Title:

Montreal Cognitive Assessment (MoCA):

Validation study for Mild Cognitive Impairment and Alzheimer´s Disease.

Title suitable for the running head: MoCA in MCI and AD

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Abstract

The Montreal Cognitive Assessment (MoCA) was recently proposed as a cognitive screening test for milder forms of cognitive impairment, having surpassed the well-known limitations of the Mini-Mental State Examination (MMSE). This study aims to validate the MoCA for screening Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) through an analysis of diagnostic accuracy and the proposal of cut-offs. Patients were classified in two clinical-groups according to standard criteria: MCI (*n*=90) and AD (*n*=90). The two control-groups (C_MCI: *n*=90; C_AD: *n*=90) consisted of cognitively healthy community dwellers selected in order to match patients in gender, age and education. The MoCA showed consistently superior psychometric properties than the MMSE, and higher diagnostic accuracy to discriminate MCI (AUC=.856; 95%IC=.796-.904) and AD patients (AUC=.980; 95%IC=.947-.995). At an optimal cut-off of below 22 for MCI and below 17 for AD, the MoCA achieved significantly superior values in comparison to the MMSE for sensitivity, specificity, PPV, NPV, and classification accuracy. Furthermore, the MoCA revealed higher sensitivity to cognitive decline in longitudinal monitoring. This study provides robust evidence that the MoCA is a better cognitive instrument than the widely used MMSE for the screening and monitoring of MCI and AD in clinical settings.

Keywords: MoCA; neuropsychological test; cognitive screening; Mild Cognitive Impairment; Alzheimer's Disease.

Introduction

Cognitive impairment and dementia are the major health issues among older people. Alzheimer´s disease (AD) is the most common neurodegenerative disorder with a prevalence of 4.4% for those older than 65 years old, and represents at least 60% of all dementia cases[1]. The serious impact of the AD in health-care systems worldwide[2,3] and the dramatic projections for the coming years[4,5] stress the need for new effective strategies able to slow or stop the disease progression. It is now generally accepted that prodromal AD is the ideal time window for disease modifying therapies.

Mild Cognitive Impairment (MCI) is considered a transitional stage between normal cognitive aging and impaired cognition caused by several pathologies, most frequently AD. This state of continuum is characterized by a deterioration of the cognitive functioning greater than expected for the person's age and educational level, but does not cause significant functional disability and is insufficient to establish the diagnosis of dementia[6-9]. Longitudinal studies show that these patients progress to overt dementia at a rate of 10-15% *per* year, compared with a rate of 1-2% in the control subjects[9]. This explains why MCI is now the focus of prediction studies and the target of clinical trials of new disease modifying therapies.

The early screening of cognitive impairment and its differentiation from age related decline is thus extremely important. A brief and sensitive cognitive screening tool is indispensable to deal with this grey boundary area of normality between normal ageing, MCI and mild dementia. The Montreal Cognitive Assessment (MoCA)[10] is a novel international brief cognitive screening instrument developed for the detection of MCI and mild AD that may be suitable for this purpose. Previous studies have shown that the MoCA is useful and accurate in identification of milder forms of cognitive impairment, having revealed a high sensitivity in the detection of MCI and AD

patients[11-18]. One of the reasons for the good sensitivity of the test is that it allows a more comprehensive assessment of the major cognitive domains, comparatively to other screening tests. This is the case of executive function, short-term memory, language skills and visuospatial processing. Furthermore, it has been demonstrated that the MoCA´s total score is an accurate quantitative estimate of the global cognitive ability in mild and moderate stages[19,20]. Thus, beyond the routine screening, the MoCA scores can be used in longitudinal studies as an indicator of the global cognitive decline during the progression of the disease[21].

The aim of the present study is to validate the MoCA[10,22] for cognitive screening of MCI and AD patients. This was carried out through the analysis of its diagnostic accuracy as well as the establishment of the optimal cut-off points to detect MCI and AD patients. The data of a longitudinal study with MCI and AD patients has also been analyzed in order to establish the MoCA's sensitivity for cognitive decline in a short period of time.

