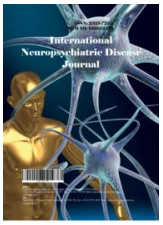

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Validation of the Hungarian Version of Addenbrooke's Cognitive Examination for Detecting Major and Mild Neurocognitive Disorders

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Authors' contributions

This work was carried out in collaboration between both authors. Author BK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author JF managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: The screening of cognitive decline is a mandatory step in the early diagnosis and appropriate treatment of dementia to begin. In order to achieve this, an easy-to-take, validated neurocognitive test with good specificity and sensitivity are essential in the assessment. The aim of this study was to evaluate the Hungarian version of Addenbrooke's Cognitive Examination (version I., ACE)- by comparing it with the conventional Mini-Mental State Examination (MMSE)- as a new form of assessment in order to screen for early dementia among the elderly.
Study Design: Descriptive cross-sectional.
Place and Duration of Study: This study is a part of a larger research, conducted among voluntary elderly from the city of Pécs (Hungary) between January 2016 and December 2018.
Methodology: The study refers to 66 patients with mild neurocognitive disorder (NCD), 51 patients with major NCD, and 133 healthy participants. The Diagnostic and Statistical Manual of Mental

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Disorders (version 5.) criteria were used for the diagnosis of dementia. Statistical analysis was performed using the receiver operator characteristics method.
Results: The optimal cut-off score for the ACE-I for detecting mild NCD was 82, with a sensitivity of 89% and a specificity of 96%. The optimal cut-off for the ACE for identifying major NCD was 76 with sensitivity of 98% and a specificity of 98%.
Conclusion: We concluded that the Hungarian version of the ACE is an accurate test for the detection of NCD, and could be adopted in various clinical practices.

Keywords: Elderly; cognitive impairment; Addenbrooke's cognitive examination; Hungary.

1. INTRODUCTION

The numbers of age-related cognitive disabilities (e.g. mild cognitive impairment, dementia) are increasing worldwide due to the extended lifespan of the elderly and aging population. Aging causes various deteriorations in cognitive functions, and old age is one of the strongest risk factors of dementia [1]. The number of researches on the early screening of dementia and mild cognitive impairments have increased in the last two decades. Alzheimer's disease – just like any other form of dementia – causes a very serious decline in memory, attention, visuospatial abilities, and executive functions. These disturbances interfere with social functions and activities of daily living, therefore the early screening of cognitive decline is a mandatory step in order to diagnose and treat dementia patients appropriately. Due to these reasons an easy-to-take, validated neurocognitive test with good specificity and sensitivity would be even more essential in order to assess mild cognitive impairment and dementia accurately. Compared to the Anglo-Saxon areas, there is a smaller number of cognitive tests obtainable in Hungary for screening and assessing cognitive decline in patients, however, there are some validated and screened clinical tests available to assess cognitive disabilities specifically among persons with Parkinson's disease such as the Addenbrooke's Cognitive Examination- III, the Mini-Addenbrooke's Cognitive Examination, Frontal Assessment Battery, Mattis Dementia Rating Scale [2], and the Montreal Cognitive Assessment [3,4]. Additionally, the Montreal Cognitive Assessment (MoCA) [5], the Paired Associates Learning (PAL) tests [6] are available for "normal", i.e. non-Parkinson's individuals, while the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog) [7] and Test Your Memory (TYM) [8] tests can be used for patients with Alzheimer's disease. Any formerly mentioned measurement tool could be used with other patients – not only with persons living with Parkinson's or Alzheimer's disease –, however, there are no cut-off scores available of these tests for the population of non-Parkinson's people in Hungary at the moment.

The MMSE [9] is one of the most widely used tests in terms of cognitive disabilities assessment, mainly because of its easy administration and evaluation process, but limitations- such as its low level of difficulty, its small number of tasks and narrow range of cognitive abilities-, however, have been demonstrated [10]. Additional limitations include its poor sensitivity in detecting the early stages of dementia [11], uncovering frontal symptoms and distinguishing the different types of dementia.

While Hungary is slightly behind in terms of cognitive disorder tests, Volosin et al. [5] validated Montreal Cognitive Examination (version I.) for the Hungarian population in order to detect mild cognitive impairments and Alzheimer's disease. Their results were published in Hungarian with a low number of healthy participants since the purpose of their study was not to actually analyze normative data.

