Title: The Montreal Cognitive Assessment (MoCA) as a screening test for cognitive dysfunction in Multiple Sclerosis

Title suitable for the running head: MoCA as a screening test in MS

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Conflict of Interest

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Abstract

Objective: This study investigates the utility of the Portuguese version of Montreal Cognitive Assessment (MoCA) as a screening-method for identifying cognitive dysfunction (CD) in multiple sclerosis (MS). Method: The 118 participants with comprehensive neuropsychological assessment were divided into two subgroups: (I) MS group (n = 59) and (II) control group (n = 59). The MS patients were classified as cognitively intact (n = 26) or impaired (n = 33, 56%). Results: The results indicated that the MoCA is a psychometrically valid instrument in assessment of MS patients. The Multiple Linear Regression analyses highlighted the significant influence of *Modified Fatigue Impact Scale* and *Irregular Word Reading Test* on MoCA performance. The MoCA total score showed a good discriminative capacity between cognitively impaired and cognitively intact subjects. In addition, there were significant differences in MoCA cognitive domain scores between groups. The MoCA total score cut-off point for identifying CD in MS patients was a score below 26 points (AUC = 0.837, CI = 0.736-0.937). A proposed EM-MoCA-Subscore for identifying the MS-related cognitive impairment (max.score = 19 points, cut-off < 17 points, AUC = 0.871, CI = 0.784-0.958), can reduce administration time for cognitive screening in clinical settings. Conclusions: The MoCA is a useful and sensitive instrument to identify the MS-related cognitive impairment.

Keywords: Multiple Sclerosis; Cognitive Impairment; Early Diagnosis; Neuropsychological Tests; Diagnostic Accuracy.

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating and degenerative disease of the central nervous system that primarily affects young adults (Hemmer, Nessler, Zhou, Kieseier, & Hartung, 2006). In the last few decades, cognitive dysfunction (CD) has been recognized as a common and early manifestation of MS, with reported prevalence rates of between 40 and 70% of patients (Amato, Zipoli, & Portaccio, 2006). CD has a remarkably negative impact on functionality, compromising employment status, social activities, treatment adherence and quality of life (Langdon, 2011).

The pattern of MS-related CD is well characterized, and rather than presenting as a global impairment, it is typically confined to specific cognitive domains: information processing speed, episodic memory and executive function (Strober et al., 2009). Nevertheless, there is some degree of inter-patient variability due to the heterogeneous pathological substrates of MS and individual cognitive reserves (Sumowski, Wylie, Chiaravalloti, & DeLuca, 2010), which make more challenging and complex the cognitive evaluation in this clinical population.

CD is found in all disease stages but may be dissociated from physical disability, and patients may not be fully aware of their cognitive deficits (Langdon et al., 2012). A comprehensive neuropsychological evaluation is time-consuming, expensive, and requires well-trained professionals, thus hindering its use in clinical settings. Furthermore, the MS-related fatigue can also be an impediment for administering extensive assessment batteries. The most common neuropsychological batteries that have been validated for use in MS patients are the 45-min Brief Repeatable Battery of Neuropsychological tests (BRB-N) (Rao, 1990) and 90-min Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2006). Recently, a Brief

International Assessment of Cognition for MS (BICAMS) has been proposed by an expert consensus committee of neurologists and neuropsychologists (Langdon et al., 2012). The battery comprises the Symbol Digit Modalities Test, California Verbal Learning Test - II (first five recall trials), and Brief Visuospatial Memory Test - Revised (first three recall trials). However, even though its validation is currently under development in different languages and countries, the process has been completed only in a few countries (Dusankova, Kalincik, Havrdova, & Benedict, 2012; Eshaghi et al., 2012; Giedraitienė, Kizlaitienė, & Kaubrys, 2015; Goretti et al., 2014; O'Connell, Langdon, Tubridy, Hutchinson, & McGuigan, 2015; Sandi et al., 2015; Spedo et al., 2015; Walker et al., 2016) and therefore is not yet worldwide available for use in clinical practice. Furthermore, some instruments have been recommended for the screening of CD in MS patients, namely the Symbol Digit Modalities Test (SDMT; Rao, 1991; Smith, 1982), with reported high sensitivity (.91) but poor specificity (.60) (Van Schependom et al., 2014) and good reliability in monitoring cognitive function over time (Morrow et al., 2010). Finally, the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) is widely used, although it does not give appropriate screening measures of cognitive impairment in MS (Benedict et al., 2008). As widely reported, the MMSE is not an adequate measure for milder forms of cognitive impairment because the high probability of false negatives cases, which is especially critical under the emphasis placed upon the early detection of cognitive impairment and its impact on treatment and respective course of disease. This lack of sensitivity results from the low complexity of the tasks for assessment of memory, language and visuospatial dysfunctions and from the lack of tasks for the evaluation of executive function (Freitas et al., 2012; Naugle & Kawczak, 1989), which can compromise the detection of MS-related cognitive impairment. The Montreal Cognitive

