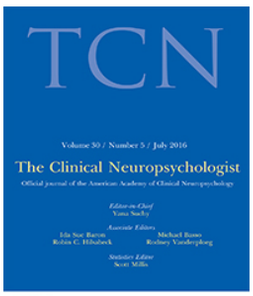

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Validation study of the Alzheimer's disease assessment scale–cognitive subscale (ADAS-Cog) for the Portuguese patients with mild cognitive impairment and Alzheimer's disease

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ABSTRACT

Objective: The Alzheimer's disease assessment scale–Cognitive Subscale (ADAS-Cog) is a battery to assess cognitive performance in Alzheimer's disease (AD) and was developed according to the core characteristics of cognitive decline in AD: memory, language, praxis, constructive ability, and orientation. The aim of this study was to explore the diagnostic accuracy and discriminative capacity of the ADAS-Cog for Mild Cognitive Impairment (MCI) and AD, using cut-off points for the Portuguese population. **Method:** The European Portuguese version of the ADAS-Cog was administrated to 650 participants, divided into a control group (n = 210), an MCI group (n = 240), and an AD group (n = 200). The clinical groups fulfilled standard international diagnostic criteria. Controls were healthy cognitive participants actively integrated in the community. The neuropsychological assessment protocol included the ADAS-Cog, the Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Adults and Older Adults Functional Assessment Inventory (IAFAI). **Results:** The ADAS-Cog revealed good psychometric indicators, and the total scores were significantly different between the three groups ($p < .001$: Control < MCI < AD). The optimal cut-off points established were: MCI > 9 points (AUC = .835; sensitivity = 58% and specificity = 91%) and AD > 12 points (AUC = .996; sensitivity = 94% and specificity = 98%). **Conclusions:** Our findings confirmed the capacity of the ADAS-Cog total score to identify cognitive impairment in AD patients, with poor sensitivity for MCI, in a Portuguese cohort.

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ADAS-Cog; neuropsychological assessment; mild cognitive impairment; Alzheimer's disease; dementia

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Introduction

The progressive increase in life expectancy during the twentieth century led to a dramatic rise of the incidence and prevalence of dementia, including its most common cause, Alzheimer's disease (AD; Prince et al., 2013; World Health Organization [WHO], 2012). AD patients present insidious and progressive cognitive decline and behavioral impairment (Albert et al., 2011; Sperling et al., 2011). The transitional state between normal aging and dementia has been described as Mild Cognitive Impairment (MCI), a heterogeneous neuropsychological and clinical condition (Petersen, 2004; Petersen et al., 1999). The amnestic MCI subtype is the most prevalent, and epidemiological, clinical, and neuropathological research suggests that in the majority of amnestic MCI patients, a prodromal form of AD is already present (Mitchell et al., 2002; Morris & Price, 2001; Petersen et al., 1999, 2014; Santana, 2003). Neuropsychological assessment continues to be a privileged method to assess cognitive functioning, which is essential for the diagnosis of dementia. In addition, brief neuropsychological batteries remain the best method to monitor the progression of decline, and the efficacy of interventions (Strauss, Sherman, & Spreen, 2006). So it is crucial to use versions these tests that are adapted to the cultural context of the patients as to ensure the quality and validity of information provided by these instruments.

