REVIEW

Addenbrooke's cognitive examination III in the diagnosis of dementia: a critical review

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Abstract: Addenbrooke's cognitive examination III is a screening test that is composed of tests of attention, orientation, memory, language, visual perceptual and visuospatial skills. It is useful in the detection of cognitive impairment, especially in the detection of Alzheimer's disease and fronto-temporal dementia. The aim of this study is to do a critical review of the Addenbrooke's cognitive examination III. The different language versions available and research about the different variables that have relationship with the performance of the subject in the ACE-III are listed. The ACE-III is a detection technique that can differentiate patients with and without cognitive impairment, is sensitive to the early stages of dementia, and is available in different languages. However, further research is needed to obtain optimal cutoffs for the different versions and to evaluate the impact of different age, gender, IQ, and education variables on the performance of the test.

Keywords: dementia, cognitive assessment, memory, screening, cognitive impairment

Introduction

The Addenbrooke's cognitive examination (ACE) was developed by Hodges et al as an extended cognitive screening technique, designed to detect dementia and differentiate Alzheimer dementia from fronto-temporal dementia.[1] It was also developed to overcome the neuropsychological omissions present in the Mini Mental State Examination (MMSE).[2] The aim of ACE was to be a screening technique that evaluates the principal cognitive functions and grants free access to health professionals.[3] In this way, ACE turns into a brief cognitive screening tool, which takes 15–20 minutes to administer and is useful in the detection of dementia syndromes.[4]

The ACE is composed of tests of attention, orientation, memory, language, visual perception and visuospatial skills.[3] All of these measures have significant correlations with the classical neuropsychological tests.[4]

The aim of this study is to critically review the Addenbrooke's cognitive examination III.

Description of ACE-III

The ACE-III was developed to remove the MMSE elements from the ACE and ACE-R, as the MMSE was no longer open access in the year 2001.[5] Because of this, recent guidelines have provided alternatives to the MMSE, and the ACE-III has been recommended by the Department of Health and the Alzheimer's Society in the UK.[6] In this way, the MMSE items present in the ACE-R were substituted for by similar items.[1] For example, in the attention section the spelling of the word "WORLD" backwards was omitted, leaving only the subtraction of serial 7s. In the language section,

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the written command "close your eyes" was omitted, the denomination of a pencil and clock was replaced by a book and a spoon, and the three-step command was replaced by three single-step commands, due to the lack of sensitivity to cognitive impairment.[1,4] Finally, in the same section, the writing of a single sentence was replaced by writing two or more sentences. In the visuospatial section, the intersecting pentagons were replaced with intersecting lemnisci.[3] Hence, with these changes the administration of the ACE-III makes scoring the MMSE void.[4] As the ACE-III is designed to address the weakness of the ACE-R, the verbal repetition item was modified due to the poor performance of this item in healthy adults.[3]

As previously described, the ACE-III is composed of five cognitive domains, attention, memory, language, verbal fluency, and visuospatial abilities. The ACE-III takes ~20 minutes to complete (Table 1). Similarly to the ACE-R, the total score of the ACE-III is based on a maximum score of 100, with higher scores indicating better cognitive functioning.

The index study of the ACE-III demonstrated high sensitivity and specificity, with cutoffs recommended as for the ACE-R as follows: 1) 88 (sensitivity =1.0; specificity =0.96) and 2) 82 (sensitivity =0.93; specificity =1.0).[4]

Correlation of ACE-III with neuropsychological tests

It has been demonstrated that the subtests of the ACE-III have significant correlations with neuropsychological tests in that domain. The memory domain of the ACE correlated with two classical neuropsychological tests of memory, Free and Cued Selective Reminding Test and the Rey Auditory Verbal Learning Test.[4,7] The language domain correlated with the Boston Naming Test, the attention domain correlated with tests that evaluate attention and executive functions (the trail making test, memory span, Stroop test), and the fluency scores correlated with executive functions.[7] Therefore, the administration of this screening technique quickly provides the clinician with a neuropsychological profile.

The cutoff points of ACE-III show strong correlations with the cutoff points of the ACE-R,[4] suggesting that this screening technique is capable of differentiating patients with and without cognitive impairment, and mild cognitive impairment (MCI).[3] In addition, the ACE-III performance has broader clinical implications in that it relates to carer reports of functional impairment in most common dementias.[8]

Comparison of the ACE-III with other screening techniques

In different studies that compare the ability to discriminate healthy people and people with dementia, the ACE-III showed similar results to other screening techniques[9] (MoCA[10] and RUDAS[11]).

