Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog): Normative Data for the Portuguese Population

Escala de Avaliação da Doença de Alzheimer - Subescala Cognitiva (ADAS-Cog): Dados Normativos para a População Portuguesa

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ABSTRACT

Introduction: The Alzheimer's Disease Assessment Scale – Cognitive Subscale is a brief battery developed to assess cognitive functioning in Alzheimer's disease that encompasses the core characteristics of cognitive decline (e.g. memory, language, praxis, constructive ability and orientation). The early detection, as well as the monitoring of cognitive decline along disease progression, is extremely important in clinical care and interventional research. The main goals of the present study were to analyze the psychometric properties of the Portuguese version of the Alzheimer's Disease Assessment Scale – Cognitive Subscale, and to establish normative values for the Portuguese population.

Material and Methods: The Portuguese version of Alzheimer's Disease Assessment Scale – Cognitive Subscale was administered to 223 cognitively healthy participants according to a standard assessment protocol consisting of the Mini-Mental State Examination, the Montreal Cognitive Assessment and the Adults and Older Adults Functional Assessment Inventory. Normal performance on the assessment protocol was the inclusion criteria for the study.

Results: The Alzheimer's Disease Assessment Scale – Cognitive Subscale revealed good psychometric properties when used in the Portuguese population. Age was the main predictor of the Alzheimer's Disease Assessment Scale – Cognitive Subscale total score (R^2 = 0.123), whereas the influence of education level was lower (R^2 = 0.027). These two variables explained 14.4% of the variance on the Alzheimer's Disease Assessment Scale – Cognitive Subscale scores and were used to stratify the normative values for the Portuguese population presented here.

Conclusion: On the total sample, the average total score in the Alzheimer's Disease Assessment Scale – Cognitive Subscale was 6 points. The normative data were determined according to age and educational level as these were the sociodemographic variables that significantly contributed to the prediction of the Alzheimer's Disease Assessment Scale – Cognitive Subscale total scores, explaining 14.4% of their variance. The normative data are of the utmost importance to ensure proper use of this battery in Portugal.

Keywords: Alzheimer Disease; Cognitive Dysfunction; Neuropsychological Tests; Portugal; Surveys and Questionnaires; Translations

RESUMO

Introdução: A Escala de Avaliação da Doença de Alzheimer – subescala cognitiva (ADAS-Cog) é uma bateria neuropsicológica breve desenvolvida para caracterizar o desempenho cognitivo de doentes com doença de Alzheimer. Avalia as funções tipicamente mais comprometidas na doença de Alzheimer considerando os seguintes domínios cognitivos: memória, orientação, linguagem, praxia e capacidade construtiva. A deteção precoce das alterações cognitivas assim como a sua monitorização são fundamentais para a prática em ambos os contextos clínico e de investigação. O presente estudo tem como objetivos analisar as propriedades psicométricas da versão portuguesa da Escala de Avaliação da Doença de Alzheimer – subescala cognitiva e estabelecer dados normativos para a população portuguesa.

Material e Métodos: A versão portuguesa da Escala de Avaliação da Doença de Alzheimer – subescala foi administrada a 223 participantes cognitivamente saudáveis. Todos os participantes foram avaliados com os seguintes instrumentos: *Mini-Mental State Examination*, *Montreal Cognitive Assessment* e Inventário de Avaliação Funcional de Adultos e Idosos. Considerou-se como critério para a inclusão no estudo obter um desempenho normal nestas três provas.

Resultados: A Escala de Avaliação da Doença de Alzheimer – subescala revelou boas propriedades psicométricas quando utilizada na população portuguesa. A idade demonstrou ser o principal preditor do desempenho na Escala de Avaliação da Doença de Alzheimer – subescala (R^2 = 0,123), tendo a escolaridade menor influência (R^2= 0,027). Em conjunto, estas variáveis sociodemográficas explicaram 14,4% da variância na pontuação total da Escala de Avaliação da Doença de Alzheimer – subescala, sendo ambas consideradas na estratificação dos dados normativos para a população portuguesa.