The Alzheimer's disease assessment scale—cognitive sub-scale (ADAS-Cog; Mohs, Rosen, & Davis, 1983; Rosen, Mohs, & Davis, 1984) is a brief battery developed to assess cognitive performance in AD patients in clinical trials and clinical practice. From 1992 onwards, drug regulatory agencies such as the Food and Drug Administration (FDA) require the ADAS-Cog as an efficacy measure for clinical trials in AD and MCI, as well as a primary cognitive outcome (Davis et al., 1992; Doraiswamy et al., 1997; Schneider & Sano, 2009; Skinner et al., 2012; Vellas, Andrieu, Sampaio, Coley, & Wilcock, 2008). However, some authors have suggested that the ADAS-Cog shows poor efficacy when assessing milder forms of dementia, revealing limitations for its use in clinical trials with MCI patients (Sano et al., 2011). Specifically, these limitations include the undervaluation of critical functions in AD (e.g. attention, working memory and executive functions), the low sensitivity for milder forms of the disease (e.g. MCI) that are mostly caused by either floor and ceiling effects, and the inadequate weighted score system (Karin et al., 2014; Skinner et al., 2012; Verma et al., 2015). Nevertheless, and despite its structural short-form (Monllau et al., 2007), it is commonly accepted that the ADAS-Cog can predict the conversion to AD with acceptable sensitivity and specificity. Interestingly, the results of some validation studies (Monllau et al., 2007; Youn et al., 2002; Zainal, Silva, Lim, & Kandiah, 2016) focusing on the establishment of diagnostic parameters corroborate our results. This is especially true for Monllau et al.'s study (2007) on a Spanish sample, because of the similarities between the Portuguese and Spanish cultures. In a similar vein, Zainal et al. (2016) studied a population in an Asian context, and showed that the optimal cut-off point obtained for AD was similar to the Korean one. Furthermore, both studies had similar age mean and similarities in cultures, which are important variables to consider in the comparison between validation studies.

In Portugal, the ADAS-Cog was translated, adapted and transculturally validated by Guerreiro, Fonseca, Barreto, and Garcia (2008). The first normative study of the European Portuguese version of the ADAS-Cog used an adult and an elderly cognitively healthy group, from which preliminary cut-off values by age and level of education (including illiterate individuals) were defined (Guerreiro et al., 2008). Recently, the norms according to age and

Table 1. Sociodemographic and cognitive characterization of the groups.

	Control	MCI	AD
n	210	240	200
Age	69.13 ± 8.72	69.62 ± 8.20	69.14 ± 9.84
Education level	7.70 ± 4.52	6.85 ± 4.46	6.74 ± 4.05
Gender	125(59.5)	141(58.8)	125(62.5)
MMSE score	29.02 ± 1.04	27.24 ± 2.20	21.70 ± 3.86
MoCA score	23.56 ± 3.14	19.30 ± 4.82	10.27 ± 3.60
ADAS-Cog score	6.16 ± 2.49	10.68 ± 4.01	21.03 ± 7.51

Notes: Gender is presented by female's *n* and its respective percentage *(%)*. The others variables are presented as means ± standard deviation. MCI = Mild Cognitive Impairment; AD = Alzheimer's Disease; MMSE = Mini Mental State Examination (maximum score = 30); MoCA = Montreal Cognitive Assessment (maximum score = 30); ADAS-Cog = Alzheimer;. Disease assessment scale—cognitive subscale (maximum score = 68).

educational level of the Portuguese population were updated (Nogueira et al., 2018). The Portuguese version of the ADAS-Cog is often used by clinicians to monitor the progression of AD and follows the same administration and scoring instructions as the original version (Mohs et al., 1983; Rosen et al., 1984).

The present study aims to validate the European Portuguese version of the ADAS-Cog for the cognitive assessment of MCI and AD (mild to moderate severity) patients. More specifically, we aim to present an exploratory analysis on its psychometric properties, analyze the cognitive performance of the study groups (Control group vs. MCI, Control group vs. AD, and MCI vs. AD), and determine the respective optimal cut-off points and diagnostic accuracy.

Methods

Participants and procedures

The study sample was composed by 650 participants distributed between three groups: a Control group with 210 cognitively healthy adults, a MCI group with 240 patients and an AD group with 200 patients. The demographic data of each group are presented in Table 1.