Methods

Design

In the current study three groups of participants were considered: (I) MCI group, (II) AD group and (III) Control group. Patients were recruited at the Dementia Clinic, Neurology Department of the Coimbra University Hospital (Coimbra University Hospital, Coimbra, Portugal). Control subjects were selected from the database of the MoCA's normative study for the Portuguese population[23] in order to match patients in gender, age and educational level. Two subgroups of patients belonging to both clinical groups (MCI and AD) were assessed at a second time point for preliminary longitudinal analysis.

Participants

The total study sample is composed of 360 participants distributed between three subgroups: (I) the MCI group with 90 patients, (II) the AD group with 90 patients, and (III) the Control group with 180 cognitively healthy adults. The demographic data of the participants in each group are provided in Table 1.

In order to exclude other causes of cognitive decline apart from a degenerative process, all patients were examined by a neurologist (IS) and a standard investigation were always performed, including laboratory routine exams/analysis - Apolipoprotein E (APOE) genotyping and imaging studies - structural (CT and/or MRI) and functional (SPECT). PET and cerebrospinal fluid analysis were carried out more restrictively, although considered in younger patients. All patients underwent a comprehensive neuropsychological assessment battery comprised at least by the following instruments: Mini-Mental State Examination (MMSE)[24,25], Alzheimer´s Disease Assessment Scale (ADAS)[26,27], Clinical Dementia Rating scale (CDR)[28,29], Irregular Word Reading Test (TeLPI)[30] for pre-morbid intelligence estimate, Subjective Memory Complaints scale (SMC)[31,32] and Geriatric Depression Scale (GDS-30)[33,34]. The MoCA was never used for diagnostic purposes. The diagnosis was established by a multidisciplinary team consensus considering the results of the comprehensive assessment and based on international criteria for MCI of the Petersen workgroup[7] and probable AD[35,36]. The MCI group included patients classified as "amnestic MCI" (single or multidomain)[8] with a classification of 0.5 in the CDR. The AD group only included patients with mild to moderate severity (classified with CDR ≤ 2 and MMSE ≥ 12 points).

Control group participants were selected, as referred above, from the database of the MoCA's normative study for the Portuguese population[23]. Each patient was matched

to a cognitively healthy adult on variables shown to affect the MoCA´s performance (educational level and age)[23] and additionally on gender, resulting in a perfect match between MCI and associated controls (then designated as the C-MCI group) and between AD and associated controls (C-AD group). Details regarding the controls' recruitment procedure, inclusion and exclusion criteria, and neuropsychological assessment have been described on the previous study[23].

Procedures

All participants were recruited between September 2008 and July 2010 and each participant was assessed in a single session by an expert in neuropsychology. Only patients with a stable clinical condition (without significant comorbidities), a complete clinical evaluation and already with a well-established diagnosis, according to the above international criteria, were considered to be eligible for this study. For each patient who was considered suitable for the study and at the time of the data collection, a diagnosis was recorded by the neurologist in the clinical file. These restrictive criteria imposed the exclusion of 30 patients that were still waiting for data considered essential in the differential diagnosis between AD and other dementias, and of those whose classification between MCI and AD was not fully established by the multidisciplinary team. Also at the outset of this study the exclusion criteria taken into account in the patients' selection were: higher dementia severity (CDR > 2 and MMSE < 12 points), recent psychiatric comorbidities or therapeutic changes (6 months prior to the current neuropsychological evaluation), and significant motor, visual or auditory deficits, all of which may influence the neuropsychological assessment results.

For the preliminary analysis of the MoCA´s sensitivity to global cognitive decline in longitudinal monitoring we assessed two subgroups of patients (35 with MCI

and 40 with AD) at a second time point, on average 176.81 ± 67.09 days apart (min.= 63; max.= 340).

