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The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening

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SUMMARY

There is a clear need for brief, but sensitive and specific, cognitive screening instruments as evidenced by the popularity of the Addenbrooke's Cognitive Examination (ACE).

Objectives We aimed to validate an improved revision (the ACE-R) which incorporates five sub-domain scores (orientation/attention, memory, verbal fluency, language and visuo-spatial).

Methods Standard tests for evaluating dementia screening tests were applied. A total of 241 subjects participated in this study (Alzheimer's disease = 67, frontotemporal dementia = 55, dementia of Lewy Bodies = 20; mild cognitive impairment–MCI = 36; controls = 63).

Results Reliability of the ACE-R was very good (alpha coefficient = 0.8). Correlation with the Clinical Dementia Scale was significant ($r = -0.321$, $p < 0.001$). Two cut-offs were defined (88: sensitivity = 0.94, specificity = 0.89; 82: sensitivity = 0.84, specificity = 1.0). Likelihood ratios of dementia were generated for scores between 88 and 82: at a cut-off of 82 the likelihood of dementia is 100:1. A comparison of individual age and education matched groups of MCI, AD and controls placed the MCI group performance between controls and AD and revealed MCI patients to be impaired in areas other than memory (attention/orientation, verbal fluency and language).

Conclusions The ACE-R accomplishes standards of a valid dementia screening test, sensitive to early cognitive dysfunction.

KEY WORDS — Addenbrooke's Cognitive Examination; dementia; Alzheimer's disease; mild cognitive impairment

BACKGROUND

The need for brief, inexpensive and sensitive screening cognitive tests is widely acknowledged. The Addenbrooke's Cognitive Examination–ACE, (Mathuranath *et al*., 2000) was developed to provide a brief test sensitive to the early stages of dementia, and capable of differentiating subtypes of dementia including Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy and other parkinsonian syndromes (Mathuranath *et al*., 2000; Bier *et al*., 2004; Bak *et al*., 2005; Dudas *et al*., 2005; Galton *et al*., 2005; Larner, 2005). It has been used in Cambridge for over a decade, and has been adopted in several international sites on five continents, (Mathuranath *et al*., 2004; Sarasola *et al*., 2004; Bier *et al*., 2005; Newman 2005; Garcia-Caballero *et al*., 2006). Our extensive clinical and research experience has highlighted strengths and weaknesses, which has led us to modify the test.

Design changes were implemented to make the test easier to administer. Content modifications were also made in order to facilitate cross-cultural usage and translation, and also to hopefully increase sensitivity. For instance, the naming component of the old ACE suffered ceiling effects, while the visuospatial component was very limited. Another innovation was the creation of three different alternative

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versions–A, B and C, with different stimuli for the name and address recall, in order to prevent recalling from previous clinic visits. Finally, the individual 26 components were combined to produce five sub-scores, each one representing a specific cognitive domain and contributing fairly equally to the total score.

The first aim in this study was to demonstrate that these changes could improve sensitivity and specificity for detecting dementia based upon likelihood ratios that could fill the gap between the two currently used cut-off scores. As well as providing more detailed normative data for the ACE-R total score, we aimed to provide normative sub-scale scores. Given the importance of early detection in dementia we aimed to define the profile of performance on the ACE-R in patients with mild cognitive impairment (MCI). Finally, we aimed to analyse its properties in order to validate the ACE-R for clinical use.

METHODS

The instrument

The ACE-R takes between 12 and 20 min (average 16) to administer and score in a clinical setting. It contains 5 sub-scores, each one representing one cognitive domain: attention/orientation (18 points), memory (26 points), fluency (14 points), language (26 points) and visuospatial (16 points). ACE-R maximum score is 100, composed by the addition of the all domains.