The goal of present research is to look for an easily administrable and sensitive cognitive test to screen cognitive disabilities in the Hungarian population hence the use of the first version of Addenbrooke's Cognitive Examination (ACE).

The ACE was published in 2000 by Mathuranath and his colleagues [12] and it includes the MMSE test while maintaining a multi-faceted and multidimensional measuring aspect for attention, orientation, memory, language, visuospatial and executive function. Each domain is individually evaluated with the total score ranging between 0 and 100. It can be easily and quickly administered at a bedside and requires no additional training to conduct while taking 15-20 minutes total. The original ACE has been translated and adapted into several other languages [e.g.13,14,15,16,17,18,19,20,21]. The ACE is not only effective in the diagnosis of dementia but also it has distinguished Alzheimer's disease (AD) from frontotemporal dementia (FTD) using the VL/OM ratio = (verbal

fluency + language) / (orientation + delayed recall). It has been developed from observing the phenomenon of AD patients performing better at the verbal fluency and language questions compared to the FTD patients [12].

Several subsequent versions of ACE exist such as the Addenbrooke's Cognitive Examination-Revised (ACE-R) [22] developed in 2006 from an earlier ACE which also contains the MMSE while having clearly defined subdomain scores. It contains modifications on the naming and visuospatial component, and three alternative versions on the name and address recall have been created in order to facilitate cross cultural utilization. Addenbrooke's Cognitive Examination III (ACE III) [23] was developed in 2013 with the purpose of omitting the MMSE part from it. Major changes have been made in the language and visuospatial subdomains (the three-stage command was replaced by a short grammatical comprehension test and the intersecting pentagons were replaced by intersecting lemnisci). This final version contained the same points (with the maximum score of 100) as the ACE and ACE-R. The ACE-R and ACE-III scores correlated very high, and suggesting the results would be similar relating to diagnostic utility [23]. ACE III has a mobile and iPad version (acemobileorg@gmail.com) as well, both are effective at reducing errors compared to the standard paper and pen test version. Mini-Addenbrooke's Cognitive Examination (M-ACE) [24] was developed in 2015 from the longer ACE-R and ACE-III versions. This version with a 30-point scale takes about 5 minutes to perform while measuring attention, memory (7-item name and address), letter fluency, clock drawing and memory recall domains.

At the time of the preliminary planning of our research, only ACE was available to conduct in Hungarian. The aim of this cross-sectional study was to determine the psychometric properties of the Hungarian version of ACE while examining reliability, sensitivity, and specificity in order to identify major and mild neurocognitive disorders. Present psychometric evaluation focused on the effects of age, education, gender on subdomains and total scores.

2. METHODOLOGY

2.1 Research Design and Sampling Methods

A cross-sectional, descriptive study was performed. This study was a part of a larger research, conducted among voluntary elderly from the city of Pécs (Hungary) between January 2016 and December 2018. The sample consisted of two hundred and fifty volunteers, recruited from various community day care centres and senior residents. A self-reported medical, neurological and psychiatric history was obtained from each participant. Inclusion criteria were: age over 60 years; having normal vision and hearing; absence of any conditions related to mental status impairment, such as history of alcoholism, psychiatric illness (e.g. depression), hypothyroidism, or decompensated systematic disease. Patients with depression were excluded from investigation (score > 18 on Montgomery-Asberg Depression Rating Scale) in order to minimize the impact of affective symptoms on cognitive performance. The Diagnostic and Statistical Manual of Mental Disorders (version 5.) criteria [25] were used for the diagnosis of neurocognitive disorder.

2.2 Measures

The Hungarian version of the following tests and scales were administered to all participants: Montgomery-Asberg Depression Rating Scale (MADRS) [26] to measure the possibility of depression; while Mini Mental State Examination [27], and Addenbrooke's Cognitive Examination [21] were included to evaluate the cognitive state of participants.

The Montgomery-Asberg Depression Rating Scale' consists of 10 items evaluating symptoms of depression: apparent and reported sadness, inner tension, reduced sleep and appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts. Items are rated on a 0 to 6 severity scale (0=no abnormality, 6=severe), with higher scores indicating a greater severity of depression. The MADRS is relatively fast to administer taking up to 15-20 minutes to complete.