Conclusão: A pontuação total média na Escala de Avaliação da Doença de Alzheimer – subescala foi de 6 pontos. Os dados normativos

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foram estabelecidos de acordo com a idade e escolaridade, sendo estas variáveis sociodemográficas as que mais contribuíram para a predição do desempenho na Escala de Avaliação da Doença de Alzheimer – subescala, explicando 14,4% da variância. Os dados normativos são de extrema importância para o uso adequado desta bateria em Portugal.

Palavras-chave: Disfunção Cognitiva; Doença de Alzheimer; Inquéritos e Questionários; Portugal; Testes Neuropsicológicos; Traduções

INTRODUCTION

Currently there is a demographic aging phenomenon occurring worldwide. Demographic projections indicate that by 2050 the world population above 60 years old will be over two billion, comparing with the 841 million in 2013. Moreover, by 2047 elderly people will exceed the number of children.[1] The prevalence of dementia increases exponentially with age and, as a result, the number of patients is expected to grow in the next decades. A study developed in Portugal between 2003 and 2008, suggested that at least 12.3% suffered from cognitive decline.[2,3] In 2014, the number of deaths caused by Alzheimer's disease (AD) reached a total of 1650, of which 64% were women.[4] More importantly, the number of Portuguese individuals with dementia among those aged 60 years old or above was recently estimated as 160 287, representing 5.91% of this population-stratum. AD is responsible for 50% - 70% of all dementia cases – as such, there may be between 80 144 and 112 201 AD patients in Portugal.[5] These data reflect an increase in the prevalence rate of dementia comparing with the equivalent estimate for 1991.[6] Based on the 1991 census of the Portuguese population and the EURODEM data, Garcia and colleagues pointed out a prevalence rate of 4.6%, corresponding to 92 470 patients with dementia of which 48 706 patients had Alzheimer's disease.[6] According to these data, finding effective responses for these aging-related issues is one of the most important societal and scientific challenges we face today.[7,8] In the dementia spectrum, early detection as well as monitoring cognitive decline along disease progression are extremely important in clinical care and interventional research. Brief neuropsychological batteries remain the most accepted instruments in both settings and the neuropsychological assessment is still considered as a strategy to use in monitoring and diagnosis, according to the most updated norms for the target population.[9,10] However, to ensure the quality of the information collected, we need to use psychometrically validated instruments and obtain normative data for the reference population.

The Alzheimer's Disease Assessment Scale – cognitive sub-scale (ADAS-Cog)[11-13] is a brief battery developed to assess cognitive status in AD patients. The ADAS-Cog has also been used as a primary outcome measure in clinical trials for AD, as a way to index the global level of cognitive functioning in response to new drugs.[14-16] The ADAS-Cog was developed to tackle the core characteristics of cognitive decline in AD: memory, language, praxis, constructive ability and orientation.[17] It is divided in two formal evaluation parts: the first is a brief interview that aims to assess several spontaneous language features (as fluency in speech, naming, comprehension and quality of speech); the second is a battery of tests aimed at assessing multiple cognitive domains including: Word recall; Naming; Commands; Constructional praxis; Ideational praxis; Orientation; Word recognition; Remembering test instructions; Spoken language ability; Word finding difficulty and comprehension of oral language.[18] In Portugal, the ADAS-Cog was translated, adapted and transculturally validated by Guerreiro and colleagues (2008). These authors also defined cut-off values by age and level of education (including illiterate individuals).[13] Nonetheless, this preliminary Portuguese validation study used a restricted group of subjects living in an urban area, and the psychometric studies were also limited. Besides, higher formal education levels and better health care nowadays, as well as access to new technologies, may lead to higher cognitive reserve and better performance on cognitive tasks. Therefore, the update of normative values according to these hypothetic population's improvements is imperative for the batteries that are more often used in clinical diagnosis.[19]

The main goals of this study are to demonstrate the validity of ADAS-Cog and to establish robust norms to evaluate the performance of the Portuguese population. For this, we will explore the psychometric characteristics of the Portuguese version of the ADAS-Cog, and investigate the sociodemographic variables that have a major influence on the scores of the ADAS-Cog. These will be used as criteria to stratify and establish the normative data for the Portuguese population.

