

Enhanced cued recall has a high utility as a screening test in the diagnosis of Alzheimer's disease and mild cognitive impairment in Turkish people

Esen Saka^{a,*}, Ebru Mihci^b, M. Akif Topcuoglu^a, Sevin Balkan^b

^a Department of Neurology, Faculty of Medicine, Hacettepe University, 06100 Ankara, Turkey

^b Department of Neurology, Faculty of Medicine, Akdeniz University, 07059 Antalya, Turkey

Abstract

Enhanced cued recall (ECR) is highly sensitive and specific in discrimination of demented from non-demented elderly persons. The nature of the test promises that it can be applicable to subjects in different cultures and education level. We studied the utility of the test in a Turkish population. Eighty consecutive cases with dementia or mild cognitive impairment (MCI) and 33 elderly controls were studied. The utility of ECR was high in discriminating dementia from controls (area under curve (AUC) of the ROC curve: 0.907 (95% confidence interval (CI): 0.830–0.953 for total recall), Alzheimer's disease from controls (AUC: 0.990 (95%CI: 0.934–0.998 for total recall)) and moderate (AUC: 0.625 (95%CI: 0.545–0.812 for third free recall)) in discriminating MCI from controls. Education did not affect the utility of the test. We conclude that ECR is a valuable test in assessment of elderly Turkish patients with a complaint of memory impairment.

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Keywords: Alzheimer's disease; Dementia; Enhanced cued recall; Memory; Mild cognitive impairment; Screening test

1. Introduction

In the absence of an ideal biomarker for the diagnosis of Alzheimer's disease and other degenerative dementias, neuropsychologic evaluation remains the most important diagnostic utility, especially in early stages of the diseases. Several screening tools are in use to aid the clinicians for diagnosis of dementia and for assessing the progression of the disease. The ideal screening instruments are needed to be short, easy to use, able to test more than one cognitive function and unaffected by the education, language and cultural differences (Parker & Philp, 2004). Mini mental state examination (MMSE) meets most of these requirements, and is standardized and widely used throughout the world including Turkey (Güngen, Ertan, Eker, Yaşar, & Engin, 2002). One of the drawbacks of MMSE as a screening tool is its insufficiency of assessing the full extent of the memory impairment. The other is its insufficiency to test cognitive functions in the illiterate population. Alzheimer's disease is the most prevalent form of the dementia, in which the impairment of recent memory is the key feature. Therefore, assessment of memory impairment is important not only for the diagnoses of the disease, but also for evaluation of the disease progression and response to treatment. For these purposes, a number of verbal or visual memory tests are developed, and some of them have currently been in wide use

* Corresponding author. Tel.: +90 312 3051809; fax: +90 312 3093451.

E-mail address: esensaka@hacettepe.edu.tr (E. Saka).

(Spreeen & Strauss, 1998). However, most of them take time to administer and highly demanding. These tests can also be difficult and frustrating for especially uneducated, elderly, and memory-impaired patients.

In contrast to most of others, enhanced cued recall test (ECR) seems to be appropriate to administer in elderly patients with cognitive slowing since the test introduces some mnemonic strategies to enhance the storage and the retrieval of information (Grober, Buschke, Crystal, Bang, & Dresner, 1988). ECR has been used either as a separate test or as a screening test that incorporated its adapted form (7 min test) (Solomon et al., 1998). These studies have demonstrated its high sensitivity and specificity in discrimination of demented from non-demented elderly persons (Boeve et al., 2003; Gebner et al., 1997; Holzer & Warshaw, 2000; Meulen et al., 2004; Solomon et al., 1998; Traykov et al., 2005). The test scores are also predictive in future development of dementia (Grober, Lipton, Hall, & Crystal, 2000).

In this study, we aim to extend findings summarized above and to explore the utility of the ECR test in discrimination of the patients with dementia, AD and MCI as well as elderly controls in a Turkish population. We predicted that the test would aid us to differentiate AD, MCI cases and elderly controls with a high sensitivity and specificity. We also predicted that the utility would be valid for both educated and uneducated group. We think that proving these hypotheses will help to show that the test is applicable to the subjects in a variety of education and cultural level.