Modifications. The attention/orientation components were not modified. In the memory domain several changes were made: the name and address test scoring was modified so that only the final trial contributed to the sub-score, and a recognition component was added. Three versions of the name and address recall and recognition test were designed. Retrograde memory questions were simplified as controls had difficulty answering previous ones, which were also not easily translated. These changes reduced the memory domain weight in the final score, which allowed other domains to have a more balanced contribution to the final score. The fluency tests had their scaling scoring revised. In the language domain, comprehension of commands was removed, new semantic comprehension questions were added, the pictures for the naming test were changed to reduce ceiling effects and reading of regular words was excluded. Adding new tasks of perceptual abilities, counting of dot arrays and identification of fragmented letters augmented the visuospatial domain. The scoring of the clock face drawing was expanded (0–5) to reflect a better range of abilities.

These changes underwent numerous cycles of interactive modification after piloting in various patients before the final version of the ACE-R was given to the patients and controls reported here.

Participants

A total of 241 subjects participated, consisting of three groups: a dementia group (Alzheimer's disease = 67, frontotemporal dementia = 55, dementia of Lewy Bodies = 20), a mild cognitive impairment–MCI group ($n = 36$) and a control group ($n = 63$).

Dementia group

This group comprised of consecutive patients assessed in one of our three cognitive clinics at Addenbrooke's Hospital (Memory Clinic, Early Onset Dementia Clinic and Drug monitoring Clinic) between May 2004 and March 2005. Subjects were included in the study if: (1) they could perform the assessment; (2) had a carer; (3) the Clinical Dementia Rating (Morris, 1997) had been completed within 90 days. They were excluded if presenting: (1) a significant psychiatric disorder (depression, schizophrenia); (2) evidence of a mixed concomitant dementia processes (e.g. AD and vascular dementia); and (3) causes of cognitive impairment other than neurodegenerative disease (e.g. epilepsy, head injury, alcoholism). Criteria used for selecting patients for the study were similar to those used for the validation of the first version (Mathuranath *et al*., 2000). For classifying subgroups of dementia we used the following criteria: National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association–NINCDS-ADRDA (McKhann *et al*., 1984) and the FTD consensus criteria (Neary *et al*., 1998). FTD group here comprises the three variants–Frontal variant FTD, Semantic Dementia and Progressive non-fluent Aphasia. Dementia with Lewy bodies (DLB) was diagnosed in accordance with the McKeith *et al*. criteria (2000).

MCI group

Patients met widely accepted criteria for amnestic MCI, notably: (1) memory complaint, corroborated by an informant; (2) abnormal memory function, documented by a delayed recall of one paragraph from the Logical Memory II subtest of the Wechsler Memory Scale Revised; (3) normal general cognitive

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function, as determined by a clinician's judgement based on a structured interview with the patient and an informant and a Mini-Mental State Examination (MMSE) score greater than or equal to 24; (4) no or minimal impairment in activities of daily living (ADLs), as determined by a clinical interview with the patient and an informant; and (5) not sufficiently impaired, cognitively and functionally, to meet National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for AD (Grundman *et al*., 2004).

Control group

Controls ($n = 63$) were recruited from the volunteer panel at the Medical Research Council, Brain Sciences Unit ($n = 43$) or were spouses of patients attending the clinics ($n = 18$) (see Table 1).

Statistical analyses

Statistical analyses were either performed using the Statistical Package for the Social Sciences 11 for Windows (SPSS Inc., Chicago, IL USA) or Excel for Windows XP (Microsoft, USA).

Demographics and ACE-R sub-scores were compared across different groups' means using independent *t*-tests, applying Levene's test for equality of variance and Bonferroni corrections.

Reliability was calculated using the Cronbach alpha coefficient (McDowell and Newell, 1996). Concurrent and convergent validity was calculated using a two-tailed Spearman correlation between ACE-R final scores and CDR scores (McDowell and Newell, 1996; Streiner, 2003b). Sensitivity, specificity, positive predictive values and negative predictive values were calculated using discriminant analyses. Likelihood ratios of probability of dementia were based on the above discriminant analyses' results (Sackett *et al*., 1991). ACE-R comparisons with ACE were performed using simple *t*-tests.

Descriptive analysis of MCI, AD and control performance was generated by analysis of variance and *t*-tests.