MATERIAL AND METHODS

Study population, materials and procedures

The study group was composed of cognitively healthy adults and older individuals that are actively involved in the community. These individuals were recruited from aging support groups and associations and health care centers. Several demographic and clinical inclusion criteria were considered in the initial selection of participants including being 50 years or older; being Portuguese native speakers; and having at least one year of formal education (i.e., ability to read and write). After this first selection stage, participants were interviewed by a psychologist using a standard clinical interview. This interview included a sociodemographic questionnaire and collected data on habits, medical history and current medication intake. Based on the data collected in this interview we excluded participants with a current history of psychiatric or neurologic diseases (including the presence of relevant depressive symptomatology) or under medications with possible impact in cognition. The third step was a global assessment composed by the following instruments – which have transcultural adaptation and validation studies for the Portuguese population – that were administered to each participant in this fixed order: the Mini-Mental State Examination (MMSE),[20,21] the Montreal

Cognitive Assessment (MoCA),[22,23] the Adults and Older Adults Functional Assessment Inventory (IAFAI)[24] and the ADAS-Cog.[11-13] According to this objective cognitive and functional assessment we further excluded individuals with a score that fell outside the normative range by age and education level for the Portuguese population[23,25] in the MMSE[20,21] and the MoCA,[22,23] as well as people with functional deficits in daily living autonomy and emotional dependence as measured by the IAFAI. The ADAS-Cog was never used as a criterion for selection or classification. This study was approved by local ethics committee and all participants gave written informed consent prior to participation.

Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS), Version 21 for Windows. Descriptive statistics were used for the sample's characterization. Differences within subgroups according to sociodemographic variables were explored using the Student's *t* test and one-way between-groups analysis of variance (ANOVA), complemented by Tukey HSD and Bonferroni *post hoc* test. To assess internal consistency of ADAS-Cog we used the Cronbach α index. Construct validity was indexed by calculating Pearson correlations between items, subtasks and total scores of ADAS-Cog (*r*).[27] Convergent validity was determined using Pearson correlation coefficients between the ADAS-Cog, the MoCA, and the MMSE scores (*r*).[27] The influence of sociodemographic characteristics, as age and education level, in ADAS-Cog scores was addressed with multiple linear regression (MLR) analysis (Enter method). Finally, the normative values of ADAS-Cog were stratified and determined according to the sociodemographic variables most significantly associated with ADAS-Cog scores showed by MLR analysis. The normative values are presented as means ± standard deviations (*SDs*), and the distributions of means below 1 *SD*, 1.5 *SDs*, and 2 *SDs*.

RESULTS

A total number of 228 participants were enrolled. Three were excluded in the clinical interview due to psychiatric history and two showed cognitive performances that were below the normal score for their educational level and age on the tests used. These cases were further referred for clinical evaluation where the diagnosis of cognitive decline was confirmed.

The final sample was composed of 223 participants and the sociodemographic characterization by age, education level, and gender is presented on Table 1. Participants were stratified according to age and educational level. We divided our sample in three age groups: those between 50 and 64 years of age (mean age = 58.18 ± 3.58), those between 65 and 74 years of age (mean age = 70.05 ± 3.44), and those 75 and older (mean age = 79.39 ± 2.86). We also divided our sample into three education levels: 1 - 4 years of education (primary school), 5 - 9 years of education (middle school), and over 10 years of education (high school and college). The cognitive and functional characterization of the sample can be seen in Table 2.

The ADAS-Cog showed internal consistency: we obtained a Cronbach α of .323 for the subtasks of the battery, and a Cronbach α of .554 for its items. Internal consistency did not improve with the exclusion of any items/subtasks. The correlation between the MMSE and the ADAS-Cog, as well as between the MoCA and the ADAS-Cog were significant and negative in the total sample (MMSE-ADAS-Cog: r = -0.37, p < 0.01; MoCA-ADAS-Cog: r = - 0.42, p < 0.01), suggesting strong convergent validity. In order to explore indicators of construct validity, we calculated a set of correlations. Specifically, we calculated correlations between items, between items and subtasks, between items and the total score of the ADAS-Cog, and between the subtasks and the total score of the ADAS-Cog. For the correlations between items, our coefficients negatively ranged from -0.01 (p = 0.90) to -0.26 (p < 0.01) and positively ranged from 0.01 (p = 0.91) to 1 (p < 0.01), (there were no null correlations). For the correlations between items and subtasks, our coefficients negatively ranged from -0.01 (p = 0.84) to -0.85 (p < 0.01) and positively ranged from 0.05 (p = 0.52) to 0.81 (p < 0.01), (there were no null correlations). Importantly, items were more correlated with their own subtask. For instance, one trial of word recall presented a significant positive correlation with the word recall subtask