The present research complied with the ethical guidelines for human experimentation stated in the Declaration of Helsinki and was approved by the Ethics Board of Coimbra University Hospital, by the "Fundação para a Ciência e Tecnologia" [Portuguese Foundation for Science and Technology] and by the Faculty of Psychology and Educational Sciences Scientific Committee. An informed consent was obtained from all the participants after the aims and research procedures were fully explained by a member of the study group. For the AD patients who were incapable of providing consent on his/her behalf, a legal representative provided it.

Neuropsychological testing and Materials

In the clinical interview the demographic and clinical data was collected through a complete sociodemographic questionnaire, an inventory of past habits and of the current clinical health status as well as of the medical history. Following this, the same neuropsychologist administered the MMSE[24,25] and the MoCA[10,22], in that fixed order for all the subjects. The MMSE is a widely recognized and used brief screening instrument for cognitive decline and therefore it is not described in detail here. Both the MMSE and the MoCA are in paper-and-pencil format and are scored out of a possible total score of 30 points, with higher scores indicating better cognitive performance. The MoCA was developed in order to screen milder forms of cognitive impairment, through the assessment of six cognitive domains: executive functions; visuospatial abilities; short-term memory; language; attention, concentration and working memory; and temporal and spatial orientation[10]. It is composed by a one-page test, with an application time of approximately 10 to 15 minutes, and by a manual where explicit instructions

concerning its administration and scoring system are available. The cultural adaptation process of the MoCA for the Portuguese population involved the translation, retroversion, linguistic improvement of the instrument and of the administration and scoring instruction manual, studies with the MoCA's Portuguese experimental version, the revision and adjustments required to finalize the MoCA's Portuguese final version, and an analysis of the equivalence between the original and the Portuguese final version, as described by Freitas and collaborators[37]. In the current study, the MoCA's total score refers to the raw score without correction point for education effects, considered in the original study[10], since this correction is not used in the Portuguese population[23].

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 19.0) (IBM SPSS, Chicago, IL). Descriptive statistics were used for sample's characterization, and the χ^2 test and the two-sample *t*-test allowed the group comparisons. Cronbach´s alpha was considered as an index of internal consistency. To assess test-retest reliability, intraclass correlation coefficients between scores at baseline and at follow-ups three and eighteen months later for the control participants were calculated. Interrater reliability was calculated using the Pearson correlation coefficient between the scoring of two independent evaluators. The convergent validity was determined using Pearson correlations coefficients between the MoCA scores and MMSE scores. The group differences were examined using two-sample *t*-test and analysis of covariance. The preliminary data of longitudinal study were analyzed using paired-sample *t*-test.

The diagnostic accuracy of the MoCA and the MMSE for the prediction of the clinical diagnosis of MCI and AD was assessed through the receiver operating characteristics (ROC) curve analysis implemented in MedCalc (version 11.6) (MedCalc Software, Mariakerke). In this analysis, the areas under the curve (AUC) can vary between 0.5 and 1, with larger AUC indicates better diagnostic accuracy. The ROC curves were compared according to AUC comparison method of Hanley and McNeil[38]. The optimal cut-off points for each screening instrument that yielded the highest Youden index were selected, with higher Youden index indicating maximization of the sensibility and specificity. For the analysis of the predictive value of these tests we calculated, for the each cut-off point, the sensitivity (the probability for subjects with cognitive impairment to have a positive test), specificity (the probability for subjects without cognitive impairment to have a negative test), positive predictive value (PPV, the probability of disease in subjects who have a positive test), negative predictive value (NPV, probability of the classification "lack of disease" in subjects who have a negative test) and classification accuracy (probability of correct classification of subjects with or without cognitive impairment).

Results

Sample Characterization

Characteristics of the study sample, and in more detail of all the subgroups, are provided in Table 1. For this description were considered the following variables: sample size, educational level, age, gender, MMSE score and MoCA score.