Mini Mental State Examination assesses orientation (10 points), memory (3 points), visuospatial abilities (1 point), attention, calculation (8 points), and language skills (8 points). The maximum score is 30 points in MMSE with a Cut-off score for dementia being 24 among Hungarian patients [28].

Addenbrooke's Cognitive Examination assesses the domains of orientation (10 points), attention (8 points), memory (35 points), verbal fluency (14 points), language (28 points) and visuospatial

abilities (5 points). The maximum score is 100 points in ACE [29]. ACE was translated and adapted into Hungarian language [21].

Volunteers were divided into three groups according to DSM-5 criteria: participants with major, mild neurocognitive disorders with the control group consisting of participants without any NCD.

2.3 Statistical Analysis

Statistical analyses were performed by IBM SPSS software package (version 19, SPSS Inc, MN) and R for Windows 3.1.2 statistical software. Because most data followed non-normal distribution, non-parametric tests (k-independent-sample test) were applied. $\chi 2$ tests were used for comparison of categorical data (gender). When statistically attainted differences were significant, linear regression analysis was carried out to investigate possible associations between the demographic variable which varied significantly across the groups and the participants' performance in the ACE. Cronbach's α coefficient was calculated for the internal consistency. To measure specificity and sensitivity for neurocognitive batteries, receiver operating characteristic (ROC) curve analysis was obtained. We used the area under the curve (AUC) as a scale of each test's ability to differentiate between groups of participants (mild and major NCD; mild NCD and normal). The level of significance was set at .05.

3. RESULTS

Seventeen patients had coexistent depression; therefore, they were excluded from further analyses. Three more individuals had hypothyroidism and two cases had severe visual impairments. 133 persons had cognitive profiles within the normal range out of the 250 previously evaluated participants, while 66 had mild and 51 major neurocognitive impairments based on the DSM 5 classification.

ACE reliability was very good (Cronbach's alpha coefficient = 0.91).

The range of the age was between 60 and 98 (mean=75.4, SD=8.7) years. 64 (25.6%) elderly persons were males and 186 (74.4%) were females. The education level varied from 4 to 25 years (mean=10.9, SD=4.1). Based on more detailed educational data 31 person had lower than 8 years (means has no primary school), 169 person had between 8 and 12 years (means secondary education, such as vocational training or graduation), and 50 person had higher than 12 years in education (means higher education, such as college or university). 64 (25.6%) elderly persons were males and 186 (74.4%) were females. 21 (8,4%) elderly were unmarried, 52 (20,8%) were married or in a relationship, 28 (11,2%) were divorced, and 149 (59,6%) elderly were widowed. In terms of living conditions 96 (38,4%) voluntary lived in their own house/apartment, and 154 (61,6%) lived in senior residents. Pension rate was low (lower than appr. 150 Euro/month/capita) by 19 elderly (7,6%) and high (higher than appr. 450 Euro/month/capita) by 38 (15,2%). To the question of whether your income is sufficient to cover your expenses, twenty-four individuals (9,6%) answered "yes and could even set aside some", and thirty-one (12,4%) said "no, needs help".

The mean score was 27.5 (SD=2.3) on the Mini Mental State Examination, and 7.2 (SD=4.8) on the Montgomery-Asberg Depression Scale. Mean (SD) score on ACE scale was 82.4 (10). The comparison of the main demographic and clinical characteristics between normal cognition, mild and major neurocognitive disorder groups is presented in Table 1.

The linear regression analysis, using the ACE scores as dependent variable and diagnosis (normal cognition or NCD), age and education distribution as independent factors ($F = 34.915$, $p<0.0001$) pointed that the impact of independent factors was significant (Table 2).

In ROC curve analysis, the results of ACE, and MMSE tests were examined against presence or absence of the clinical diagnosis of neurocognitive disorder to obtain optimal cut-off scores, specificity and sensitivity values. Table 3 shows the sensitivity, specificity and the areas under the ROC curve (AUC) at the optimal cut-off scores of ACE and MMSE. The optimal cut-off was determined as a score where Youden's index was maximized.