2. Methods

2.1. Patients

One hundred thirty seven consecutive patients referred to dementia outpatient clinics of Akdeniz University Hospitals in the period of July 2004–July 2005 with the complaint of forgetfulness were evaluated. A medical history was obtained from each subject, including presence of cerebrovascular disorders and other active neurologic or psychiatric disorders, and systemic illnesses. A detailed neurologic examination was performed. Complete blood count, biochemistry for hepatic and renal functions, thyroid function tests and Vitamin B12 level were studied. Brain imaging with magnetic resonance imaging was performed in all. A screening of general cognitive function was carried out by MMSE. Geriatric depression scale (GDS) was introduced. Detailed neuropsychological testing, including digit span, reciting months forwards and backwards, trial A and B, Rey auditory verbal learning test, clock drawing, verbal fluency, category fluency, Boston naming test were administered to eligible patients (according to their education level and cognitive functioning). Diagnosis of dementia was performed according to DSM-IV criteria. MMSE of patients with dementia were 24 or less. Sixty-two cases of dementia met the criteria for “probable Alzheimer’s disease” (AD) according to National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association Work Group (McKhann et al., 1984). Thirty-two cases were classified as either vascular dementia or other degenerative dementias according to established diagnostic criterias (McKeith et al., 1996; Neary et al., 1998; Roman et al., 1993).

Patients, who did not met DSM-IV criteria of dementia and were independent in activities of daily living as assessed through the Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969), were further evaluated for the objective evidences of memory impairment. Eighteen cases demonstrated impairment of memory and met the Mayo Clinic Criteria for mild cognitive impairment (MCI) (Peterson et al., 2001) and are classified as amnesic MCI.

2.2. Controls

Spouses of the patients evaluated in the dementia outpatient clinics have constituted the control group. They were asked for the complaint of memory impairment. Spouses claimed to be independent in the activities of daily living and without a complaint of forgetfulness were further evaluated. The evaluation included a detailed medical history and neurologic examination, MMSE, and GDS. Cases with a history of psychiatric or neurological disorder were excluded.

2.3. Enhanced cued recall test (ECR)

In all patients and controls, enhanced cued recall test was administered following MMSE and GDS in a fixed order. This test was originally produced by Grober et al. (1988), adapted and incorporated to 7 min test by Solomon et al.

(1998). The same items of the test were presented and the names of the items were translated to the Turkish. The translated form of the test was administered according to procedure described by Grober et al. (1988). ECR was not used in the diagnostic process to avoid criterion contamination.

In this test, black and white drawings of 16 items were presented to subjects in 4 different cards (4 items in each card). First, card 1 was presented. While subject was looking the card, examiner verbally expressed the semantic cue to every item and asked subject to name the matching drawing (e.g., one of the items of the card 1 is grapes. Examiner asks “there is a fruit on this card; what is it”. If the patient says “grapes”, examiner moves to the next item. If the patient does not say “grapes”, examiner says “those are grapes” and then moves to the next item). After all four items of the card were identified correctly, the card was removed. Then, immediate recall of those four items was tested by presenting the same semantic cues of each item (e.g., the examiner asks “I showed you a fruit; what was it”). If the subject successfully recalled all of the items, examiner presented the second card containing the next set of four items; but if the subject could not recall any one of the items, the card 1 was presented once more. Every item of the card was re-studied and immediate recall of the items of card 1 was tested again. The card was not presented as a third time, even if the patient still cannot recall any one of the items. In this case, second card containing the next set of four items was presented. The same testing protocol was followed for card 2, 3, and 4.

After four of the cards were studied, three recall trials were presented. Either counting the months forward and backward or clock drawing test separated recall trials. In each recall trial, first the subjects were asked to recall as many items as possible without providing them a semantic cue (free recall), and secondly the specific semantic (category) cue was given to help recall of the remaining items (cued recall). Total recall was the sum of free and cued recall items.