RESULTS

Reliability and validity

The alpha coefficient of the ACE-R was 0.80, which is considered very good (McDowell and Newell, 1996; Streiner, 2003a). In order to assess concurrent and convergent validity, the ACE-R was compared to the CDR. Spearman rho correlation coefficient between ACE-R and CDR was significant (−0.321, two tailed, $p < 0.000$). The negative value reflects the fact that as CDR scores increase, ACE-R total scores decrease.

Table 1. Comparison of demographic data, MMSE, ACE-R total and sub-scores in control, MCI and dementia groups ($n = 241$, standard deviation in parenthesis)

	Control $n = 63$	MCI $n = 36$	Dementia $n = 142$	Dementia vs Control p values	Dementia vs MCI p values	MCI vs Control p values
Gender, male	28	17	99			
Age	64.4 (5.7)	68.8 (9)	65.7 (8)	n.s.	n.s.	n.s.
Education, years	12.7 (2.1)	12.8 (3.4)	11.9 (2.7)	n.s.	n.s.	n.s.
MMSE	28.8 (1.3)	27.7 (1.5)	22.8 (4.3)	**	**	**
ACE-R total score 100 points maximum	93.7 (4.3)	84.2 (7.3)	65.4 (15.9)	**	**	**
Attention & Orientation 18 points maximum	17.7 (0.5)	17.2 (1)	14.4 (3.2)	**	**	n.s.
Memory 26 points maximum	23.4 (2.7)	17.8 (4.7)	12.4 (5.8)	**	**	**
Fluency 14 points maximum	11.9 (1.7)	10.1 (2.4)	6 (3.5)	**	**	**
Language 26 points maximum	25.1 (1.5)	23.9 (1.6)	20 (5.6)	**	**	*
Visuospatial 16 points maximum	15.7 (0.7)	14.9 (2)	12.6 (3.5)	**	**	n.s.

n.s = non significant.
*$p < 0.005$. Levene's test for equality of variance; Bonferroni corrected.
**$p < 0.001$.

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Table 2. Lower limit of normal (cut-off scores) for total ACE-R and sub-scores according to age (50–59, 60–69, 70–75), showing control mean minus two standard deviations

Age range	Education (years)	Total ACE-R score	Attention/Orientation	Memory	Fluency	Language	Visuospatial
50–59	12.7	86	17	18	9	24	15
60–69	12.9	85	17	19	8	21	14
70–75	12.1	84	16	17	9	22	14

Normative data

Control data were used to generate normative scores for the total ACE-R and domain sub-scores based upon the mean minus two standard deviations for three age bands (50–59; 60–69; 70–75). As shown in Table 2, there was relatively little effect of age. A mixed ANOVA revealed that there was no main effect of age range ($F_{(5,300)} = 1.449$, $p = 0.243$), and the age range by ACE-R sub-scores interaction was not significant ($F_{(5,300)} = 1.659$; $p = 0.090$). The lower limit of normal, as judged by the controls' total score minus two standard deviations, decreased by one point only from the younger to the older age group. Attention/Orientation score decreased one point for the older group in comparison to the other two. Memory score increased one point from the younger to the next age range group, and then dropped two points for the oldest group. Fluency score was the same for the younger and older groups, varying one point lower for the mid range age group. Visuospatial score decreased one point for the two older groups.

Diagnostic interpretation

Cut-off scores: two total ACE-R cut-offs (88 and 82) were identified based on the calculations of sensitivity, specificity and positive predictive values (PPV) at different prevalence rates. As shown in Table 3, the PPV rose to 1.00 at the lower cut-off regardless of the estimated prevalence rate. The higher cut-off (88) had a better sensitivity (94%) but lower PPV especially with low prevalence rates.

Likelihood ratios were calculated for several cut-off scores based on the sensitivity and specificity analyses. The likelihood ratio contrasts the proportions of patients with and without dementia and reflects the odds that a given score is likely to come from a patient with dementia (Sackett *et al*., 1991). As shown in Table 4, with descending cut-offs from 88 to 82, the likelihood ration rate rose from 8.4 to 100, which means that a score of 82 is 100 times more likely to come from a patient with dementia than one without.