The MCI and AD patients were recruited at the Memory Clinic of the Neurology Department of a central hospital. All patients underwent: a medical exam by a neurologist; complementary diagnostic exams (e.g. laboratory analysis—with genotype study of Apolipoprotein E, APOE–structural imaging exams—by axial computed tomography and magnetic resonance—and functional—SPECT); other complementary medical exams (e.g. PET analysis and Cerebrospinal fluid analysis through lumbar puncture). AD patients were assessed with the "Bateria de Lisboa para a Avaliação da Demência" (Guerreiro, 1998), and by an extensive neuropsychological protocol used to determine the progression of cognitive decline, composed by the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; Guerreiro et al., 1994), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Simões et al., 2008), the ADAS-Cog (Guerreiro et al., 2008; Mohs et al., 1983; Nogueira et al., 2018; Rosen et al., 1984), the Clinical Dementia Rating scale (CDR; Garret et al., 2003; Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993), the Geriatric Depression Scale (Barreto, Leuschner, Santos, & Sobral, 2008; Simões & Firmino, 2013; Yesavage et al., 1983), the Subjective Memory Complaints test (Ginó, Guerreiro, & Garcia, 2008; Schmand, Jonker, Hooijer, & Lindeboom, 1996), the Neuropsychiatric Inventory (NPI; Cummings, 1997;

Cummings et al., 1994; Leitão & Nina, 2008), the Blessed Dementia Scale (Blessed, Tomlinson, & Roth, 1968; Garcia, 2008) and the Disability Assessment for Dementia (DAD; Gelinas, Gauthier, McIntyre, & Gauthier, 1999; Leitão, 2008). A final diagnosis was established by a multidisciplinary team following the international criteria for MCI (Albert et al., 2011; Petersen et al., 1999) and probable AD following the recommendations of NINCDS-ADRDA (McKhann et al., 2011). The MCI group included only patients with amnestic form, and the AD group included patients presenting mild to moderate dementia.

The Control group was composed of cognitively healthy elderly individuals actively inserted in the community. The inclusion and exclusion criteria in the initial selection of participants included being 50 years or older, being Portuguese native speakers, and having had at least one year of formal education (i.e. acquired ability to read and write). The participants were interviewed by a neuropsychologist using a standard clinical interview, including a sociodemographic and personal questionnaire (i.e. 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 (e.g. psychotropic or psycho-active drugs). Autonomous functioning in both basic and instrumental activities of daily living was assessed through the Adults and Older Adults Functional Assessment Inventory (Sousa, Vilar, & Simões, 2013). Normal global cognitive status was ensured through a neuropsychological assessment that included, in this specific order, the MMSE (Folstein et al., 1975; Freitas, Simões, Alves, & Santana, 2015; Guerreiro, 1998), and the MoCA (Freitas, Simões, Alves, & Santana, 2011; Nasreddine et al., 2005; Simões et al., 2008), and that was followed by the administration of the ADAS-Cog (Guerreiro et al., 2008; Mohs et al., 1983; Nogueira et al., 2018; Rosen et al., 1984). We further excluded individuals with a score that fell outside the normative range by age and education level for the Portuguese population in the MMSE (Freitas et al., 2015) and the MoCA (Freitas et al., 2011).

All participants signed an Informed Consent form that included a through explanation of research aims, procedures and the confidentiality of the information provided. This thorough explanation was also provided to the legal representatives, companions, or caregivers. The present research complied with the ethical guidelines for human experimentation stated in the Declaration of Helsinki and was approved by the Ethics Board and Scientific Committee of the affiliated Portuguese institutions.

Materials

The ADAS-Cog is divided in two formal evaluation parts: the first is a brief interview that aims to assess several spontaneous language features (e.g. as fluency in speech, comprehension and quality of speech); the second part assesses multiple cognitive domains: memory, language, praxis, constructive ability, and orientation. It is composed by 11 subtests: 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 (Connor & Schafer, 1994). The ADAS-Cog total score ranges from 0 to 70 points, where higher scores reflect poorer performances or greater cognitive impairment (Lezak, Howieson, & Loring, 2004).

Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 22 (IBM Corp., Armonk, N.Y., USA, 2013). Descriptive statistics were used to characterize the sample. Two-sample *t*-test and one-way between-groups analysis of variance (ANOVA) were used to explore group differences. Internal consistency of the ADAS-Cog was measured by Cronbach's alpha. Pearson's correlation coefficients were conducted to explore the concurrent and construct validities. Estimates of effect size were also calculated through analysis of eta squared (η^2; Cohen, 1988). The diagnostic accuracy of the ADAS-Cog for the identification of MCI and AD patients was assessed with receiver operating characteristics (ROC) curve analysis, wherein larger areas under the curve (AUC) indicated better diagnostic accuracy. The optimal cut-off points were determined by Youden's index formula, where higher Youden index indicated maximization of sensibility and specificity. For each cut-off point we calculated the sensitivity (the probability for subjects with disease to have a positive test), specificity (the probability for subjects without disease to have a negative test), positive predictive values (PPV; the probability of disease in subjects who have a positive test), negative predictive value (NPV; probability of the classification "without disease" in subjects who have a negative test), and classification accuracy (probability of correct classification of subjects with or without disease). The comparative analysis between the AUC values was performed through the statistical software MedCalc for Windows, version 18 (MedCalc Software, Ostend, Belgium, 2018).

Results

Sample characterization

The characteristics of the total study sample and of each group are presented in Table 1. We present data on the sample size, age, education level, gender, MMSE score, MoCA score, and ADAS-Cog score. No statistically significant differences were found on mean age ($F_{(2, 647)}$ = .22; p = .80) and mean educational level ($F_{(2, 647)}$ = 3.05; p = .05) between the groups. According to *post hoc* tests, we obtained the same pattern for each comparison (mean age: control = MCI = AD; mean education level: control = MCI = AD).

There were statistically significant differences between the groups on cognitive performance on the MMSE total score ($F_{(2, 647)}$ = 446.02; p < .01) and MoCA total score (F(2, 647) = 115.58; p < .01). According to *post hoc* analysis, in both instruments the control group had higher performance levels, followed by the MCI group, and by the AD group with the lowest performance.

Psychometric properties

We used the Cronbach's alpha (α) of the ADAS-Cog as an index of internal consistency. We obtained a result of .791 for the total study sample. This analysis was also computed for each clinical group: α(MCI) = .744 and α(AD) = .706. The results also indicated that the internal consistency would not improve with the exclusion of any items/subtasks.

To explore concurrent validity, we computed the correlations between the MMSE total score and the ADAS-Cog total score, as well as between the MoCA total score and the ADAS-Cog total score. The results were significant and negative in the total sample (MMSE: r = –.85,

Table 2. Sociodemographic and cognitive characterization of the groups.

	Control	MCI	AD	
n	210	240	200	Differences between groups
Total score	6.16 ± 2.49	10.68 ± 4.01	21.03 ± 7.51	$F_{(2, 647)} = 470.43$, $p<.01$
WR	3.61 ± 1.35	4.89 ± 1.43	6.73 ± 1.31	$F_{(2, 647)} = 269.33$, $p<.01$
NM	.08 ± .27	.31 ± .52	.54 ± .68	$F_{(2, 647)} = 39.53$, $p<.01$
CO	.20 ± .45	.26 ± .51	.85 ± 1.02	$F_{(2, 647)} = 53.56$, $p<.01$
CP	.39 ± .59	.66 ± .64	1.31 ± .96	$F_{(2, 647)} = 83.97$, $p<.01$
IP	.08 ± .29	.31 ± .52	.67 ± .76	$F_{(2, 647)} = 57.51$, $p<.01$
OR	.08 ± .29	.46 ± .88	2.67 ± 1.83	$F_{(2, 647)} = 298.54$, $p<.01$
WR	1.74 ± 1.33	3.41 ± 1.99	6.22 ± 2.77	$F_{(2, 647)} = 238.5$, $p<.01$
RTI	.02 ± .18	.18 ± .53	1.06 ± 1.49	$F_{(2, 647)} = 78.1$, $p<.01$
SPA	.00 ± .00	.03 ± .18	.36 ± .89	$F_{(2, 647)} = 32.98$, $p<.01$
WFD	.00 ± .00	.04 ± .21	.38 ± .98	$F_{(2, 647)} = 29.02$, $p<.01$
COL	.00 ± .00	.01 ± .11	.29 ± .75	$F_{(2, 647)} = 30.04$, $p<.01$

Notes: WRT = Word Recall Task; NT = Naming Task; COM = Commands; CP = Constructional Praxis; IP = Ideational Praxis; OR = Orientation; WR = Word Recognition; RTI = Remembering Test Instructions; SLA = Spoken Language Ability; WFD = Word Finding Difficulty; COL = Comprehension of Oral Language.
These subtasks are presented as means ± standard deviation.