Table 1. Comparison of demographic data, MMSE, ACE total and subscores, MADRS score in control, mild, and major neurocognitive disorder groups (mean scores and in parenthesis are standard deviations)

Variables	Normal cognition(n=133)	Mild NCD(n=66)	Major NCD(n=51)	p value*
Gender (n) male/female	28/105	16/50	20/31	.304
Age in years	73.7 (8.7)	76.6 (7.7)	78.4 (8,9)	<.001
Education in years	12.2 (4.3)	10.1 (3.6)	8.7 (3.0)	<.001
MMSE total	28.9 (1)	27.3 (1.3)	24.3 (2.2)	<.001
ACE total	90.1 (4.4)	78.2 (4.4)	67.5 (4.9)	<.001
Orientation	10 (0)	9.8 (0.3)	9.3 (0.5)	<.001
Attention	7.98 (0.1)	7.6 (0.7)	6.5 (1.2)	<.001
Memory	29.7 (2.7)	23.4 (2.4)	17.9 (3.5)	<.001
Verbal fluency	10 (2.2.)	6.9 (2)	5.7 (2.4)	<.001
Language	27.7 (0.7)	26.6 (1.9)	26 (1.9)	<.001
Visuospatial abilities	4.5 (0.7)	3.7 (1.1)	2.3 (1.4)	<.001
MADRS	6.5 (4.6)	7.4 (5.1)	8.6 (4.5)	.103

*MMSE Mini-mental State Examination, ACE Addenbrooke's Cognitive Examination, MADRS Montgomery-Asberg Depression Scale, NCD neurocognitive disorder; *k-independent-sample test were performed using Kruskal Wallis test*

Table 2. Linear regression analysis of ACE scores, age, education and diagnosis

	Unstandardized Coefficients		Standardized Coefficients	t	p value
	B	Std. Error	Beta		
(Constant)	94,362	2,760		34,192	,000
Age (years)	-,105	,032	-,091	-3,251	,001
Education (years)	,280	,071	,114	3,938	,000
NCD	-10,671	,362	-,837	-29,484	,000

NCD: neurocognitive disorder

Table 3. Optimal cut-off scores and psychometric properties ACE and MMSE scores for identifying mild and major NCD

	ACE	MMSE
Differentiation between mild NCD and normal controls		
Cut-off score	82	27
Sensitivity	0.89	0.60
Specificity	0.96	0.90
AUC (SE)	0.96 (0.01)	0.81 (0.02)
Youden-index	0.85	0.50
Differentiation between major NCD and normal controls		
Cut-off score	76	26
Sensitivity	0.98	0.84
Specificity	0.98	0.90
AUC (SE)	0.98 (0.01)	0.97 (0.01)
Youden-index	0.96	0.74
Differentiation between cognitively impaired (mild and major NCD) and normal controls		
Cut-off score	82	27
Sensitivity	0.93	0.76
Specificity	0.96	0.90
AUC (SE)	0.97 (0.01)	0.89 (0.02)
Youden-index	0.89	0.66

MMSE: Mini-mental State Examination, ACE: Addenbrooke's Cognitive Examination, NCD: neurocognitive disorder, AUC: areas under the ROC curve, SE: standard error

The area under the ROC curve of Addenbrooke's Cognitive Examination was .096 [95% confidence interval (CI): .933 to .988]; whereas, the best cut-off score identify mild NCD was 82 points (sensitivity = 89%, specificity = 96%). To identify major NCD the best cut-off score was 76 points (sensitivity = 98%, specificity = 98%,). The optimal cut-off scores to distinguish normal from the cognitively-impaired group were the same at 82, giving a sensitivity of 0.93, and the same specificity of 0.96.

For MMSE, the area under the curve was .818 (95% CI: .748-.889). Best cut-off value for MMSE was 27 points that differentiates the normal and mild neurocognitive disorder groups with the sensitivity of 60.1% and specificity of 90.6%. To identify major NCD the best cut-off score was 26 points (CI: 0,753 to 0,919), sensitivity = 84.3%, specificity = 90.2%. The cut-off for differentiation between cognitively impaired and normal controls were 27 (sensitivity = 76.2%, specificity = 90.1%).

