Addenbrooke Cognitive Examination-III and detection of Alzheimer's disease: a comparison of ACE-III, M-ACE and ECAS in a Greek Alzheimer's disease population.

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Abstract

Introduction: The present study attempted to adapt into Greek and validate the Addenbrooke's Cognitive Examination-III (ACE-III) and Mini-ACE (M-ACE) against their predecessors Addenbrooke's Cognitive Examination-Revised (ACE-R) and Mini-Mental State Examination (MMSE) in an Alzheimer's disease (AD) population. Notably, the present study also aimed to appraise the utility of each screen by conducting a comparison of the psychometric properties of ACE-III, M-ACE, ACE-R, MMSE, and Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in detecting AD.

Methods: Forty AD patients were recruited and matched with 38 controls. Bayes correlation analysis was conducted to examine convergent validity. Receiver operating characteristics curve analysis was implemented to appraise the sensitivity and specificity of the tests.

Results: The ACE-III, M-ACE and ECAS and its sub-scores robustly correlated with ACE-R and MMSE. The ACE-III and the ECAS-ALS Non-Specific score were the most sensitive and specific tools in detecting AD, closely followed by ECAS Total score and M-ACE. Solely ECAS Total score correlated with the duration of disease.

Discussion: ACE-III and M-ACE are validated and showed very good psychometric properties in detecting AD and may be considered in hectic clinical settings. ECAS total score and ECAS-ALS Non-Specific showed comparable psychometric properties and may be considered in poly-pathological clinics for the detection and monitoring of AD in patients with motor impairments common to neurodegenerative diseases.

Keywords: Greek; ACE-III; M-ACE; ECAS; Alzheimer's disease; motor disabilities; comparison; detection of AD;

1. Introduction

Cognitive assessment is crucial for the detection of Alzheimer's disease (AD) and differential diagnosis from other dementias such as frontotemporal dementia (FTD) [1]. A comprehensive assessment of cognition and behaviour has clinical implications for patient care, regarding the available treatment options, survival expectancy, competency to drive or give informed consent, ability to live independently at home, the carer's burden, and quality of life [2]. However, in hectic clinical settings, briefer cognitive screens are often the test of choice, with patients with more complex needs or diagnostic uncertainties being referred for full neuropsychological assessment [2].

The Addenbrooke's Cognitive Examination-Revised (ACE-R) and the embedded Mini-Mental State Examination (MMSE) are the only brief screening tests for dementia in Greek with administration times of approximately 15 and 5 mins respectively [3]. These were designed to briefly examine a wide range of cognitive domains – attention, memory, language, visuospatial components, and verbal fluency [4]. The ACE-R aids in the detection, differentiation, and monitoring of cognitive decline in dementia syndromes such as FTD and AD [5–8].

However, the ACE-R has several limitations [9], for example healthy adults repeatedly fail on the verbal repetition item, which might be a result of hearing problems or distraction [9, 10] and ceiling effects have been observed in the measure of comprehension [11]. The acknowledgement of these weaknesses led to the development of the Addenbrooke's Cognitive Examination-III (ACE-III). While the ACE-III does not incorporate MMSE, it continues to assess the same five cognitive domains, with new items of verbal repetition and verbal comprehension, while backwards spelling was replaced by serial 7s subtraction [9–12].

The ACE-III has been validated against extensive neuropsychological tests [2, 9]. However, even the ACE-III which demands 15–20 minutes to administer has been suggested to be excessive for some busy clinical settings [2]. The Mini-Addenbrooke's Cognitive Examination (M-ACE), was developed subsequently and appears to be more sensitive and specific than its widely used precursor, MMSE [2, 13].

The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) was developed recently [14] and adapted for Italian [15], German [16], Chinese [17], and Spanish [18] populations. The ECAS is also a brief assessment similar to the ACE-III, but the ECAS was designed for patients with various motor impairments, and was found sensitive in ALS, Parkinson's disease, and Progressive supranuclear palsy [14–21]. The ECAS has been specifically designed to detect types of cognitive and behavioural impairment in ALS of an executive nature similar to that found in FTD. The ECAS comprises an ALS-specific component (executive function and social cognition, verbal fluency, and language) and a carer's interview to detect the behavioural and psychotic changes typical in FTD. This focus on executive functions distinguishes the ECAS from the ACE-III. However, the ECAS was also designed to assess the functions typically affected in other diseases common in older adults such as AD and, therefore, includes an ALS-non-specific segment (memory and visuospatial function) [14–21]. We have previously demonstrated that the ALS Non-Specific score is a highly sensitive and specific to identify the cognitive changes typical to AD and help differentiate AD from ALS [22].

This study attempted to adapt the ACE-III and M-ACE to Greek and validate them in an AD population. A secondary aim was to compare the performance of AD patients on the ACE-III and M-ACE with their performance on the ECAS.