$p < .01$; MoCA: $r = -.78$, $p < .01$), as well as in MCI (MMSE: $r = -.60$, $p < .01$; MoCA: $r = -.68$, $p < .01$) and AD groups (MMSE: $r = -.68$, $p < .01$; MoCA: $r = -.51$, $p = .008$).

In order to explore indicators of construct validity, we calculated correlations between subtasks and the total score of the ADAS-Cog for each group. In the total sample, the coefficients ranged between $r = .83$ ($p < .01$; word recognition subtask) and $r = .45$ ($p < .01$; ideational praxis subtask). In the MCI group, these correlations ranged between $r = .17$ ($p < .01$; comprehension of oral language) and $r = .67$ ($p < .01$; word recall subtask). In the AD group, the coefficients ranged between $r = .29$ ($p < .01$; ideational praxis subtask) and $r = .68$ ($p < .01$; comprehension of oral language).

Group differences

There were statistically significant differences between ADAS-Cog total scores of the three groups ($F_{(2, 647)} = 471.34$, $p<.01$, $\eta^2 = .594$). According to *post hoc* analysis, the control subgroup obtained the lowest total score and the AD subgroup obtained the highest total score. The same pattern (control < MCI < AD) was observed when we compared the scores of ADAS-Cog subtasks between groups, with statistically significant differences in all subtasks (Table 2).

Cut-off points

Receiver operating characteristics (ROC) curve analysis and the diagnostic accuracy parameters were computed in order to evaluate the diagnostic accuracy of the ADAS- Cog total score in the discrimination of MCI and AD patients from controls, as well as between MCI and AD. The area under the curve (AUC) for MCI was .835 [95% confidence interval (CI) = .799–.871] (Figure 1). For AD, we obtained an AUC of .996 [95% (CI) = .992–1.000], presented in Figure 2. We also calculated the discriminative potential of the ADAS-Cog between MCI and AD, with an AUC of .927 [95% (CI) = .903–.951], presented in Figure 3. We also computed the ROC curve analysis to comparatively analyze the diagnostic accuracy of the MMSE and the

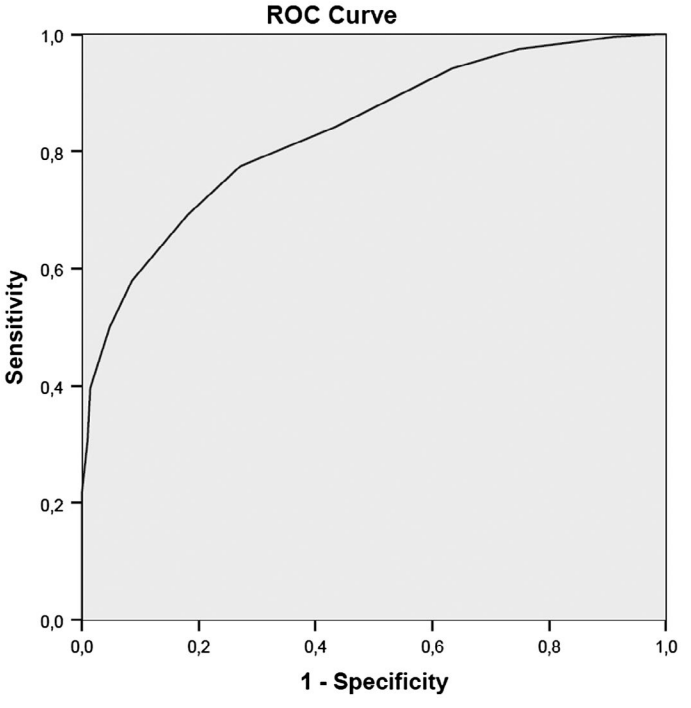

Figure 1. ROC curve analysis of the ADAS-Cog to detect MCI.