2.4. Statistical methods

All values were displayed as “mean \pm standard deviation” and “percentages” as appropriate. Mann–Whitney *U* and ANOVA with post hoc Tukey tests were appropriately used to compare groups in terms of numerical variables. Chi-square test was used for comparison of the categorical variables. *p*-Value lower than 0.05 was set statistically significance level.

Receiver Operator Characteristics (ROC) curves were generated to test diagnostic yield of the ECR test to differentiate demented from non-demented subjects; AD from MCI; AD from controls; and MCI from controls. ROC curves represent a graph that plots true positive rate (sensitivity) versus the false positive rate (100 – specificity) at various cut-off points. Area under curve (AUC) and its 95% confidence intervals (95% CI) and standard error for ROC curves were calculated. Sensitivity (and its 95% CIs), specificity (and its 95% CIs) and positive and negative likelihood ratios (+LR and –LR, respectively) for the various cut-offs were determined. Finally, based on the optimal sensitivity and specificity values, the cut-off points were determined (Hanley & McNeil, 1982). *t*-Test was used for pairwise comparison of the ROC curves.

Ratio between the proportion of negative tests among those with the disease to the proportion of negative tests among those without disease is known as –LR, which is calculated with the formula of “(1 – sensitivity)/specificity”. The ratio between the proportion of a positive test result given the presence of the disease and the proportion of a positive test result given the absence of the disease is known as +LR, which is equivalent to “sensitivity/(1 – specificity)”. LRs are most useful when their values are farthest away from 1. Good tests have +LR value between 5 and 10 and –LR less than 0.1–0.2. We have chosen LRs instead of negative and positive predictive values because of their independence of the prevalence of the disease and applicability under varying clinical circumstances (Jaeschke, Guyatt, & Sackett, 1994a; Jaeschke, Guyatt, & Sackett, 1994b).

Correlation between education status and MMSE and total ECR scores were searched with Pearson’s test. 95% CI of the regression coefficient was calculated. Correlation between scores of MMSE and ECR were investigated with the Passing–Bablok test. For this analysis, MMSE scores were plotted against total ECR scores; 95% CIs of intercept *A* and slope *B* were calculated. *A* is considered as significant indicating both methods differ at least by a constant amount when its CI does not contain the value 0. *B* is considered as significant indicating presence of at least a proportional difference between the tests when its CIs does not contain 1. Following these analyses, Cusum test for linearity was performed (Passing & Bablok, 1983).

SPSS[®] 13.0 and MedCalc[®] statistical package-programs were used for the analyses.

Table 1
Demographic features

	MCI	AD	Non-AD	Control
<i>n</i>	18	45	17	33
Gender (female/male)	10/8	24/21	9/8	13/20
Age	69.4 ± 8.3	73.8 ± 6.1	65.2 ± 10.0*	72.7 ± 6.7
Education years	8.4 ± 5.0	6.7 ± 4.9	7.7 ± 4.9	8.4 ± 4.9

Notes: MCI, mild cognitive impairment; AD, probable Alzheimer's disease.

* Less than AD and controls.

3. Results

Among 94 cases with dementia, 62 were able to perform ECR test (45 patients with AD and 17 with non-AD dementia). All of the patients unable to complete the test had MMSE score of 11 or less. Additionally 4 patients with decreased visual acuity intervening test performance were not able to perform the test. All of the MCI patients ($n = 18$) and controls ($n = 33$) successfully completed the ECR test. Demographic features of the groups are summarized in Table 1. The mean age was marginally lower in MCI and non-AD dementia groups in comparison with those with AD and the controls. The education status was comparable across the groups.

The mean scores of MMSE and ECR (and its sub-items) in four groups were summarized in Table 2. Total recall and free recall scores were lower in AD compared to the other groups ($p < 0.05$). Patients with non-AD dementias had lower scores of total recall and free recall in comparison with MCI and controls ($p < 0.05$). MCI subjects had marginally lower scores of total recall compared to the controls ($p < 0.05$).