Assessment (MoCA; Nasreddine et al., 2005) overcomes these well-known limitations of the MMSE. In this context, a brief screening instrument that evaluates the most important cognitive domains would be extremely valuable, covering both the detection of MS-related cognitive impairment and evolution monitoring in everyday clinical practice.

The MoCA is a screening instrument which allows a global cognitive measurement to be made through the assessment of a wide range of cognitive functions, such as (i) short-term memory, (ii) executive functions, (iii) visuospatial abilities, (iv) language, (v) attention, concentration and working memory, and (vi) temporal and spatial orientation (Nasreddine et al., 2005). The MoCA has been shown to be a sensitive tool for milder states of cognitive impairment, not only in the spectrum of Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) (Freitas, Simões, Alves, & Santana, 2013; Nasreddine et al., 2005; Roalf et al., 2013) but also for cognitive impairment associated with many other clinical conditions [e.g. vascular cognitive impairment (Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010), Parkinson's Disease (Hoops et al., 2009), Huntington's Disease (Videnovic et al., 2010), and tumors (Olson et al., 2010)]. These results, which are consistently good as a measure of global cognitive function, have led to the widespread use of the MoCA in both clinical and research contexts. Its extensive validation, international recognition and recommendation in various guidelines make it a useful brief cognitive screening tool (Arnold et al., 2007; Gauthier et al., 2011; Hachinski et al., 2006).

The few published studies on the MoCA in MS seem to corroborate its usefulness as a brief screening instrument for the detection of cognitive impairment in MS patients. Two independent studies found convergent results, demonstrating that the MoCA cognitive performance of MS patients was significantly lower than the

performance of normal subjects, with major deterioration in the language, memory, attention and executive domains of the MoCA (Abraham & Rege, 2012; Aksoy et al., 2013). Danegais and collaborators (2013) observed significant differences in the MoCA total score between cognitively intact and cognitively impaired MS patients, and significant correlations between scores in MoCA domains and the corresponding factors derived from the comprehensive neuropsychological assessment. Finally, Kaur, Kumar and Singh (2013) also examined the MoCA and its 5-minute protocol (Hachinski et al., 2006) in MS patients, concluding that both MoCA versions were effective in detecting CD in this group. This allows the short version to be administered when there is underlying visual or motor disability in these patients. Overall, none of these studies examined the diagnostic accuracy of the MoCA for detecting CD in MS, nor were cut-off points for this purpose clearly defined.

In the last few years, the MoCA has been the subject of a systematic investigation plan within the Portuguese population. After the normative study (Freitas, Simões, Alves, & Santana, 2011), various validation studies were conducted. Some of these studies further emphasize the psychometric characteristics of the instrument (e.g. Freitas, Simões, Marôco, Alves, & Santana, 2012; Freitas, Prieto, Simões, & Santana, 2014), while others primarily focus on specific clinical groups [e.g., vascular dementia (Freitas, Simões, Alves, Vicente, & Santana, 2012)]. The present study was undertaken with the aim of further validating the MoCA's Portuguese version for a brief assessment of CD in MS patients. This was carried out through the analysis of its psychometric properties, investigation of the influence of sociodemographic variables on MoCA performance, exploration of the cognitive performances of this clinical group, analysis of its diagnostic accuracy and establishment of the optimal cut-off point for detecting CD in MS patients. To date, and as far as we know, there have been no other validation

studies proposing a cut-off point for identifying the cognitive clinical alterations in MS patients and examining the respective diagnostic accuracy of the MoCA. This represents a considerable gap in the full validation of this instrument and significantly limits its usefulness in clinical practice.

Method

Participants and procedures

The study sample was composed of 118 participants divided into two subgroups: (I) the MS group with 59 patients and (II) the control group with 59 cognitively healthy adults.