Like the other screening techniques (MMSE, MOCA, RUDAS), the ACE-III provides the clinician with a quick and brief global cognitive screen of the patient specifying both the overall cognitive profile and measures of each of the evaluated domains.[9,10] In this way, ACE-III provides the clinician with a more comprehensive assessment view of the cognitive profile of the patient, helping to provide a differential diagnosis.[12] Moreover, as the ACE-III includes different scores for each domain, in addition of the general

Table 1 Cognitive domain, tasks, and sub-total score of ACE-III

Cognitive domains	Tasks	Sub-total score
Attention	Attention is tested by asking the patient about the date, including the season and the current location; repeating back three simple words; and serial subtraction	18 points
Memory	Memory is tested by asking the patient to recall three words previously repeated; memorizing and recalling a fictional name and address; and recalling widely known historical facts	26 points
Fluency	Fluency is tested by asking the patient to say as many words as they can think of starting with a specified letter within 1 minute; and naming as many animals as they can think of in 1 minute	14 points
Language	Language is tested by asking the patient to complete a set of sequenced physical commands using a pencil and piece of paper such as "place the paper on top of the pencil," to write two grammatically complete sentences, to repeat several polysyllabic words and two short proverbs; to name the objects shown in 12 line drawings, and to answer contextual questions about some of the objects; and to read words with irregular sound-spelling correspondence	26 points
Visuospatial	Visuospatial abilities are tested by asking the patient to copy two diagrams, to draw a clock face with the hands set at a specified time, to count sets of dots, and to recognize four fragmented letters	16 points

Abbreviation: ACE-III, Addenbrooke's cognitive examination III.

score, it allows for tracking the progression of cognitive deficits over time.[13]

The MMSE lacks sensitivity to identify fronto-temporal dementias, whereas the ACE-III had demonstrated accuracy for detecting fronto-temporal dementia.[4] An important limitation of the MMSE is the lack of sensitivity for the early stages of dementia,[14] whereas the ACE-III had demonstrated accuracy in detecting MCI. The ACE-III showed better sensitivity for detecting dementia compared to the MMSE.[15] The ACE-III more efficiently identifies everyday functional impairments compared with both the MMSE and MoCA.[16]

Despite the above considerations, the MMSE continues to be the preferred screening instrument for many neurologists. For this reason, a conversion table between ACE-III and MMSE has been developed and is used for clinical and research purposes.[17]

In addition, a study by Larner investigated the relationship between administration time and diagnostic accuracy in cognitive screening tests. The author reports positive correlations between the accuracy and time of administration of the test and significant correlations between the accuracy and the number of items included in the test. These observations suggest that tests with more items (ie, longer tests) are more accurate.[18] The number of items of the MMSE is 30 compared with the ACE-III, which have 100 items.

Utility of the ACE-III in the detection of cognitive impairment

Dementia has been declared a global challenge, causes a great burden for the families of the patients, and leads to enormous global annual costs, which are expected to increase significantly in the next few decades.[20–22] Although several risk factors are implicated, the principal risk factor is age, and wit aging and growing populations dementia is becoming more prevalent.[22] Therefore, it is essential that a sensitive and specific screening tool that not only identifies patients with dementia but also identifies them in the early stages of the disease will be widely used to allow earlier diagnosis and intervention and to postpone dementia.[23]

MCI

MCI is the prodromal phase associated with brain disorders, including of Alzheimer's disease,[24] Parkinson's disease,[25] cerebrovascular disease,[26] and fronto-temporal dementia.[27]

The ACE-III has shown high diagnostic accuracy for MCI, being the memory domain the most sensitive in early stages of Alzheimer's disease patients.[7] Moreover, the

ACE-III has demonstrated high diagnostic accuracy in individuals with subjective cognitive impairment.[28]

Dementia

The ACE-III, like its predecessors, was designed for the detection of dementias in early stages.[3] Good levels of sensitivity have been reported in the distinction between healthy controls and patients with some type of dementia in initial stages.[4,7]

Research reports that ACE-III is one of the most sensitive screening tools for the detection of dementia, compared to other screening tests such as MMSE and MOCA.[3] It has been reported that a cutoff point of 61 on the ACE-III is sensitive for distinguishing mild dementia from moderate dementia.[16] Considering that the ACE-III has properties similar to that of its predecessors, it can be considered to be a useful instrument for longitudinal follow-ups as its predecessors.[29,30]