Results of the ROC analyses were given in Table 3. Firstly, the diagnostic utility of discrimination of demented versus non-demented subjects was tested (Table 3A). "First free recall" (cut-off: 5), "second free recall" (cut-off: 6), "third free recall" (cut-off: 6), "total free recall" (cut-off: 18) and "total recall" (cut-off: 41) were all useful for discriminating dementia and non-dementia patients. As can be seen in Table 3A, the third free recall is the most useful item in this respect with very high +LR (10.66) and very low -LR (0.20). Based on these results, further analyses of ROC curves were performed only for "first free recall", "second free recall", "third free recall", "total free recall" and "total recall" items to detect their discrimination potentials of AD from controls and MCI (Table 3B and D) and MCI from controls (Table 3C). With almost same cut-off values, all of the items were significantly useful for discrimination of AD from controls. Of note, "third free recall" reached to 100% specificity and "total recall" to 100% sensitivity. These tests were also useful for discrimination of AD and MCI even though cut-off and corresponding sensitivity values decreased slightly (Table 3D). It is interesting to see that "third free recall" (cut-off: 4) and "second free recall" (cut-off: 4) reached to the 100% specificity. To differentiate AD from MCI, the sensitivity and specificity of the cut-off value of 35 was 82.25 and 94.4%. When considering cut-off value of 41, the sensitivity reached to 100% with decrease

Table 2
MMSE and enhanced cued recall scores by group

	MCI	AD	Non-AD	Control
MMSE score	26.6 ± 1.7	18.0 ± 4.1*	20.9 ± 3.0	27.4 ± 1.7
1st free recall	8.4 ± 2.5	2.7 ± 2.4*	5.0 ± 2.3**	8.4 ± 2.3
1st cued recall	6.1 ± 1.8	5.2 ± 3.1*	7.4 ± 2.3	6.7 ± 1.9
2nd free recall	9.2 ± 3.1	2.7 ± 2.7*	6.0 ± 3.1**	10.0 ± 2.0
2nd cued recall	5.0 ± 2.0	5.0 ± 2.6	6.6 ± 2.9	5.2 ± 1.8
3rd free recall	9.3 ± 2.7	2.9 ± 3.1*	5.9 ± 3.1**	11.1 ± 1.9
3rd cued recall	5.0 ± 1.6	4.8 ± 2.9	5.8 ± 2.4	4.2 ± 1.7
Total free recall	26.9 ± 7.8	8.3 ± 7.5*	16.9 ± 7.9**	29.8 ± 5.7
Total cued recall	16.1 ± 4.8	15.0 ± 7.9*	19.9 ± 6.5	16.2 ± 4.7
Total recall	43.0 ± 4.7***	23.2 ± 11.2*	36.8 ± 10.6**	45.7 ± 2.9

Notes: MCI, mild cognitive impairment; AD, probable Alzheimer's disease; MMSE, mini mental state examination.

* Less than others.