ACE-R versus ACE

A direct comparison of controls' performance in the old and new ACE is shown in Figure 1a. Sub-score analyses revealed significantly better performance on the memory and visuospatial domains ($t = 3.071$, $df = 44$, $p < 0.05$; $t = 3.789$, $df = 43$, $p < 0.001$, respectively) and significant difference in the total score on the ACE-R ($t = 2.115$, $df = 45$, $p = 0.04$). For the dementia group (Figure 1b), there were significant

Table 4. Likelihood ratios for probability of dementia at various ACE-R cut-off scores

ACE-R score	Likelihood ratio of dementia
88	8.43
87	11.5
86	14.2
85	18.9
84	27.6
83	52.5
82	100

Table 3. Sensitivity, Specificity and Positive Predictive Values (PPV) at different prevalence rates of two cut-off total ACE-R scores. Values in parentheses represent the respective Negative Predictive Value

ACE-R cut off	Dementia		PPV at different prevalence rates			
	Sensitivity	Specificity	5%	10%	20%	40%
88	0.94	0.89	0.31 (1.0)	0.48	0.68	0.85 (1.0)
82	0.84	1.00	1.0 (0.96)	1.0	1.0	1.0 (0.90)

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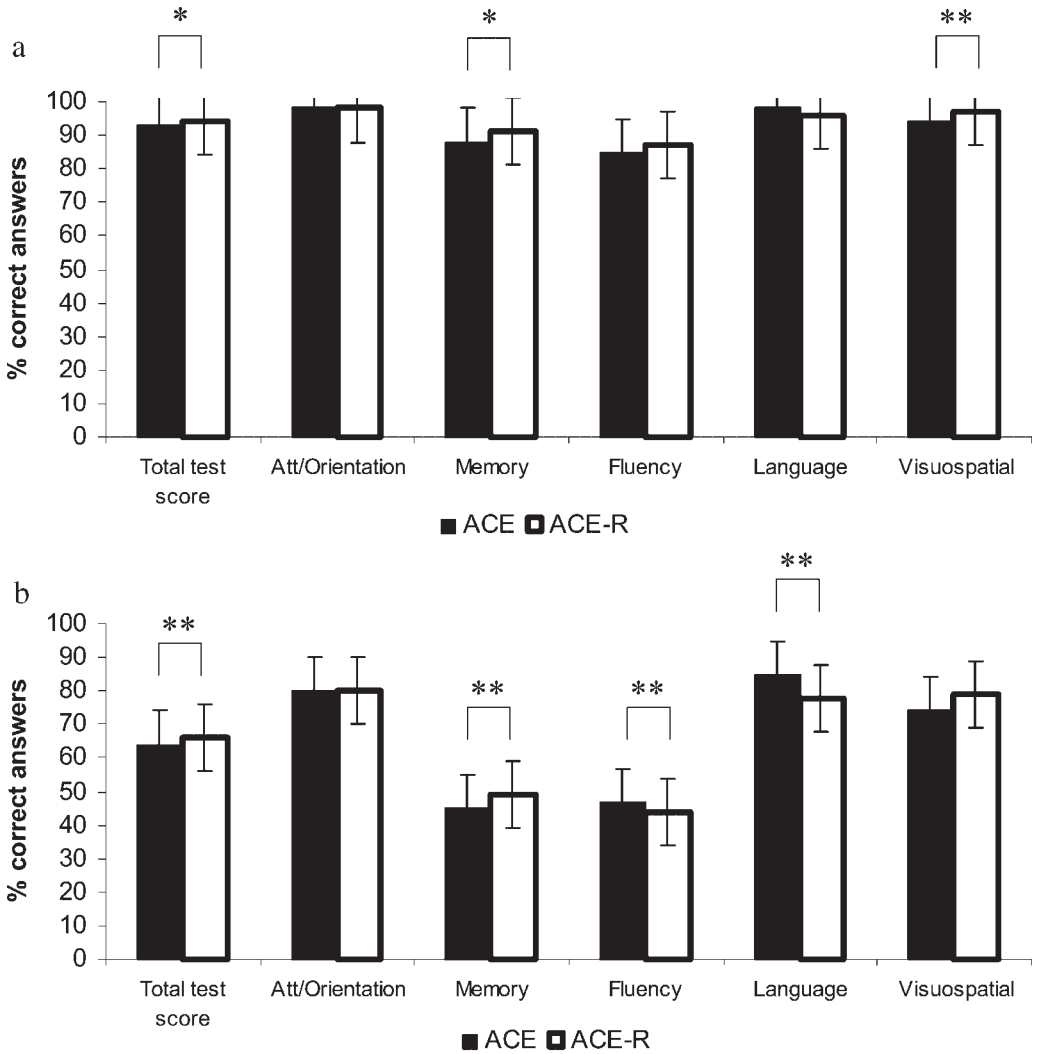

