a differentiated objective picture of cognitive deficits with the objective of supporting diagnosis and differential diagnosis. In our study the comparison of the mean scores of VaD and AD groups on different ACE subtests revealed a tendency to differences in memory performance and in verbal fluency performance, though the differences did not attain statistical significance. AD patients performed better in verbal fluency tasks, whereas VaD patients performed better in memory tasks. Our data are in accordance with previous findings emphasizing that for similar levels of overall cognitive decline, VaD patients are likely to have a relative preservation of memory and greater deficits in frontal functioning than AD patients [24]. However, our findings are based on a relatively small cohort size and can be wide given their sample size. Therefore, further studies with larger samples are required to replicate our findings.

The optimal cut-off score of the German version of the ACE was slightly higher than that of the English version. This could be a consequence of the translating process, since a few questions are easier to answer in German than in the original version of the test (for example: instead of repeating the sentence 'no ifs, ands or buts', German people should repeat 'keine wenn und aber').

Although the ACE was found to be a reliable instrument, there was no significant difference between the ACE and the MMSE in the ability of detecting patients with AD and VaD, as the κ values imply. In our study the MMSE achieved an unexpectedly higher capacity in distinguishing between cognitively normal participants and patients with AD and VaD (sensitivity 96 and 94% respectively) than in another study [25], although our data confirm previous findings [15, 26]. The differences could be due to the lack of standardized testing instructions and scoring criteria for the MMSE [4]. This means that different ways of testing or evaluating of the performance, or both, could lead to different results. The MMSE is actually a fairly instrument. Given the faster administration of the MMSE, it would be a choice of clinicians to use it optimally, recognizing that the MMSE is inferior to the ACE and to other tests in terms of its characteristics. In contrast to our findings, the ACE was proven to be superior to the MMSE in identifying dementia in a French- and in an English-speaking population.

Our study has several limitations. The participants were recruited at a university center. Thus our results apply only to a clinic-based patient population. The applicability and reliability of the ACE in community samples require investigation. We did not take into consideration the ethnicity of the participants. The evaluation was confined to patients with AD and VaD. Therefore we were not in the position to evaluate the effectiveness of the ACE in detecting other forms of dementia, such as FTD or dementias with Lewy bodies. The reproducibility and repeatability of the ACE were not evaluated in this study, but as the ACE assesses cognitive functions in an objective manner the rater related bias is likely to be low. The inter-rater reliability was shown to be very high correspondingly to the results of the validation study of the French ACE [7]. We used the clinical diagnosis based on a comprehensive diagnostic workup and on international diagnostic criteria, as the ultimate gold standard. Despite the high validity of the diagnostic criteria, the clinical diagnoses are not always confirmed at autopsy. Thus we should also take into account the wrong clinical assessments [27]. Therefore, the validity of the ACE could be lower than our results suggest.

The broad range of cognitive abilities, that are examined with the ACE, as well as the different difficulty levels of the questions could be of great significance in detecting mild cognitive impairment, being a transition state between normal aging and dementia [28–31]. This could be a task for future studies.

In conclusion, the German version of the ACE is an accurate test battery which constitutes a valid neuropsychological instrument for detecting cognitive impairment, assessing a broad range of cognitive functions and supporting the diagnosis of early AD and mild VaD.

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