** Less than MCI and controls.

*** Less than controls.

Table 3
Results of the receiver operating characteristics (ROC) curve analyses

	Cut-off	Se (%95 CI)	Sp (%95 CI)	AUC	S.E.	%95 CI	+LR	–LR
A, Dementia vs. non-dementia								
1st free recall	5	80.3 (68.2–89.4)	88.5 (76.5–95.6)	0.909	0.030	0.840–0.955	6.96	0.22
1st cued recall	3	29.5 (18.5–42.6)	94.2 (84.0–98.7)	0.562	0.054	0.465–0.655	5.11	0.75
2nd free recall	6	83.6 (71.9–91.8)	84.6 (71.9–93.1)	0.909	0.030	0.841–0.955	5.43	0.19
2nd cued recall	6	37.7 (25.6–51.0)	80.8 (67.5–90.4)	0.533	0.054	0.437–0.628	1.96	0.77
3rd free recall	6	82.0 (70.0–90.6)	92.3 (81.4–97.8)	0.916	0.029	0.849–0.960	10.66	0.20
3rd cued recall	6	39.3 (27.1–52.7)	90.4 (79.0–96.8)	0.575	0.054	0.479–0.668	4.09	0.67
Total free recall	19	85.2 (73.8–93.0)	88.5 (76.5–95.6)	0.928	0.027	0.863–0.969	7.39	0.17
Total cued recall	18	44.3 (34.5–57.6)	80.8 (67.5–90.4)	0.518	0.055	0.422–0.613	2.30	0.69
Total recall	41	91.8 (81.9–97.3)	80.8 (67.5–90.4)	0.907	0.030	0.830–0.953	4.77	0.10
B, AD vs. control								
1st free recall	6	95.6 (84.8–99.3)	81.8 (64.5–93.0)	0.955	0.026	0.882–0.989	5.26	0.05
2nd free recall	6	91.1 (78.8–97.5)	93.9 (79.7–99.1)	0.973	0.020	0.909–0.996	15.03	0.09
3rd free recall	6	88.9 (75.9–96.3)	100 (89.3–100)	0.967	0.023	0.899–0.994	–	0.11
Total free recall	19	93.3 (81.7–98.3)	97.0 (84.2–99.5)	0.982	0.016	0.923–0.998	30.8	0.07
Total recall	41	100 (92.1–100)	93.9 (79.7–99.1)	0.990	0.013	0.934–0.998	16.5	0.00
C, MCI vs. control								
1st free recall	6	27.8 (9.8–53.5)	81.8 (64.5–93.0)	0.493	0.086	0.350–0.637	1.53	0.88
2nd free recall	7	38.9 (17.4–64.2)	87.9 (71.8–96.5)	0.567	0.083	0.426–0.705	3.21	0.70
3rd free recall	9	55.6 (30.8–78.4)	78.8 (61.1–91.0)	0.690	0.075	0.545–0.812	2.17	0.74
Total free recall	23	38.9 (17.4–64.2)	87.9 (71.8–96.5)	0.593	0.082	0.447–0.729	3.21	0.70
Total recall	42	50.0 (26.1–73.9)	90.9 (75.6–98.0)	0.625	0.080	0.479–0.757	5.50	0.55
D, MCI vs. AD								
1st free recall	5	84.4 (70.5–93.5)	88.9 (66.2–98.3)	0.943	0.039	0.854–0.985	7.60	0.18
2nd free recall	4	77.8 (62.9–88.8)	100 (81.3–100)	0.943	0.039	0.853–0.985	–	0.22
3rd free recall	4	73.3 (58.1–85.4)	100 (81.3–100)	0.927	0.044	0.832–0.977	–	0.27
Total free recall	16	88.9 (75.9–96.3)	88.9 (65.2–98.3)	0.950	0.037	0.864–0.988	8.00	0.13
Total recall	35	82.2 (67.9–92.0)	94.4 (72.6–99.1)	0.952	0.036	0.866–0.989	14.8	0.19

Notes: MCI, mild cognitive impairment; AD, probable Alzheimer's disease; Se, sensitivity; Sp, specificity; AUC, area under curve; S.E., standard error; %95 CI, 95% Confidence interval; +LR, positive likelihood ratio; –LR, negative likelihood ratio.

of specificity to 61.1%. For discrimination of MCI from control subjects, the only useful test was “third free recall” (cut-off: 9). The likelihood ratios indicated this test was moderately useful for this purpose (Table 3C).

When all groups were combined, ECR scores (first free recall, second free recall, third free recall, total free recall and total recall) were all correlated well to MMSE scores (r values between 0.771 and 0.832). For example, when MMSE scores were plotted against to total recall, intercept A was 8.8 (5%CI: 5.45–10.41) and slope B was 0.40 (0.35–0.45), indicating a difference of scores proportionally and/or by a constant amount, but correlation coefficient (r) was 0.832 (95%CI: 0.765–0.881) indicating presence of a strong correlation.

A weak correlation between MMSE scores and the education levels in years [$r=0.27$ (95%CI: 0.09–0.44)] was noted. However, except than first free recall ($r=0.212$ (95%CI: 0.003–0.381), no correlation was seen between ECR items and the education years: $r=0.175$ (95%CI: –0.0105 to 0.348) for “total recall”; $r=0.1458$ (95%CI: –0.040 to 0.3218) for “total free recall”; $r=0.179$ (95%CI: –0.0059 to 0.3521) for “second free recall” and $r=0.0914$ (95%CI: –0.0949 to 0.2715) for “third free recall”.