The MS patients were recruited consecutively between January 2012 and December 2013 from follow-up consultations at the Neurology Department of a central hospital. The diagnosis of MS had been established by a team of highly trained neurologists (SB and LS) according to the revised 2010 McDonald criteria (Polman et al., 2012). For this study we only recruited MS patients with Relapsing-Remitting or Secondary-Progressive forms of the disease, aged between 18 and 55 years, and in a stable condition (no relapses or steroid pulse treatment for 8 weeks preceding evaluation). The primary progressive MS and progressive relapsing MS cases were not included in the study sample since these other subtypes represent a minority of MS patients and some studies have shown them to be cognitively distinct from the other subtypes (Ruet, Deloire, Charré-Morin, Hamel & Brochet, 2013).

The healthy group was composed of cognitively healthy community members voluntarily recruited from a convenience sample, without developmental delays or other major medical disorders that may compromise cognitive function. All participants performed normally in the neuropsychological assessment battery compiled for this

study, taking into account the Portuguese-validated data. These volunteer participants were further selected in order to match each patient regarding gender and variables that were found to be predictive of the MoCA's performance (educational level and age; Freitas et al., 2012).

The following exclusion criteria were considered for the eligibility of both groups: (I) the absence of Portuguese language skills adequate for cognitive testing; (II) a current or past history of neurological disease (other than MS for the study group), traumatic brain injury or psychiatric disorder, including depression; (III) previous or current alcohol abuse or other substance abuse; (IV) severe visual or auditory impairment that would negatively affect the ability to satisfactorily complete tests or understand test instructions; or (V) current or prior use of antipsychotic medication.

Informed consent was obtained from all the participants after the research aims, procedures, and confidentiality requirements were fully disclosed by a member of the research team. 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 and Neuropsychological Assessment

The same psychologist (AA), with expertise in neuropsychological assessment and blinded to the cognitive status of the participants administered the MoCA (Nasreddine et al., 2005; Simões et al., 2008) to all participants. The clinical interview and neurologic examination were performed by one of the neurologists (SB). Demographic and clinical data were collected through a complete sociodemographic questionnaire and an inventory of past habits, current clinical health status and medical history. For the MS patients, we also considered relevant clinical data, namely disease

subtype classification, age of disease onset, age at diagnosis, disease duration and current disease-modifying treatment. Physical disability was evaluated using the detailed Kurtzke Expanded Disability Status Scale (EDSS; Kurtzke, 1983).

All study participants were investigated with a comprehensive neuropsychological assessment battery administered in a fixed order, and which included the following instruments: the *Symbol Digit Modalities Test, Rao adaptation* (SDMT) - as a measure of visual information-processing speed (Rao, 1991; Smith, 1982); the *Paced Auditory Serial Addition Test, Rao adaptation* (PASAT) - as a measure of auditory information-processing speed and working memory (Gronwall, 1977); the *Brief Visuospatial Memory Test- Revised* (BVMT) – for the evaluation of visuospatial learning and memory (Benedict, 1997); the *California Verbal Learning Test* (CVLT) - for the assessment of verbal episodic learning and memory (Delis, Kramer, Kaplan, & Ober, 1987); the *Judgment of Line Orientation Test* (JLO) - to assess spatial perception (Benton, Sivan, Hamsher, Varney, & Spreen, 1994); and to evaluate executive functions: the *Stroop Test* (ST; Golden & Freswater, 2002), the *Trail Making Test A* and *B* (TMT-A and TMT-B; War Department Adjutant General's Office, 1944), the *Verbal Fluency Test* (VFT; Rosen, 1980) and the *Raven's Advanced Progressive Matrices* (RAPM; Raven, Court, & Raven, 1983). Portuguese translations of the neuropsychological tests were used. The process of translating these tests into our language and adapting them to our cultural context followed the guidelines proposed in the literature (Hambleton, 2005; Hambleton & Patsula, 1999; Herdman, Fox-Rushby & Badia, 1998; International Test Commission, 2001; Vijver & Poortinga, 2005).

We considered the following criteria to define cognitive impairment, as reported previously in other studies (Benedict et al., 2004; Batista et al., 2012): a) a z score of < -1.5 across four tests, or b) the presence of one severe ($z < -2.0$) and two mild ($z < -1.5$)

cognitive defects, or c) two severe defects ($z < -2.0$), across all cognitive measures of the neuropsychological assessment battery compiled for this study, excluding the MoCA (target tool of the study).