Table 1. Descriptive statistics for the sample's subgroups

	n	Education	Age	Gender	MMSE	MoCA
MCI	90	6.50 ± 4.565	70.52 ± 7.950	55 (61.1)	27.08 ± 2.395	18.31 ± 3.868
C-MCI	90	6.53 ± 4.498	69.59 ± 7.053	55 (61.1)	28.88 ± 1.297	23.64 ± 3.223
AD	90	6.23 ± 4.119	74.22 ± 8.212	52 (57.8)	20.88 ± 4.091	10.06 ± 4.410
C-AD	90	6.24 ± 4.128	73.10 ± 7.539	52 (57.8)	28.09 ± 1.577	22.33 ± 3.471
Clinical Group	180	6.37 ± 4.338	72.37 ± 8.270	107 (59.4)	23.98 ± 4.565	14.18 ± 5.851
Control Group	180	6.39 ± 4.307	71.34 ± 7.490	107 (59.4)	28.48 ± 1.493	22.99 ± 3.404
Total	360	6.38 ± 4.316	71.86 ± 7.895	214 (59.4)	26.23 ± 4.073	18.59 ± 6.503

Abbreviations: MCI: Mild Cognitive Impairment patients; C-MCI: subgroup of controls matched with MCI patients; AD: Alzheimer's Disease patients; C-AD: subgroup of controls matched with AD patients; Clinical Group: all patients with MCI and AD; Control Group: all controls; MoCA: Montreal Cognitive Assessment (maximum score = 30); MMSE: Mini Mental State Examination (maximum score = 30);
Note: Gender is characterized by female's *n* and respective percentage (%). Data of others variables are presented as mean ± standard deviation.

As mentioned above, the control participants were selected from the database of MoCA's normative study for the Portuguese population[23] in order to match in educational level, age and gender to patients of clinical groups. No statistically significant differences were found on the educational level (t (178) = .049, p = .961), age (t (178) = .833, p = .406), and gender (χ^2 (1) = .000, p = 1.0) between the MCI and the C-MCI groups. Likewise, the AD and the C-AD group did not differ on the educational level (t (178) = .018, p = .986), age (t (178) = .955, p = .341) and gender (χ^2 (1) = .000, p = 1.0). The MCI group and the AD group did not differ on the educational level (t (178) = .411, p = .681) and gender (χ^2 (1) = .092, p = .761), but nevertheless the AD patients were significantly older than MCI patients (t (178) = 3.071, p = .002), due the average onset of symptoms in MCI precedes the onset of AD.

Psychometric properties

Cronbach´s alpha of the MoCA as an index of internal consistency was 0.903 for the total study sample, and the respective value for the MMSE was .856. Regarding the analysis of which MoCA items could be eliminated to increase the consistency, the results indicate that none should be excluded. Cronbach´s alpha values in subgroups are provided in Table 2. The test-retest reliability was measured through the intraclass correlation coefficient between the baseline and the follow-up data. This analysis was done only for the sub-sample of the control group in two follow-up settings: 3 months (n = 30; on average 146.87 ± 42.937 days apart; min. = 68 days and max. = 200 days) and 18 months (n = 30; on average 515.04 ± 154.195 days apart; min. = 101 days and max. = 676 days). The obtained MoCA's values were respectively .909 and .877 and the correspondent values for the MMSE were respectively .755 and .665 (Table 2). Interrater reliability data was collected from a sub-sample of 60 tested participants of all groups and the obtained intraclass correlation index for the MoCA was .988. Another observation was that MoCA scores were highly and positively associated with MMSE scores (total study sample: r = .849, p < .001), which is indicative of convergent validity. The correlation's values in subgroups are presented in Table 2.