Figure 1. a: Comparison of performance on ACE and ACE-R in controls ($n = 63$). $^{**}p < 0.001$, $^{*}p < 0.05$. b: Comparison of performance on ACE and ACE-R in dementia patients ($n = 142$). $^{**}p < 0.001$, $^{*}p < 0.05$

differences in total and in each domain score except for the visuospatial domain (total score $t = 6.528$, df = 136, $p < 0.001$; memory $t = 4.534$, df = 134, $p < 0.001$; fluency $t = 3.932$, df = 134, $p < 0.001$). Higher scores were found on the total ACE-R, memory and visuospatial, but lower scores for fluency and language.

The VLOM ratio

The VLOM ratio sub-score was designed to differentiate AD from FTD patients. It comprises the ratio of the scores of verbal fluency plus language to orientation plus name and address delayed recall memory (V + L)/(O + M). For this analysis we included the dementia patients ($n = 88$) who had a CDR < or = 1 (AD = 49, FTD = 21, DLB = 12). We applied the same criteria for calculating the VLOM ratio to distinguish AD from FTD, which were published on the first ACE paper (Mathuranath *et al.*, 2000), and found that sensitivity and specificity values were virtually identical. Figure 2 shows that a VLOM ratio of < 2.2 could differentiate FTD from non-FTD (sensitivity of 58% and specificity of 95%) and a VLOM ratio of > 3.2 could differentiate AD from non-AD (sensitivity of 74% and specificity of 85%).

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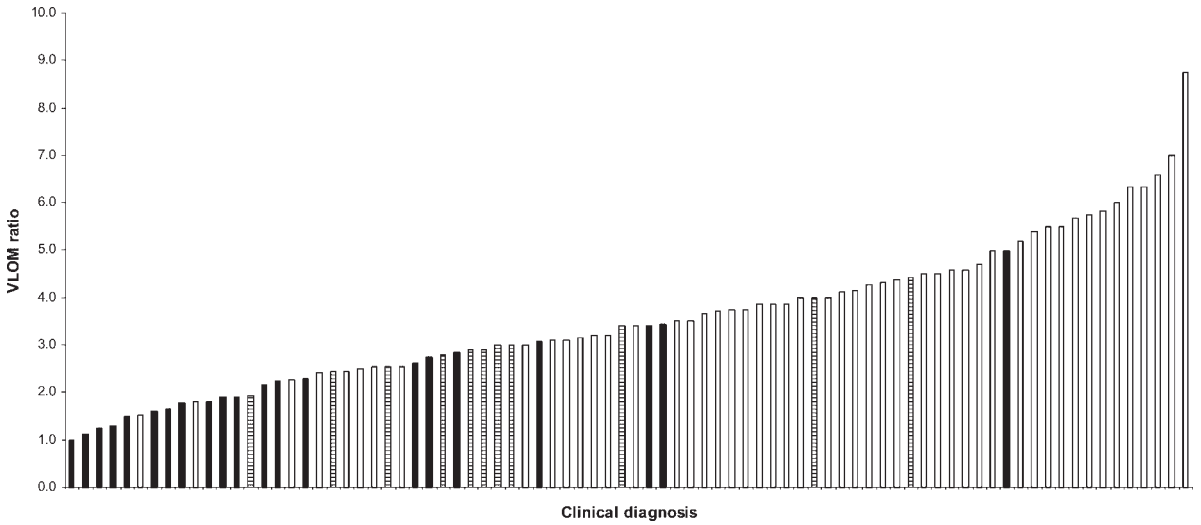