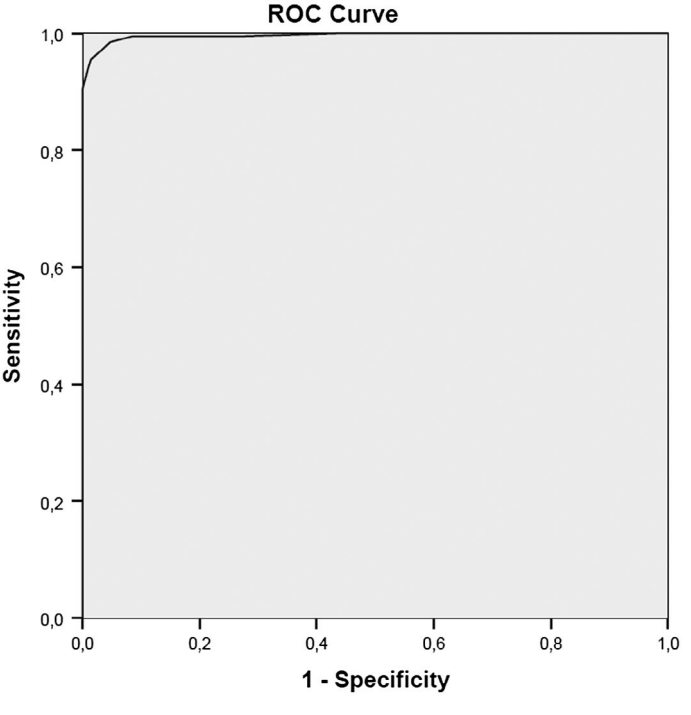

Figure 2. ROC curve analysis of the ADAS-Cog to detect AD.

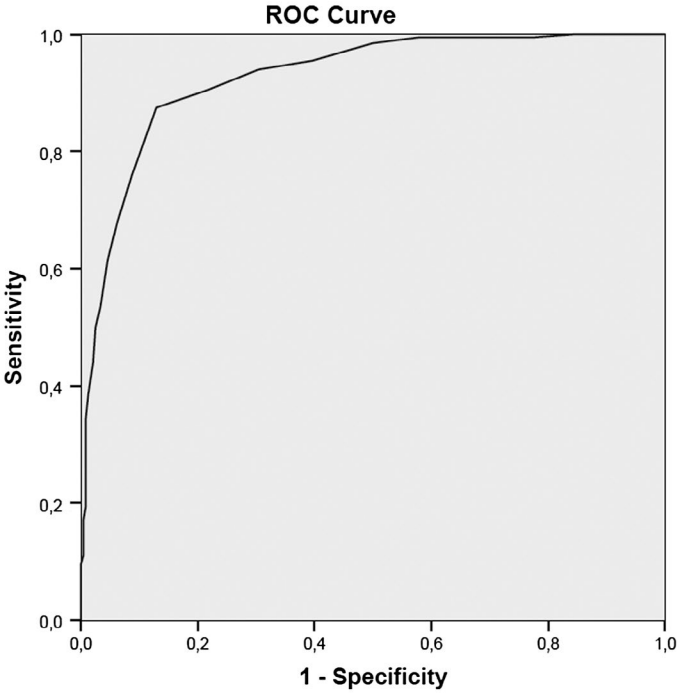

Figure 3. ROC curve analysis of the ADAS-Cog to distinguish MCI from AD.

Table 3. Diagnostic classification accuracy of the ADAS-Cog, the MMSE and the MoCA.