Table 2. Psychometric Properties

	Internal Consistency		**Reliability**			**Convergent Validity**
	Cronbach's α		Test-Retest		Interrater	Correlations MoCA / MMSE
	MoCA	MMSE	MoCA	MMSE		
MCI (*n* = 90)	.723	.617	3 months: .909 18 months: .877	3 months: .755 18 months: .665	.988	.601
AD (*n* = 90)	.824	.771				.700
C-MCI (*n* = 90)	.648	.457				.637
C-AD (*n* = 90)	.677	.402				.600
Total (n = 360)	.903	.856				.849

Abbreviations: MCI: Mild Cognitive Impairment patients; C-MCI: subgroup of controls matched with MCI patients; AD: Alzheimer's Disease patients; C-AD: subgroup of controls matched with AD patients; MoCA: Montreal Cognitive Assessment (maximum score = 30); MMSE: Mini Mental State Examination (maximum score = 30);
Note: Correlations values at a significant level $p < .01$

Group Differences

When analyzing the total sample, the MoCA scores were lower in AD group than in all other groups, and lower in MCI group than in both control groups, which do not differ between them (t (178) = 2.626, p = .225) (Table 1). Furthermore, we can observe that there were statistically significant differences when MoCA scores were compared between MCI and C-MCI groups (t (178) = 10.050, $p < .001$, mean difference = 5.333 ± .531) and between AD and C-AD groups (t (178) = 20.756, $p < .001$, mean difference = 12.278 ± .592). Since AD patients were significantly older than MCI patients, the analysis of differences in scores between clinical groups was performed using an analysis of covariance in order to control for the effects of age. It can be observed that the differences between MCI and AD patients scores (F (1,177) = 160.052, $p < .001$, $\eta^2 = .48$, mean difference = 7.930 ± .627) were in fact significant. The corresponding values for the MMSE were: I) MCI and C-MCI group: t (178) = 6.270, $p < .001$, mean difference = 1.800 ± .287; II) AD and C-AD group: t (178) =

15.603, $p < .001$, mean difference = 7.211 ± .462; and III) MCI and AD group: $F(1,177) = 146.899$, $p < .001$, $\eta^2 = .45$, mean difference = 6.231 ± .514. These results indicate that although the differences in the MMSE scores are statistically significant, the score differences obtained with the MoCA are more pronounced. A more detailed analysis reveals that there were statistically significant differences in all cognitive domains of the MoCA in the three comparisons: I) MCI and C-MCI groups; II) AD and C-AD groups; and III) MCI and AD groups. Table 3 summarizes the results.

Table 3. Group differences in cognitive domains of the MoCA

Cognitive Domains	MCI and C-MCI	AD and C-AD	MCI and AD
Executive Functions	$t(178) = 4.975$, $p < .001$	$t(178) = 9.766$, $p < .001$	$t(178) = 7.073$, $p < .001$
Visuospatial Skills	$t(178) = 5.564$, $p < .001$	$t(178) = 9.616$, $p < .001$	$t(178) = 7.006$, $p < .001$
Short-term Memory	$t(178) = 9.773$, $p < .001$	$t(178) = 20.732$, $p < .001$	$t(178) = 6.581$, $p < .001$
Language	$t(178) = 2.964$, $p = .003$	$t(178) = 8.800$, $p < .001$	$t(178) = 7.010$, $p < .001$
Attention, Concentration and Working Memory	$t(178) = 5.199$, $p < .001$	$t(178) = 11.123$, $p < .001$	$t(178) = 7.217$, $p < .001$
Temporal and Spatial Orientation	$t(178) = 2.974$, $p = .003$	$t(178) = 13.886$, $p < .001$	$t(178) = 12.038$, $p < .001$

Abbreviations: MCI: MCI: Mild Cognitive Impairment patients; C-MCI: subgroup of controls matched with MCI patients; AD: Alzheimer's Disease patients; C-AD: subgroup of controls matched with AD patients.

Cut-off points

The receiver operating characteristics (ROC) curve analysis and the predictive values were performed to evaluate the diagnostic accuracy of MoCA to discriminate MCI and AD patients from cognitively healthy adult. Graphic representations of the ROC curves are provided in Figure 1.