4. DISCUSSION

The present study shows that Hungarian version of ACE has good reliability and diagnostic capacity in the contact of mild and major NCD since – even when compared to MMSE, another widely used screening method – the cut-off scores were associated with more balanced levels of sensitivity and specificity. The distinction between the healthy and the major NCD groups was very satisfactory, with a significant area under the curve and high values of sensitivity and specificity. The ACE is a practical and valuable bedside tool, for the investigation of cognitive functions. All items of MMSE are included in ACE but the differences are significant between the two measurement tools. ACE allows for serial learning, verbal fluency (to test frontal executive function), extended language and reading abilities to be evaluated. With assigning a greater scope for visuospatial function evaluation, the MMSE pentagon drawing task is complemented by three dimensional cube and clock drawings [30].

Dementia is often not diagnosed early enough in the primary care, therefore it is essential to develop a sensitive enough cognitive test, which is able to measure possible cognitive impairments, that is quickly and easily administered even in congested consulting rooms and conducted by busy doctors or untrained assistants. MMSE is still the most widely used measurement tool in Hungary at the moment [31].

By comparing our results with other European countries, the findings are similar. French optimal cut-off score was 83 [14], German 85 [13], Danish 86 [19] and English was 88 [12]. The Spanish [16] validation were found lower cut-off score (68 points), which emphasizes the importance of the number of years in education.

Thus, in spite of the fact that the Addenbrooke's Cognitive Examination has long been further developed internationally, it would fill a gap in Hungary as in our aging society there would be an increasing need for early screening, detection, and professional follow-up in dementia. Based on our current results, we believe, that this cognitive test should be added to the already scarce range of measurement tools.

Other research, in context with the various health variables and diseases, still frequently use the first version of the Addenbrooke's Cognitive Test, as in many places only this version is available with validated results, so for the purposes of the future statistical analysis, this version could be used with the best results. This is emphasized, among other things, by a particular Czech research study examining post-stroke conditions [32].

Additionally, ACE has been used in association with migraines [33], with cognitive changes associated with amyotrophic lateral sclerosis (ALS) [34], in ALS-related respiratory impairment [35] and in association with normal-pressure hydrocephalus [36]. Further examinations, such as profiling cognitive deficits in intra- and extra-axial tumours using ACE as a screening tool [37], Vermani et al. [38] demonstrated a link between elevated blood pressure and decreased cognitive function. Faria et al. [39] examined post-stroke cognitive rehabilitation benefits, Charernboon and Patumanond [40] researched the correlation with social cognition in schizophrenia and Szots et al. [41] examined structural and metabolic brain abnormalities following leucin-rich glioma-inactivated 1 protein (LGI1) encephalitis and correlated findings with acute and follow-up clinical outcomes with the Addenbrooke's Cognitive Examination being used as well.

Present research has some limitations. Firstly, due to the study's voluntary quality, there was small influence on the following factors: gender, age distribution, and other demographic

variables. Individuals who volunteer typically represent a selected group of very healthy and highly functioning elderly, who differ from the general elderly population, especially from the group of elderly referred for dementia evaluation.

The second limiting factor stems from regional limitations resulting in a low participation rate. The study was conducted in the city of Pécs with a lower number of elderly people with only a few of them available to meet the inclusion criteria and the ethical requirements. Thirdly, the reduced number of participants made it difficult to determine the diagnostic utility of ACE in terms of the differentiation between various types of neurocognitive disorders. Having used strict inclusion-exclusion criteria, we tried to mitigate these anomalies.

Thus, our statistical results are of limited value in this respect. Future research should be conducted and these factors should be further investigated based on our current findings.

5. CONCLUSION

The major utility of the present study is to give an easily administered and sensitive cognitive test for screening cognitive disabilities in Hungarian population. Therefore, in conclusion, the Hungarian version of ACE has proven to be a valid instrument in the context of mild and major NCD while it also shows better discrimination capacity in comparison to MMSE. This is especially relevant for the prompt identification of patients that need a more extensive neuropsychological and neurological assessment.

CONSENT AND ETHICAL APPROVAL

Prior to the initiation of the study, all procedures was reviewed by ethical and research committee, University of Pécs (Ethical Permit Number: 3734). Written informed consent was obtained from all participants, they were informed about the nature and objectives of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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