		Cut-off	AUC	Confidence Intervals	Sensitivity	Specificity	PPV	NPV	Classification accuracy
ADAS-Cog	MCI	>9	.835	(.799–.871)	58	91	87	67	74
	AD	>12	.996	(.992–1.000)	94	98	98	94	96
	AD/MCI	>15	.927	(.903–.951)	76	91	88	79	83
MMSE	MCI	<29	.769	(.726–.812)	67	74	74	66	70
	AD	<27	.983	(.974–.993)	89	97	97	91	93
	AD/MCI	<26	.899	(.870–.927)	84	81	79	86	82
MoCA	MCI	<21	.765	(.701–.829)	57	84	79	65	70
	AD	<17	.993	(.982–1.000)	96	96	86	99	96
	AD/MCI	<14	.928	(.875–.980)	85	88	63	96	87

Notes: Sensitivity, specificity, PPV, NPV, and classification accuracy values were expressed in percentage. Cut-off points indicate the minimum score required for presence of signal.

MoCA with the ADAS-Cog. So, we established the optimal cut-off points for this study sample for all instruments compared. The cut-off point founded for MoCA (<21) on MCI was slightly different from the validation study already published by Freitas, Simões, Alves, and Santana (2013). On Table 3, we described the optimal cut-off point for maximum accuracy (according to Youden index) and the respective values of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and classification accuracy for the optimal cut-off points considered.

For those comparisons, we did not find significant differences between the AUC values of the ADAS-Cog and the MoCA (MCI: $p = .829$; AD: $p = .128$; AD/MCI: $p = .989$) and between the AUC values of the ADAS-Cog and the MMSE (MCI: $p = .818$; AD: $p = .228$; AD/MCI: $p = .864$).

Conclusions

The results of the present study show that the ADAS-Cog is a psychometrically valid and reliable instrument for the cognitive assessment of AD and MCI patients. Internal consistency was acceptable, confirming the adequacy of this scale to examine Portuguese patients within the spectrum of AD. Moreover, the significant and negative correlations between the ADAS-Cog, the MMSE, and the MoCA total scores were suggestive of concurrent validity. Regarding construct validity, in both clinical groups we observed that the correlations between the ADAS-Cog total score and its subtasks were all significant and positive. Thus, each subtask had a statistically significant contribution for the structure of the ADAS-Cog.

The analysis of group differences suggested that the ADAS-Cog total score was able to distinguish between clinical and control groups, as well as between the clinical conditions studied here. Furthermore, we observed statistically significant differences between the performances of the three groups on the ADAS-Cog subtasks, which reinforces its discriminative power.

As expected, the analysis of the diagnostic validity of the ADAS-Cog suggests a higher discriminative potential of the ADAS-Cog total score for AD than for MCI patients, as already presented in international studies (Chu et al., 2000; Monllau et al., 2007; Youn et al., 2002). Effectively, for the optimal cut-off points established, the respective AUC and diagnostic parameters were higher for AD patients. The optimal cut-off point for AD was above 12 for the total score. This value is close to other studies regarding the diagnostic validity of the ADAS-Cog (e.g. cut-off point of 15 by Youn et al., 2002; cut-off point of 12 by Monllau et al., 2007). With this cut-off point, the ADAS-Cog total score showed a high sensitivity (94%) and specificity (98%) to identify cognitive impairment in AD patients. Our results were slightly higher than the values reported by Monllau et al. (2007) with 89.19 and 88.53%, or by Chu et al. (2000) with 90 and 94.7%, respectively. In MCI patients, we obtained an AUC value of .835, which is similar to previous validation studies of the ADAS-Cog validation for MCI patients in other populations—for instance, Papp and colleagues (Papp, Pákáski, Drótos, & Kálmán, 2012) found an AUC of .875 for MCI patients. These results confirm that the ADAS-Cog is a more efficient cognitive battery to assess dementia due to AD, revealing lower diagnostic accuracy and sensitivity for MCI patients. Additionally, we also investigated the discriminative power of ADAS-Cog total score between AD and MCI patients, which can be an useful indicator of conversion to dementia, with an optimal cut-off point of 15 (76% sensitivity and 91% specificity). According to the comparative analysis of diagnostic accuracy of the MMSE, the MoCA, and the ADAS-Cog, there were no significant differences between the diagnostic parameters used for the identification of cognitive impairment on MCI or AD patients. As so, this comparative analysis showed the diagnostic accuracy's equivalency of the three screening measures.