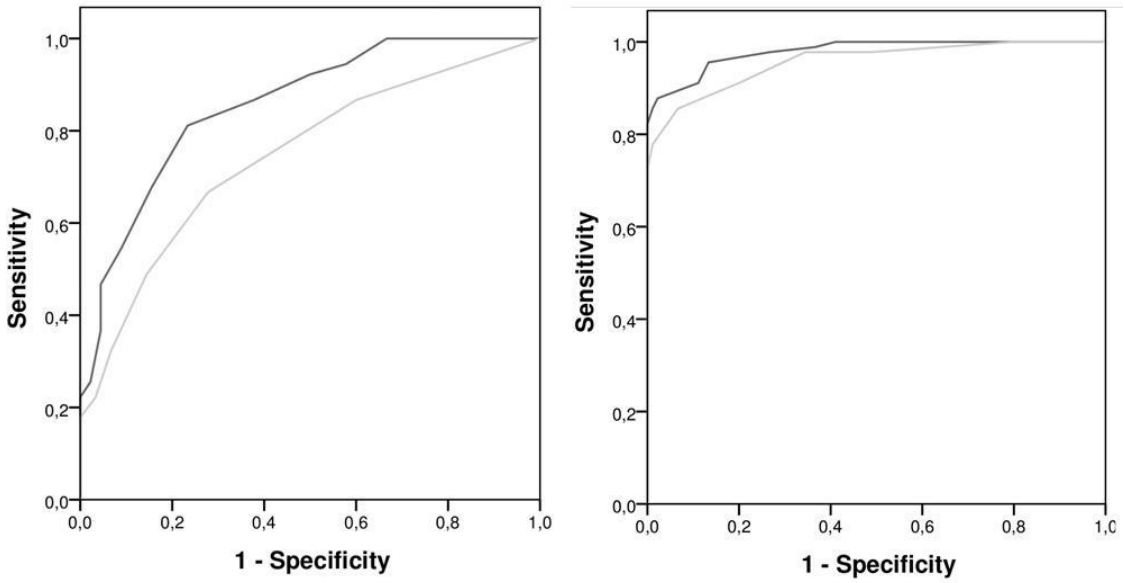

Figure 1. ROC curve analysis of the MoCA (dark gray) and MMSE (medium gray) to detect MCI (left) and AD (right).

Abbreviations: MoCA: Montreal Cognitive Assessment; MMSE: Mini Mental State Examination; MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

It can be observed that both ROC curves referred to the MoCA fully include the curve for the MMSE, which is a clear indication that there is always a cut-off for the MoCA with higher sensitivity and specificity, for any cut-off chosen for the MMSE. The discriminant potential of the MoCA for MCI was high, with an AUC of .856 (95% IC = .796-.904) and for AD was excellent, with an AUC of .980 (95% IC = .947-.995). In contrast, corresponding values for MMSE were .745 (95% IC = .674-.807) and .957 (95% IC = .916-.981). The AUCs for MCI are significantly different (z = 3.372, p = .0007), according to AUC comparison method of Hanley and McNeil[37], indicating different classificatory accuracy of the instruments to milder cognitive impairment. No statistically significant differences were found between the AUCs for AD (z = 1.636, p = .1018). The optimal cut-off point for maximum accuracy (Youden index) and the

respective values of sensitivity, specificity, PPV, NPV, and classification accuracy are described in Table 4.

Table 4. Diagnostic classification accuracy

	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	Classification Accuracy
MCI							
MoCA	< 22	.856	81	77	78	80	80
MMSE	< 29	.745	67	72	71	48	69
AD							
MoCA	< 17	.980	88	98	98	89	93
MMSE	< 26	.957	85	93	93	87	89

Abbreviations: MCI: Mild Cognitive Impairment patients; AD: Alzheimer's Disease patients; MoCA: Montreal Cognitive Assessment (maximum score = 30); MMSE: Mini Mental State Examination (maximum score = 30); AUC: area under the operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value.
Note 1: Sensitivity, Specificity, PPV, NPV, and Classification Accuracy values were expressed in percentage.
Note 2: Cut-off values indicate the minimum score required for absence of signal.