Table 1 - Sociodemographic characterization of the final sample

	Age (M ± SD) [Min - Max]	**Education level** (M ± SD) [Min - Max]	**Gender** F (%)
Final Sample	(69.15 ± 8.68) [50 – 88]	(8.22 ± 4.87) [2 – 18]	130 (58.3%)

Gender is presented by female's n and its respective percentage *(%)*. The others variables are presented with its means ± standard deviation.

Table 2 - Cognitive and functional characterization of the final sample

	MMSE	MoCA	IAFAI	ADAS-Cog
Final Sample (M ± SD) [Min - Max]	(29.05 ± 1.03) [27 – 30]	(23.64 ± 3.16) [21 – 29]	(0.26 ± 1.25) [0 – 10.64]	(6.12 ± 2.46) [0 – 13]

MMSE: Mini Mental State Examination (maximum score = 30); MoCA: Montreal Cognitive Assessment (maximum score = 30); IAFAI: Adults and Older Adults Functional Assessment Inventory (maximum score = 100%); ADAS-Cog: Alzheimer Disease Assessment Scale – Cognitive Subscale (maximum score: 70).

(r = 0.81, p < 0.01). For the correlations between items and total score of the ADAS-Cog, coefficients negatively ranged from -0.01 (p = 0.96) to -0.38 (p < 0.01) and positively ranged from 0.02 (p = 0.85) to 0.60 (p < 0.01, (there were no null correlations). Finally, for the correlations between subtasks and total score of the ADAS-Cog, coefficients ranged from 0.11 (p = 0.11) to 0.73 (p < 0.01). The correlations computed between ADAS-Cog total score and its cognitive domains were significant (at the level p < 0.05 or p < 0.01) for Word recall (p < 0.01), Commands (p < 0.01), Constructional Praxis (p < 0.01), Ideational Praxis (p = 0.01), Orientation (p = 0.01) and Word Recognition (p < 0.01).

The analysis of the group differences on performance on the ADAS-Cog showed that there were no statistically significant differences between gender ($t_{(221)}$ = -1.613, p = 0.108). There were, however, significant differences between the three age groups ($F_{(2, 220)}$ = 14.045, p < 0.01). *Post hoc* t-tests revealed that the younger group (50 - 64 years old) performed significantly better than the other groups (65 - 74 and + 75 years old), whereas the older groups did not differ from each other. Performance also differed significantly between the three educational level groups ($F_{(2, 220)}$ = 3.507, p = 0.03). *Post hoc* tests revealed that the performance of the two extreme groups differed significantly ($t_{(176)}$ = 2.56, p = 0.01).

Conversely, statistically significant correlations were observed between the ADAS-Cog scores and age (r = 0.35, p < 0.01) and education level (r = -0.17, p = 0.01). We then proceeded with MLR to study the influence of age and education level on the ADAS-Cog scores, as well as to examine their contribution and interaction as significant variables. Both variables contributed significantly to the prediction of the ADAS-Cog scores ($F_{(2,220)}$ = 18.57, p < 0.01), although the beta weights suggests that age (ß = 0.343, p = 0.02, 95% CI: 0.062 - 0.132) contributes more to predicting the ADAS-Cog scores, but that education level (ß = -0.146, p < 0.01) also contributes to this prediction. The R^2 value was 0.144, which is indicates that 14.4% of the variance on the ADAS-Cog scores was explained by the model.