Diagnostic potential of the tests was also investigated according to the education categorized into two groups as longer than 5 years and equal/less than 5 years. In the latter, there were 29 AD, 9 MCI and 13 controls. Five of the AD cases and 4 of the controls were illiterate. All analyses were repeated for these two education groups and results were summarized briefly. Firstly, optimal cut-off values to discriminate AD from control or MCI and MCI from controls are 1 or 2 point higher in higher education group compared to the lower ones, e.g., cut-off of third free recall 6 and 5 for AD versus control; 10 and 8 for MCI versus controls and 6 and 5 AD versus MCI, respectively. Secondly, ECR test items are equally useful in the both educational groups. For example, AUCs of “third free recall” was 0.970 (95%CI: 0.851–0.995) and 0.963 (95%CI: 0.853–0.995) for AD versus control; 0.772 (95%CI: 0.579–0.906) and 0.628 (95%CI:

0.399–0.821) for MCI versus controls; and 0.893 (0.693–0.980) and 0.862 (95%CI: 0.716–0.950) AD versus MCI, respectively.

4. Discussion

The study demonstrated that ECR test can easily be administered to Turkish patients with mild to moderate dementia. Analyses revealed that patients with dementia, particularly with AD show impairments on the ECR test compared to individuals with MCI and age-matched controls; and the patients with MCI show impairments compared to the controls. MMSE, on the other hand, was not able to differentiate MCI cases from elderly controls. The difference was evident especially in total ECR scores. The total recall and free recall items of the test had high yield in differentiation of dementia, especially of AD. A cut-off value of 41 in total recall had specificity of 93.9% and sensitivity of 100% in differentiation of AD from elderly controls. All 45 patients clinically diagnosed as AD had a total ECR recall score of less than 41 and were correctly classified with ECR test (100% sensitivity). Among 33 control cases, only 2 had ECR total recall score less than 41 and have been misclassified (93.9% specificity). These findings are comparable to the original study of Grober et al. (1988) in which total recall score was found to be 99% specific and 94% sensitive in the differentiation of dementia with a cut-off of 44. As our study demonstrates that the test can be useful in the differentiation of Alzheimer's disease from elderly controls in a culturally different population, it gives some more additional information. Firstly, the test may also be helpful in differentiation of MCI from controls; and secondly education level does not seem to affect the performance of cases.

A prospective study on elderly persons showed a high predictive value (85% sensitivity and 80% sensitivity) of total free recall item of ECR in future development of dementia in 5 years with a cut-off of 24 (Grober et al., 2000). In our cross-sectional study, third free recall item but not the total free recall is found to be useful in discrimination of MCI from elderly controls. It is in agreement with the current understanding that the patients with MCI do not benefit from rehearsal and cueing as cognitively unimpaired elderly people.

Most of the screening and cognitive tests are sensitive to education. Especially, test items requiring writing, reading and drawing need some level of education, and therefore are not applicable to illiterate persons. Effect of cultural difference is expected to be high in language-based tests. Being free of the above considerations, the nature of ECR let us to predict that the test will be suitable to Turkish population and also to people with low or no formal education. Proving this prediction, the high utility of the test in discriminating dementia from controls, Alzheimer's disease from controls and a moderate utility in discriminating MCI from controls has been demonstrated. Education also did not affect the utility of the test. Similar to our findings, education was found to be unrelated to ECR variables in Mayo Clinic older adults' normative study (Ivnik, Smith, & Lucas, 1997).

In conclusion, ECR test is a valuable test in assessment of elderly patients with a complaint of memory impairment. The study demonstrates the high utility of ECR is also valid in Turkish population. Education level is not associated with utility of the test. The test can even be administered to illiterate persons. It takes little time, is easy to administer, and causes minimal distress for the patient. Based on these features, ECR can be useful in discriminating dementia and its preclinical form, MCI. Administration of this test either alone or in conjunction with MMSE, may provide a good evaluation of cognitive status by allowing more detailed but non-distressing examination of memory function.

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