2. Methods

2.1 Participants

All the participants and their carers signed an informed consent form in compliance with the revised Declaration of Helsinki, 1987. The present study was approved by the Psychology Research Ethics Committee of the University of Edinburgh, and the Aeginition Hospital Ethics Committee. All participants were native Greek speakers, and free from the following: (1) psychiatric disorders, (2) psychoactive drugs, antidepressants, and anticonvulsants, (3)

other neurological conditions affecting cognition (4) learning disabilities, (5) alcoholism and drug abuse, and (6) uncontrolled systemic disease.

2.1.1 AD Patients

The attendants of the Maroussi Alzheimer Clinic of the Athens Association of Alzheimer's Disease and Related Disorders, Athens, Greece, were employed for this study. A total of 40 AD patients participated; a subsample has been described in Kourtesis et al. (2019) [22]. The recruitment was conducted in accordance with the general inclusion criteria and the following criteria specific to AD: (1) a diagnosis of AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [23] and (2) the absence of a mixed concomitant dementia processes (e.g., AD and vascular dementia). Also, a neuropsychologist or psychiatrist interviewed the patients and administered the Hospital Anxiety and Depression Screen (HADS) [24] (cut-off > or = 8) to exclude the patients who presented major depression or anxiety symptoms that may compromise their performance. The duration of the disease was calculated in years, from the onset of the first symptoms to the testing date.

2.1.2 Healthy Subjects

In this study, 38 controls were recruited and matched in age, sex, and education to the patient group. They belonged to one of the following categories: (1) members of Athens Association of Alzheimer's Disease and Related Disorders, Athens, Greece, (2) relatives of AD patients, or (3) volunteers who responded to the calls of the above association. For recruitment, we implemented the aforementioned general inclusion criteria.

2.2 ***Procedures***

2.2.1 Translation-Adaptation

The adaptation of the ACE-III and the embedded M-ACE required minor adjustments since most of the tasks remained as they were in the ACE-R. The sole significant adjustment was in the section of language in the task of proverb repetition, where the pronunciation of Proverbs is required. In terms of pronunciation, the first item should be a low-difficulty proverb, i.e., 'All that glitters is not gold' and the second item should be a medium to hard difficulty proverb, i.e., 'A stitch in time saves nine'. The proverbs of the Greek version were culturally adjusted, and the counterparts of this difficulty measure were 'All that glitters is not gold' and

‘Better donkey-tying than donkey-seeking’. The adaptation of the ECAS in Greek is described in Kourtesis et al. (2019) [22].

2.2.2 Neuropsychological Testing

The administration of the tests was randomised to control for a possible practice effect [25]. All the testers were trained on the administration of the screens and were reassessed by a blind interviewer.

2.2.3 Statistical Analyses

Thresholds of $p < 0.05$ (two-tailed) and $BF10 \geq 10$ were used for statistical inference and the substantial evidence of H1 against H0. The demographic and cognitive data were analysed and compared, and between-group comparisons were made using Bayes independent sample t-tests. The associations between the screening tools were probed and quantified using Pearson’s correlation coefficient and Bayes Correlation Analysis to ensure that our results are more generalisable. Receiver operating characteristics (ROC) curve analyses and area under the curve (AUC) were implemented to appraise the psychometric properties of the screens. The statistical analyses were executed using the IBM Statistical Package for the Social Sciences (SPSS) 24.0 (Scale, ROC, and AUC analyses) [26] and JASP version 0.8.1.2 (Bayesian Correlation analyses, Bayesian T-Tests) [27].

2.2.3.1 Inter-Rater Reliability & Internal Consistency

The inter-rater reliability between the assessors who administered the screens and the independent interviewer was appraised using the Intraclass Correlation Coefficient (ICC), which displays outcomes from ‘no match’ = 0 to ‘seamless match’ = 1 [28]. The four assessors and the independent reviewer were trained equally in the administration and scoring of ACE-III and M-ACE based on relevant guidelines. The independent reviewer was blinded to the identity of the examiner as well as the examinee. The inter-rater reliability was calculated between the scores for the ACE-III and the M-ACE provided by the assessors and the independent reviewer. The internal consistency of the Greek ACE-III and M-ACE was determined by the calculation of Cronbach’s alpha coefficient. A Cronbach’s alpha coefficient of 0.70 or greater is considered substantial [29].

3. Results

3.1 Inter-Rater Reliability & Internal Consistency

The inter-rater reliability demonstrated an almost seamless agreement between the assessors, indicating substantial suitability for clinical measures [28]. ICC = 0.92 was found for the ACE-III and M-ACE [26]. The scale analyses demonstrated excellent internal consistency of the ACE-III and M-ACE with the Cronbach's alpha = 0.79 [29].

3.2 Convergent Validity in AD Patients

The statistics for the correlations are displayed in Table 1 in Supplementary Material. The ACE-III displayed a robust correlation with ACE-R. Equally, the M-ACE substantially correlated with the MMSE. Moreover, ECAS and its sub-scores significantly correlated with ACE-R. A Bayesian correlation analysis was performed to scrutinise the robustness of the results which confirmed the convergent validity of the ACE-III, M-ACE, ECAS, and its sub-scores.