Figure 2. Bar plot of the VLOM ratio ([verbal fluency + language]/[orientation + memory]) against clinical diagnosis (black = FTD, white = AD, striped = DLB)

AD, MCI and controls: performance on the ACE-R

We took subgroups of AD ($n = 23$) and MCI ($n = 23$) patients individually matched to a control group ($n = 23$) for age and education. A mixed ANOVA using the three diagnostic groups and the five ACE-R domains revealed a main effect of diagnosis ($F_{(2,66)} = 43.168$, $p < 0.001$) as well as an interaction between diagnosis and domains (Greenhouse-Geisser corrected, $F_{(2,66)} = 34.965$, $p < 0.001$). Subsequent t-tests demonstrated that the MCI group differed significantly from controls in terms of ACE-R final score ($t = 4.462$, df = 44, $p < 0.001$), attention/orientation ($t = 2.727$, df = 44, $p < 0.05$) memory ($t = 4.364$, df = 44, $p < 0.001$), fluency ($t = 2.347$, df = 44, $p < 0.05$), and language ($t = 2.730$, df = 44, $p < 0.05$). Comparing MCI and AD, *t*-tests revealed significant differences between ACE-R total score ($t = 5.313$, df = 44, $p < 0.001$), attention/orientation ($t = 5.813$, df = 44, $p < 0.001$), memory ($t = 5.046$, df = 44, $p < 0.001$), fluency ($t = 2.650$, df = 44, $p < 0.05$), language ($t = 2.591$, df = 44, $p < 0.05$), and visuospatial ($t = 2.813$, df = 44, $p < 0.05$) (see Table 5).

DISCUSSION

We hoped that changes in the ACE-R would result in better sensitivity and specificity. The most striking finding was the positive predictive value, which was 100% at the lower cut-off of 82 for a range of prevalence rates. This suggests that the ACE-R could be used to diagnose dementia in settings with very different expected rates of dementia. This finding is explicable in the light of the changes in that insensitive

Table 5. Comparison of performance on the ACE-R (total and sub-scores) in controls, MCI and AD ($n = 23$ per group). ACE-R sub-scores shown as percentage since totals vary

	Controls ($n = 23$)	MCI ($n = 23$)	AD ($n = 23$)	Controls vs MCI *p*-values	MCI vs AD *p*-values
ACE-R total score	92.6	84.2	66.4	**	**
Attention/Orientation(%)	98.6	95.4	75.4	*	**
Memory (%)	88	68.6	42.5	**	**
Fluency (%)	81.7	71.1	53.4	*	*
Language (%)	96.7	92.1	84.3	*	*
Visuospatial (%)	97	92.9	76.6	n.s.	*

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components (e.g. early repetition trials of the name and address, reading of regular words and sentence comprehension) were excluded from the revised version. Modifications on the naming test were made to present pictures with lower familiarity than the first version (Snodgrass and Vanderwart, 1980). The expansion of the visuospatial domain might have also contributed to better sensitivity and specificity.

The table of likelihood ratio offers an extra tool for a clinician when assessing patients with possible dementia. Table 4 shows that the likelihood of a given score coming from a 'case' rises from 8 to 100 with cut-offs from 88 to 82.