Finally, we set out to stratify our sample and calculate normative values. According to the results of the MLR analysis, age and education level were considered in the development of the normative values of the ADAS-Cog for the Portuguese population (Table 3). To obtain these normative values we stratified the sample according to the strata of these main variables, and calculated the means and standard deviations (M ± SD) for each subgroup, crossing the several education and age levels and presented cut-off points of 1 *SD*, 1.5 *SDs*, and 2 *SDs*. Finally, we established the same norms to 'all education levels' and 'all age' to cover situations with lack of sociodemographic information.

Table 3 - Normative values of ADAS-Cog according to age and education level

Age		Education (years) Primary (1 - 4)	Middle (5 - 9)	High (≥ 10)	All education
50 - 64	n	27	17	21	65
	M ± SD	5.48 ± 2.17	5.41 ± 2.21	3.67 ± 2.08	4.88 ± 2.28
	SD[1]	8, 9, 10	8, 9, 10	6, 7, 8	7, 8, 9
	Mode	6	4	2	6
	Median	6	5	3	5
	95% CI	[4.62 - 6.34]	[4.28 - 6.55]	[2.72 - 4.61]	[4.31 - 5.44]
65 - 75	n	47	17	33	97
	M ± SD	6.85 ± 2.57	5.89 ± 1.93	6.06 ± 1.62	6.41 ± 2.20
	SD[1]	9, 11, 12	8, 9, 10	8, 8, 9	9, 10, 11
	Mode	6	4	7	6
	Median	7	5	6	6
	95% CI	[6.10 - 7.61]	[4.89 - 6.88]	[5.49 - 6.63]	[5.97 - 6.86]
+ 75	n	27	11	23	61
	M ± SD	7.15 2.84	7.09 ± 2.26	6.70 ± 2.46	6.97 ± 2.57
	SD[1]	10, 11, 13	9, 10, 12	9, 10, 12	10, 11, 12
	Mode	6	8	6	6
	Median	7	8	7	7
	95% CI	[6.03 - 8.27]	[5.58 - 8.61]	[5.63 - 7.76]	[6.31 - 7.63]
All age	n	101	45	77	223
	M ± SD	6.56 ± 2.61	6.00 ± 2.17	5.60 ± 2.34	6.12 ± 2.46
	SD[1]	9, 10, 12	8, 9, 10	8, 9, 10	9, 10, 11
	Mode	6	5	7	6
	Median	6	6	6	6
	95% CI	[6.05 - 7.08]	[5.35 - 6.65]	[5.07 - 6.13]	[5.79 - 6.44]

[1]ADAS-Cog values above 1 SD, 1.5 SDs, and 2 SDs, respectively

DISCUSSION

In this study we established normative data on the ADAS-Cog for the Portuguese population stratified according to age and educational level, using a community-based sample of cognitively healthy adults. Despite the worldwide use of this battery as cognitive primary outcome measure in clinical trials, there are few international normative studies.[28,29] Thus, this study expands our knowledge about this instrument and allows a more accurate and reliable clinical use of the ADAS-Cog in Portugal or within the Portuguese speaking communities living abroad.

In order to demonstrate the clinical value of the instrument we firstly explored the psychometric characteristics of the Portuguese version of the ADAS-Cog. We tested the internal consistency using Cronbach's alpha which is the most commonly used measure.[30] We obtained values below the recommended minimum of 0.70, a limitation also observed in other international psychometric studies with the ADAS-Cog.[31] Several factors may potentially explain these results, namely the sample size. Note, however, that the meaning of Cronbach's alpha is still controversial within the psychometric community, suggesting that this index might not be sufficient as a reliability measure.[31]

As expected, we observed a negative correlation between ADAS-Cog scores and both MMSE and MoCA scores. This is indicative of convergent validity of the ADAS-Cog. The correlations obtained between items, subtasks, and total scores are good indicators of construct validity. We found significant positive correlations between different components of the subtasks and all of the items. Moreover, items were more highly correlated with their own subtask. Indeed, all subtasks were positively correlated with the ADAS-Cog total score revealing its construct validity.