In addition, the value of ACE-III for discriminating between Alzheimer's dementia and fronto-temporal dementia has been reported.[4,7,28,31] Patients with Alzheimer dementia and fronto-temporal dementia showed significant differences in the performance on the different components of the ACE: orientation, attention, and memory were worse in Alzheimer patients, while the fluency with letters, language, and names were worse in patients with fronto-temporal dementia. Mathuranath, using the ACE and the ACE-R,[1,3] translated this scoring pattern into an index that is considered useful for the differentiation of both types of dementia (the VLOM ratio). Many different researchers have shown the usefulness of the new version of the ACE.[4,7,28,31]

On the other hand, the usefulness of the annualized change rates (ARC) in the total ACE scores was reported. This can be calculated using the total score in the previous and current ACE and the number of months between both evaluations, according to this formula: ARC of ACE = [(last ACE score-baseline ACE score)/(months between evaluation)] × 12.[29,30]

Stroke

Stroke can involve physical and cognitive impairments. To the best of our knowledge, there is only one study that studied the utility of the ACE-III in the detection of cognitive impairment after stroke.[19] As an advantage, the ACE-III not only provides the clinician with a cutoff point but also shows an estimated cognitive profile of the patient.[7] In this way, it provides the clinician with useful information about the cognitive functions of the patient. Moreover, the application of a screening tool can accelerate the diagnostic process of cognitive deficit after stroke and implementing cognitive rehabilitation.[32]

It is fundamental when interpreting the cutoff points after stroke to understand that because many of the subtests of the ACE-III cannot be evaluated. In this way, the vast majority of patients after stroke score below the cutoff point.[19] This is due to the fact that many patients after the stroke typically present with motor difficulties, which negatively impacts the motor output subtests (example: drawing) and often have difficulties in the with language, many times because they present with aphasia.[33]

Parkinson

Currently, there are no studies that have studied the accuracy of ACE-III in the seeking of cognitive impairment in Parkinson disease (PD). Nevertheless, the coping of the wire cube, present in the visuospatial domain of ACE-III, has correlated significantly with a poor performance on other cognitive domains, suggesting that is a sensitive detector of cognitive impairment in PD.[34]

Variables to consider in the interpretation of the cutoff points

Previous studies with the ACE-R have shown that the cutoff points are influenced by sociodemographic variables.[35,36] In several studies, with the ACE-III in several studies, the influence of demographic variables has been considered as seen to be an important variable to take into account when interpreting the suggested cutoff points and to improve diagnostic accuracy.[9,38,40,44,46]

Years of education

The years of education are an important variable that must be taken into account in order to correctly interpret the cutoff points of the ACE III. Level of education has been observed to have an effect on the accuracy of this screening test in the diagnosis of dementia[15,37–40] and may be attributable to the presence of items dependent on the level of education or literacy,[40] such as the use of irregular words, phonemic verbal fluency,[41] naming task,[42] and constructional abilities.[43] Previous investigations have shown that the level of education has a significant impact on both the total score and the scores of the domains.[44,45] Thus, different cut points have been proposed depending on years of education[44] and correction factors have been proposed to adjust the raw scores and equivalent scores with cutoff values.[46]

Age

It has been found that people over 75 years old score less on the ACE-R in comparison with younger people.[47,48] Interpretation of the cognitive profile is thus limited by age, suggesting that age is an independent predictor of performance.[9,15,40] It has been shown that all sub-scores of the ACE-III were influenced by age, being orientation, repetition of three words, and serial subtraction of the less affected by this variable.[38] Hence, it is essential to ensure appropriate cutoff point for older age groups, because the prevalence of cognitive impairment increases with age.[9,38]

IQ

It has been suggested that the cutoff points for screening techniques should be adjusted depending on the premorbid IQ of the patient, for better sensitivity in the detection of dementia.[49] In previous studies, the cutoff scores of the MMSE[50] and MOCA[49] have been associated with premorbid IQ. Likewise, the ACE-III cutoff points were also affected by variation in premorbid IQ.[40] Therefore, the cutoff points must be adjusted to the premorbid IQ values to ensure correct interpretation.

Translation of different languages

Mirza et al (2017) performed a review of all the reports of translation and cultural adaptation procedures of the cognitive examination of Addenbrooke version III (ACE-III) and its predecessors.[51] In this review, it was reported that the first version of ACE is available in 12 languages, the revised version in 16 languages and the third version in 4 languages. Stott et al (2017) reported that only two studies evaluated the ACE-III, but in these studies the ACE-III showed very similar results to those of the ACE-R and these results could be applied equally to the ACE-R.[40]

In Table 2, the different versions of ACE-III currently available are listed.