The cut-off point of below 22 yielded the greatest Youden index for the MoCA in discrimination between MCI and controls. With this cut-off point, MoCA had a good sensitivity (81%), specificity (77%), PPV (78%), NPV (80%), classification accuracy (80%), and all these values were significantly superior comparing to the respective values for the MMSE. Furthermore, in what respects to the capacity of discrimination between AD patients and controls, once again the MoCA demonstrated an excellent sensitivity (88%), specificity (98%), PPV (98%), NPV (89%), and classification accuracy (93%) at the optimal cut-off of below 17 points, and again all these values were more favorable than the respective values for the MMSE.

Preliminary analysis of longitudinal study

For the preliminary analysis of the MoCA´s sensitivity to global cognitive decline during longitudinal monitoring, two clinical subgroups of patients (35 with MCI and 40 with AD) were assessed at a second time point, on average 176.81 ± 67.09 days apart (min.= 63; max.= 340). When considering all patients (n = 75) statistically significant differences on MoCA scores were observed between both assessments (t (74) = 4.278, p <.001), in opposition to what was found with the MMSE (t (74) = 1.871, p = 065). A similar analysis for each clinical subgroup showed statistically significant differences on MoCA scores for both MCI (t (34) = 2.612, p = .014) and AD patients (t (39) = .5651, p<.001). An equivalent analysis using the MMSE revealed that the differences were significant for AD group (t (39) = 2.824, p =.008), while for MCI the MMSE showed no sensitivity to cognitive decline (t (34) = 1.873, p =.070). A more detailed and parceled analysis concerning the cognitive domains of the MoCA also revealed interesting results. When considering the total sample, the differences between the two evaluations were significant for visuospatial skills (t (74) = 2.487, p =.015); short-term memory (t (74) = 2.669, p = .009); attention, concentration and working memory (t (74) = 2.213, p = .030); temporal and spatial orientation (t (74) = 4.449, p < .001), and without significance for language and executive functions. When considering the clinical sub-groups, an isolated significant difference was founded for MCI patients in short-term memory domain (t (34) = 2.390, p = .023), while the same analysis for AD sub-group revealed statistical significance for attention, concentration and working memory (t (39) = 2.071, p = .045), and also for orientation (t (39) = 5.244, p < .001).

Discussion

The main objective of this study was to validate the MoCA as a cognitive screening tool for MCI and AD. The results confirm its great potential and provide robust evidence that the MoCA is a better instrument for this purpose in comparison with the widely used MMSE. In fact, it was verified that the correlation coefficient between the two cognitive screening instruments was moderate to good, suggesting convergent validity. Nonetheless, the psychometric properties of the MoCA examined both in the total sample and in each sub-groups, showed good properties and revealed to be consistently superior to those of the MMSE. As was previously referred, we believe that the two main reasons for the higher results of the MoCA at this level were: first, the inclusion of the executive functions assessment; and second, the consideration of more complex tasks to measure short-term memory, language, attention, concentration, working memory, and visuospatial skills.

Moreover, the analysis of group differences indicates that both instruments are able to distinguish the clinical and control groups. However, the differences between the groups were much more pronounced when the MoCA was used, in comparison with the MMSE, which is reflected in the consistently higher MoCA's mean differences. Furthermore, we observed statistically significant differences in all cognitive domains of the MoCA and in all group comparisons. These results confirm the higher capacity of the MoCA to discriminate between normal aging and pathological cognitive decline as well as between MCI and dementia.