Similarly to previous studies conducted with the ADAS-Cog,[32,33] we found that age was a better predictor of the ADAS-Cog scores than education level. In fact, Graham and colleagues (2004) found no influence of this variable within people with ten or more years of education, leading them to suggest this education level as the threshold for a reliable evaluation of the ADAS-Cog's performance. Therefore, this evidence is in accordance with our results, corroborating the minor effect of education years in the ADAS-Cog's performance. The total sample of this study showed an average educational level lower than the average of the Graham and colleagues' study (2004), however, we obtained a similar performance mean in the ADAS-Cog total score. Conversely, Liu and colleagues (2002) demonstrated that level of education is important when testing individuals with very low education (e.g. zero to six years), a stratum that is also represented in our sample. Nevertheless, we should emphasize that the dominance of age *vs.* education was an unexpected result considering our previous experience with other cognitive instruments, such as the MMSE[20,21] or the MoCA where education has been the strongest predictor.[22,23,25,34-36]

Despite the fact that the MLR analysis results indicated a minor influence of educational level on the performance on the ADAS-Cog, we elected to consider both sociodemographic variables (age and education) when establishing normative values for the Portuguese population. Together, these variables contribute significantly to the prediction of the ADAS-Cog scores, explaining 14.4% of the results variance.

It is important to point out that the exclusion of illiterate individuals from our study limits the application of the ADAS-Cog to this segment of the population. The decision was based on the fact that there is evidence of floor effects in cognitive batteries that are purportedly unaffected by education like ADAS-Cog.[29,37] Cognitive evaluation needs to be adapted to ensure the reliability of scores obtained by illiterates, because illiteracy seems to influence cognitive processes well beyond the ability to read or write. Specifically, illiteracy affects language, praxis, and visuospatial abilities – all of which are main components of ADAS-Cog. For instance, difficulties can occur in naming tasks (e.g. illiterates have difficulties in naming the different fingers), in verbal commands (e.g. illiterates tend to omit sequences), in ideational praxis (e.g. the subtask is composed by familiar tasks for literates – sending a letter), and in constructional praxis (e.g. illiterates show difficulties in copying geometric figures).[17,38] Moreover, illiterate individuals have fewer strategies to process and retain verbal material (e.g. they can recruit auditory cortex to help in memorization, while literate individuals can recruit visual and auditory processes).[17] Finally, phonemic verbal fluency and speech are also prone to the effects of education.[37,38] Therefore, we believe that ADAS-Cog needs to be adapted to this special population – namely the structure, the items, the administration, and the scoring system should be modified to ensure the reliability of scores obtained by illiterate individuals.

Another potential limitation of our study is the fact that we did not use any formal scale for assessing depressive symptoms. Importantly, however, both the clinical interview and the IAFAI were used as a screening for recent psychiatric or psychological conditions or specific medication. In fact, three participants were excluded due to the presence of psychiatric clinical history identified in the interview and by the clinical and the emotional items of IAFAI.

Finally, in future studies it would be important to develop specific validation data for Mild Cognitive Impairment and dementia, allowing the complementary use of ADAS-Cog as a staging instrument in the spectrum of Alzheimer's disease. Additionally, given the modest rate of total explained variance results found in this study (14.4%), we emphasize the need to develop normative studies with larger samples that allow the better stratification by several sociodemographic variables. Finally, it will also be important in future studies to compute using Item Response Theory to analyze the fitting of the data to the model and the reliability values for the estimation of the items and persons, as well as to conduct differential item functioning (DIF) analyses in order to explore the possibility that individual subscales might work differently as a function of pathology, gender,

age or educational level.

CONCLUSION

In this study, we established normative values of the ADAS-Cog for the Portuguese population. On the total sample, the average total score in the ADAS-COG was six points. The normative data were determined according to age and educational level as these were the sociodemographic variables that significantly contributed to the prediction of the ADAS-Cog total scores, explaining 14.4% of their variance. The normative data are of the utmost importance to ensure proper use of this battery in Portugal, mainly because this battery is required by regulatory agencies as a primary efficacy measure for ongoing clinical trials testing new drugs in AD and is a widely used instrument for the crucial early detection of cognitive decline in both clinical and research contexts.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication. Informed consent was duly obtained from the patient.

CONFLICTS OF INTEREST

All authors report no conflict of interest.

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