ACE mobile

ACE mobile was designed by Newman et al (2018) to support users of the ACE-III by guiding and automating the administration, rule adherence, scoring, and reporting. The new version of the ACE-III, ACE mobile, is an iPad version. The aim is to support the clinician in capturing accurate measurement with zero measurement error. ACE mobile is very effective at reducing errors when compared with the standard paper-and-pen test. ACE mobile is currently provided as a free tool, with no restrictions for clinical use, available on iTunes.[52]

M-ACE

The Mini-Addenbrooke's Cognitive Examination (M-ACE) is a short version of the ACE and was developed and validated in dementia patients.[3,53] The M-ACE consists of 5 items with

Table 2 Different versions of ACE-III currently available

Languages	Authors	Year	Patient	Cutoff score	Sensitivity	Specificity
English	Jubb and Evans[37]	2015	Dementia (n=33) No dementia (n=26)	81	79	96
English	Hsieh et al[4]	2013	Fronto-temporal dementia (n=33) Alzheimer's disease (n=28) Healthy controls (n=25)	88	100	96
English	Elamin et al[28]	2016	Subjective memory impairment (n=15) Alzheimer's disease (n=31) Primary progressive aphasia (n=11) Behavioural-variant fronto-temporal dementia (n=18) Posterior cortical atrophy (n=11) Healthy controls (n=28)	88	91.5	96.4
Portuguese	Peixoto et al[54]	2018	Healthy controls (n=30) MCI (n=30) Dementia (n=30)	82	87.5	57.14
Spanish (European)	Matias-Guiu et al[44]	2015	Dementia (n=87) Healthy controls (n=130)	65.6	83	80
Spanish (European)	Matias-Guiu et al[7]	2017	Healthy controls (n=25) Subjective memory complaints (n=48) Amnestic MCI (n=47) Mild Alzheimer's disease (n=47) Other neurodegenerative diseases (n=33)	73/74	76.6	75
Spanish (European)	Matías-Guiu et al[38]	2016	Healthy controls (n=273)	7/8[a]	83.1	92.4
Spanish (Argentinian)	Bruno et al[31]	2018	Fronto-temporal dementia (n=31) Alzheimer's disease, (n=70) Healthy controls (N=139)	86	98.5	82.01
Egyptian Arabic	Qassem et al[55]	2015	Healthy controls (N=139)	[b]		
Italian	Pigliautile et al[46]	2018	Healthy controls (N=574)	[c]		
Thai	Charernboon et al[56]	2016	Dementia (n=30) MCI (n=29) Healthy controls (n=48)	61	100	97
Chinese	Wang et al[15]	2017	Dementia (N=177) Healthy controls (N=180)	83	91.1	83.1

Notes: [a]The author proposes a correction by age, gender, and level of education. [b]The author proposes percentiles by the total score and subtest, and no cutoff. [c]The author proposes a correction by age, gender, and level of education use the cutoff original.
Abbreviations: ACE-III, Addenbrooke's cognitive examination III; MCI, mild cognitive impairment.

a maximum score of 30. Hsieh et al (2014) identified two cutoffs: 1) ≤25/30 has both high sensitivity and specificity and 2) ≤21/30 is almost certainly a score to have come from a dementia patient regardless of the clinical setting. It has been found to be superior to the MMSE and MoCA in diagnostic utility. Although relatively good levels of sensitivity have been reported, the use of this tool should be questioned in clinical trials where high specificity and low false positive rates are more desirable.[18,24]

Conclusion

The ACE-III is a screening technique that is capable of differentiating patients with and without cognitive impairment and is sensitive to the early stages of dementia.

Unlike other screening tests (MMSE, MOCA, RUDAS), the ACE-III provides the clinician with a brief multi-component cognitive profile, since it provides specific scores for different cognitive domains: attention, memory, verbal fluency, language, and visuospatial function. It has been demonstrated that the subtests of the ACE-III have significant correlations with neuropsychological test specific for that domain.

Currently, in addition to the English version there are versions in Spanish, Italian, Chinese, Portuguese, Egyptian Arabic, and Thai.

ACE-III is influenced by demographic variables including age, education, and IQ. All of these are considered to be important variables to take into account when

interpreting the suggested cutoff points in order to improve diagnostic accuracy.

Future investigations should investigate the utility of the ACE-III in other neurological and psychiatric pathologies, such as head trauma and mood disorders.

Disclosure

The authors report no conflicts of interest in this work.

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