However, considering the widely use of the ADAS-Cog in clinical trials and clinical practice, it is important to note its advantages and valuable use in the extensive characterization of cognitive decline. The ADAS-Cog continues to be a valid and reliable instrument for the assessment and characterization of the cognitive impairment in AD, with excellent classification parameters. Moreover, it is important to note that for the AD group, we obtained higher values of sensitivity and specificity of the MMSE than those presented in other studies (Ciesielska et al., 2016; Creavin et al., 2016).

The main limitation of the present study was the exclusion of illiterate subjects, which are 25.7% of the population over 65 years old (INE & PORDATA, 2016). It has been widely reported that educational level has a strong effect on cognitive performance, being invariably considered a criterion for the establishment of normative data for cognitive tests (Brucki, 2010; Freitas, Simoes, Alves, & Santana, 2012; Schultz, Siviero, & Bertolucci, 2001). Furthermore, illiteracy has a known impact in language, praxis and visuospatial abilities, which are the three main components of the ADAS- Cog (Ardila & Rosselli, 2007; Lezak et al., 2004). Thereby, we believe that the ADAS- Cog needs to be specifically adapted for this special population, considering the structure, the items, the administration and the scoring system, in order to ensure the reliability and unbiased processing of the scores of illiterate individuals. The use of the same tests for literates and illiterates clearly penalizes illiterates, leading to an overestimation of dementia (Lezak et al., 2004). A further point to note is the absence of a depression screening test on the assessment protocol administered to control participants. Nevertheless, before the administration of the ADAS-Cog, we conducted a clinical interview which contemplated the assessment of recent psychiatric or psychological conditions, as well as the achievement of information related with current medication intake. Moreover, the absence of *latin square* design in the administration of the assessment protocol may also have affected our results. Specifically, the use of this methodology could exclude possible sequence effects. However, this methodology is applied in clinical trials to ensure the comparability of the performance of each patient over the time. Finally, the interpretation of our results should take into consideration the fact that our scores did not follow a linear model.

Despite these limitations, the present study has also a set of strengths: (1) we tested well-diagnosed and homogenous clinical groups (patients with misclassification and more advanced dementia cases were excluded, both characteristics susceptible of compromising the analysis of the discriminative capacity of the instrument); (2) we tested a control sample with subjects recruited from the community; and (3) we used equivalent sample sizes, mean age, and mean educational levels at the groups, which reduces the possible biases in statistical analysis of the differences between groups, and in the discriminative capacity of the ADAS- Cog.

As future considerations, we would like to emphasize the relevance of studies concerning the changes in the ADAS-Cog-weighted scores, and the addition of new subtasks, covering the observed low sensitivity for milder forms of the disease that mostly caused by either floor and ceiling effects (Verma et al., 2015). Moreover, we believe that the addition of the delayed recall memory subtask is important, as it is considered a cardinal feature to assess mild preclinical stages such as MCI (Skinner et al., 2012). Finally, it may be extremely important to study the clinical validity of this scale in other neurodegenerative pathologies.

In conclusion, the novelty of our results for the Portuguese population, highlights the excellent diagnostic accuracy of the ADAS-Cog total scores for dementia, and specifically, its good discriminative power for AD. However, it is important to note the need for a careful use of the ADAS-Cog with MCI population. Due to its poor sensitivity and classification accuracy (and the related high likelihood to false-negative cases), the ADAS-Cog total score should not be used alone as a single neuropsychological assessment instrument for detection of cognitive impairment in MCI patients. Furthermore, regarding the clinical trials in milder forms of dementia, our results with the Portuguese population emphasize the need to consider new versions of the ADAS-Cog or the selection of relevant outcomes specific to MCI.

These considerations could improve the reliability of the ongoing clinical trials avoiding biased results.

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