The VLOM ratio analyses of the ACE-R replicated the original results very closely (Mathuranath *et al*., 2000), which is not surprising since the elements that contribute to the ratio were changed little in the revised version. Although some studies have reported very similar findings (Sarasola *et al*., 2004; Garcia-Caballero *et al*., 2006), others have not supported the use of the VLOM ratio (Bier *et al*., 2004; Larner, 2005). This variance is likely to reflect the use of different criteria across the studies (number of patients; level of impairment according to the CDR-R; ACE-R cut-off, and FTD criteria). We suggest that the VLOM ratio does have clinical utility although it should be noted that the specificity is much better than the sensitivity.

An important additional facet of the new study is the availability of cut-off scores for the five sub-domains of the ACE-R. This allows direct comparison of a subject's score in a certain domain against normal controls performance, thus providing more parameters for a clinical judgement.

Comparison between MCI and controls revealed interesting findings. Memory impairment was a key feature, as expected. This finding seems to agree with evidence that MCI patients have memory testing performance that place this group in between normal ageing people and AD patients. (Petersen *et al*., 1999; Bozoki *et al*., 2001; De Jager *et al*., 2003; Grundman *et al*., 2004). In addition, significant impairment was also found on attention/orientation, fluency and language tests. These latter findings suggest that the ACE-R is sensitive to mild cases of dementia, such as MCI patients, and moreover shows a multi-domain impairment of MCI patients as a group. Follow up of the MCI group is needed to explore the usefulness of the ACE-R in predicting convertors to dementia, but experience with the old ACE suggests that a cut-off of 80 distinguishes very well between convertors and non-convertors (Galton *et al*., 2005) and that it compares favourably with standard neuropsychological tests.

KEY POINTS

- The ACE-R is a brief, sensitive and specific test battery to detect early cognitive dysfunction.
- The VLOM ratio of the ACE-R can be used to differentiate between AD and FTD.
- Copies of the ACE-R may be requested without charge from the corresponding author.

The ACE-R seems to accomplish satisfactory standards in terms of reliability and validity based upon standard criteria for evaluating a dementia screening test (Gifford and Cummings, 1999). We also assessed common sources of bias that affect sensitivity and specificity (Gifford and Cummings, 1999). Spectrum bias was avoided by including in the study patients with different dementia syndromes and with a broad range of impairment (MMSE scores ranging from 9 to 30). Blinding of ACE-R administrators from the patients' CDR scores prevented review bias.

There are, however, clear limitations. Our patient group was relatively young, which reflects the bias of the Cambridge clinics. It is not clear whether these findings would apply equally to an older patient group. In addition, our patient group comprised only cortical dementia diagnosis, which limits the applicability of these results in patient groups with subcortical disorders. The original version of the ACE has, however, been shown to be sensitive to cognitive dysfunction found in the atypical parkinsonian syndromes, e.g. progressive supranuclear palsy and corticobasal degeneration (Bak *et al.*, 2005).

This study was developed within a university hospital setting, therefore reflecting a very specialised population of patients and professionals involved. A further step should be the evaluation of the ACE-R in community samples, where the prevalence of dementia is going to differ considerably from a specialised service. We omitted test-retest reliability because the study was done in parallel with clinical appointments or home visits, which meant that setting up this extra reliability check would limit significantly the number of patients involved in the study.

Clinical and research settings have similar demands but typically have very different resources. Research settings are often better staffed which allows more time for assessment, whereas clinical ones need inexpensive, rapid and practical tests, which can be given without specialist training. Detailed batteries are

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time consuming and require trained testers; on the other hand, screening tests tend to be too short and only able to discriminate between demented and non-demented patients, lacking sensitivity to detect mild cases and usually not able to make any differentiation between dementia diagnoses. A test that can be used in a clinical setting without losing the psychometric characteristics bridges the clinical and research realms. It seems that the ACE-R can satisfy both worlds, as reflected by widespread interest in over 150 clinical and research centres in the UK and worldwide (Portugal, Spain, France, Belgium, Holland, Italy, Germany, Austria, Switzerland, Hungary, Czech Republic, Romania, Israel, United States, Canada, Argentina, Brazil, South Africa, India, Sri Lanka, Australia and New Zealand).

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Copies of the ACE-R may be obtained without charge from the corresponding author.

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