The ROC curve analysis of the MoCA comparatively to the MMSE also showed that the MoCA exhibits a better diagnostic accuracy to discriminate MCI and AD patients from cognitively healthy adults. In our sample, the ideal cut-off point reached was lower than the original cut-off of 26 proposed by the authors[10], as in other

published results[14,15,17,18]. We observed that at an optimal cut-off point below 22 for MCI, the MoCA had values significantly superior to the MMSE for sensitivity (81%), specificity (77%), PPV (78%), NPV (80%), and classification accuracy (80%). With an optimal cut-off of below 17 points for AD, the MoCA showed once again better results than the MMSE on sensitivity (88%), specificity (98%), PPV (98%), NPV (89%), and classification accuracy (93%). These results confirm that the MoCA is a better cognitive screening instrument for the detection of MCI and AD conditions comparatively to the MMSE, showing overall superior discrimination validity. The capacity of the MoCA to identify different severity levels of cognitive decline justifies the pertinence of considering different cut-off points for MCI and dementia. This approach seems to be more useful and informative than a single cutoff point for cognitive decline as suggested in other studies, particularly in the original work of the Nasreddine and collaborators[10].

An additional observation based on the present study regards the extremely poor diagnostic accuracy of the MMSE to identify MCI, reflected in overall low results, and mainly in poor sensitivity (67%), classification accuracy (69%), and very poor NPV (48%). This is a clear indication that whenever the MMSE is used to screen for milder forms of cognitive decline, the probability of false negatives cases is very high. This is especially critical under the current emphasis placed upon the early detection of cognitive impairment. Nonetheless, the MMSE remains the most commonly used screening tool despite the widely referred limitations in literature. Our results are a clear argument in favor of these opinions.

Finally, considering our analysis of the sensitivity of the MoCA to cognitive decline in patients that were longitudinally monitored, we could demonstrate evidences of decline in a short period of time. Furthermore, beyond its capacity to quantify

cognitive decline, the MoCA also provides comprehensive information on the differential profile of clinical deterioration in MCI and AD.

We believe that the added value of the present study is the rigorous methodology used. It included: I) well-validated study samples (patients with misclassification and more advanced dementia cases were excluded, both characteristics susceptible of compromising the analysis of the discriminant capacity of the instruments); II) homogeneity of the clinical groups; III) a control sample with subjects recruited from the community and well-characterized as cognitively healthy adults; IV) equivalent samples sizes (which reduces the possible biases of sample sizes in statistical analysis); V) perfect matching between groups regarding sociodemographic characteristics that have a significant influence on the MoCA's performance; and VI) rigorous MoCA' application, with no inter-rater variability (all participants were assessed by the same experienced neuropsychologist).

However, some limitations of the current study must be addressed. First of all, since only the amnestic subtype of MCI (single or multidomain) was considered, the generalization of the results to other forms of MCI should be cautious. Similarly, although the MoCA's Portuguese final version resulted of a rigorous process that followed the methodological guidelines for cultural adaptation studies, and the maximum equivalence between the original instrument and the MoCA's Portuguese final version was pursued[37], the generalization of these results to other target populations should be cautious. On the other hand, the present study compares people with a clear diagnosis of AD/MCI with healthy people who not present health and cognitive difficulties, like the majority of the clinical validation studies of screening instruments. However, in the context of clinical applicability of a cognitive screening instrument, such as the MoCA, the most common diagnostic challenge is to identify

clinical conditions among people with complaints of memory impairment or other cognitive difficulties or psychological disorders. Hence, we consider that such a question represents a very interesting challenge with a clear practical utility that should as such be a part of future efforts within this field of research. Finally, despite promising, the results of the preliminary analysis of the longitudinal evaluation require the corroboration by an ongoing study with longer follow ups and more robust samples.

In conclusion, this study produced several evidences of the overall superiority of the MoCA in comparison with the MMSE as a global cognitive assessment instrument, regarding the discriminant validity and the diagnostic accuracy. This was confirmed by the identification of MCI and AD and by the discrimination between both forms of cognitive decline and normal cognitive aging. Furthermore, the results suggest that the MoCA is sensitive to cognitive decline in a short period of time and may capture profiles of cognitive deterioration along the evolution of the disease. Thus, this study shows a clear advantage in the use of the MoCA comparatively to the use of the MMSE, and brings together arguments for the use of the MoCA as a reliable brief cognitive instrument, which should be recommended both for screening and follow-up in primary clinical setting and geriatric health care.

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