3.3 ***Sensitivity and specificity in the detection of AD***

ROC and AUC analyses were executed to explore the psychometric properties of the screens in detecting AD. Figure 1 presents the ROC curves of each screen and sub-score. All the tests confirmed an adequately high level of sensitivity and specificity. Additionally, the analysis computed the sensitivity and specificity respective to different cut-offs, and the optimum cut-off to determine abnormality is shown (see Table 1). The ACE-III, ECAS, ACE-R, M-ACE, and ECAS-ALS Non-Specific covered the greatest AUC.

3.4 Performance and Correlations with the duration of disease

In group comparison, AD patients performed significantly lower than healthy controls in every test (see Table 2). Also, we examined the correlation between the screens and the duration of disease in the entire sample of AD patients. Robust correlations with the duration of disease were detected solely with the total score of the ECAS (BF10 = 14.22), while with the rest of the screens and sub-scores the correlations were non-significant (see Table 2 in Supplementary Material). Fourteen patients (35%) had a duration of disease < 3 years, and 26 patients (65%) 3 to 6 years indicating that the sample were in the early and early mid-stages of AD.

4. Discussion

4.1 The ACE-III and M-ACE in a Greek Population

The present study successfully produced the Greek versions of the ACE-III and M-ACE and validated them in a group of AD patients. The tests showed robust convergent validity against the already adapted and validated Greek versions of the ACE-R and MMSE. This was supported by the magnitude and significance of the correlations as well as the evidence of the Bayesian Factor analysis. The screens exhibited substantial internal consistency, which allows for implementation in clinical and research settings [28]. The tests also showed an almost excellent inter-rater reliability, permitting extensive utilisation by various clinical practitioners [29]. Therefore, the Greek ACE-III and M-ACE can be considered as suitable tools for clinical and research purposes.

4.2 Detection of Alzheimer's Disease

In accordance with previous studies, AD patients performed significantly lower than the controls in all cognitive tasks, particularly those involving memory and visuospatial ability [2, 4, 9]. The ACE-III elicited 94.7% sensitivity and 100% specificity at the cut-off of 83 (2 SDs) as well as 97.4% sensitivity and 97.4% specificity at the cut-off of 84 in the detection of dementia within a sample pool of AD patients who were predominantly in their 1st–4th years after diagnosis. Sensitivity was a little superior to the ACE-R (89.5% to 92.1%). demonstrating that the ACE-III should be the tool of choice against the ACE-R.

A comparison of the M-ACE to the MMSE revealed superior psychometrics in the former with 97.4% sensitivity and 94.7% specificity at the cut-off of 23 (MMSE, 86.8% sensitivity and 92.1% specificity at the cut-off of 24). The higher sensitivity and the comparable specificity to MMSE is aligned with the validation study of the M-ACE [2]. Accordingly, M-ACE surfaces as the most appropriate brief screening tool to detect AD. M-ACE may be considered in hectic clinical environments, where brief screens are preferred.

Furthermore, in a previous study, the ECAS-ALS Non-Specific score was able to differentiate AD patients from non-demented ALS patients [22]. Similarly, in this study, ECAS ALS Non-Specific score was equally able to detect AD as the ACE-III with 97.4% sensitivity and specificity at the cut-off of 24. However, the other component of the ECAS (ALS Specific) appears substantially less valid in the identification of AD. Moreover, the total score of the ECAS also performed well although slightly below the ACE-III. Though, ECAS correlated

with the disease duration indicating that it may be more sensitive to cognitive decline, although this has yet to be demonstrated.

In a previous study, the ECAS was found to be substantially less dependent on the IQ and produced significantly less ceiling effects than ACE-III, which may be an advantage for use with clinical groups [30]. The ECAS also has a behavioural interview which may accompany the cognitive profile of the patient and inform the probable caregiver's burden. Lastly, the ECAS is adjusted to upper motor and speech impairments, therefore, it might be considered as an appropriate tool in patients with a motor dysfunction, which is common in many neurodegenerative diseases.

4.3 Limitations & Future Studies

The study contains certain caveats that should be noted. One of the major limitations of the study is the small size of the sample. A larger and more diverse sample would allow more solid and conclusive observations. In future studies, the acquisition of normative data should be of a size that permits the computation of distinct cut-off scores that are analogous to the educational level.

This study recruited only AD patients. It would be intriguing to investigate the capacity of the tests to differentiate between FTD and AD patients. It would also be interesting to probe the potency of the tests to identify the FTD phenotypes. The extensive and profound study of cognitive and behavioural changes in dementia patients can help ameliorate and adjust patient care and alleviate the caregivers' burden.

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Greek version of ECAS can be downloaded from https://ecas.psy.ed.ac.uk/ecas-international/#Greek.

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Declaration

The authors declare no conflicts of interest and that this study is their own work.

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