Additionally, the patients were assessed using the following scales: the *Irregular Word Reading Test* (TeLPI) – to estimate premorbid intelligence levels (Alves, Simões, & Martins, 2009); the *Beck Depression Inventory* (Vaz Serra & Pio Abreu, 1973a, 1979b) and *Modified Fatigue Impact Scale* (MFIS; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Gomes, 2011) - to evaluate depression and fatigue, respectively, as these factors are known to influence cognition.

As the MoCA is the target tool of this study, the following is a more detailed description of this neuropsychological instrument. The MoCA (Nasreddine et al., 2005; Simões et al., 2008) is a brief cognitive screening instrument developed to screen milder forms of cognitive impairment, allowing the global cognitive state to be ascertained rapidly. The MoCA comprises a one-page test, which can be administered quickly (in 10 to 15 minutes), and a manual with explicit instructions for administering the tasks and an objective presentation of the defined scoring system. A total score is generated through the sum of the points of each successfully completed task, in a range from 0 to 30 points, with higher scores indicating better cognitive performance. In the present study, the MoCA was not used as a diagnostic tool and the MoCA total score refers to the raw score without correction for the educational effects proposed in the original study (Nasreddine et al., 2005), because this correction point is not used in the Portuguese population (Freitas et al., 2011). The cultural adaptation of the MoCA to the Portuguese population involved translation, linguistic improvement of the instrument and manual, studies with the experimental version, further revision and adjustments to finalize the Portuguese version, and an analysis of the equivalence of this version to the

original (at six levels: conceptual, by item, semantic, operational, by measurement, and functional) (Freitas et al., 2010).

Statistical Analysis

Statistical analyses were conducted using the *Statistical Package for the Social Sciences* (SPSS, version 20.0) (IBM SPSS, Chicago, IL). Descriptive statistics were used to characterize the sample. The χ^2 test and the two-sample *t-test* allowed the two groups to be compared, while the effect size was estimated using Cohen's *d* (Cohen, 1988). Cronbach's alpha was considered as an index of internal consistency, and Pearson's correlation coefficients were used to assess the convergent validity (between the MoCA total scores and instruments of the neuropsychological battery assessment) and as an indicator of construct-related validity (between each item and the cognitive domains, between cognitive domains, and between each cognitive domain and the MoCA total score).

To investigate the significance of: age (in years), education (years of schooling successfully completed), BDI, MFIS, and premorbid intelligence (TeLPI score) as influencing factors in the MoCA, Multiple Linear Regression (MLR) analyses were performed using the Enter method (the standard method of simultaneous entry, where all independent variables enter the equation at the same time). Multicollinearity was examined through Tolerance and Variance Inflation Factor (VIF) statistics (Tolerance of less than 0.40 and/or a VIF of 2.5 or above indicates a multicollinearity problem - Meyers, Gamst, & Guarino, 2006), and the coefficient of determination (Adjusted R^2) was considered in the analysis of effect size in the regressions (Cohen, 1988).

Z scores were calculated by (patient's score - mean value of control group matched for age, sex, and education level)/standard deviation of the control group. The

MoCA scores differences between the MS subgroups, considering the influence of age and education, was addressed with the analysis of covariance (ANCOVA). Eta squared (η^2) was used as an estimate of the effect size and η_p^2 values of .01, .06 and .14 are considered small, medium and large effect sizes, respectively (Cohen, 1988).

The diagnostic accuracy of the MoCA for predicting cognitively impaired MS patients was assessed through the receiver operating characteristics (ROC) curve analysis. The area under the curve (AUC) was calculated, which can vary between 0.5 and 1, with a larger AUC signifying better diagnostic accuracy. The optimal cut-off point that yielded the highest Youden index was selected, with a higher index indicating the maximization of the instrument's sensitivity and specificity. To analyze the predictive value of the test for this optimal cut-off point, we calculated the sensitivity (the probability that subjects with cognitive impairment will test positive), specificity (the probability that subjects without cognitive impairment will test negative), positive predictive value (PPV - the probability of disease in subjects who test positive), negative predictive value (NPV- the probability of a lack of cognitive impairment in subjects who test negative) and classification accuracy (the probability of correctly classifying subjects who either do or do not have cognitive impairment).

Results

Sociodemographic, clinical and cognitive characterization of subgroups

The sociodemographic characteristics of the study sample, including details of the subgroups, are presented in Table 1. For this description, the following parameters were considered: sample size, gender, age and educational level. In the MS study group, patients presented an average age of disease onset and diagnosis of, respectively, 26.83

± 7.81 years and 29.31± 7.70 years, corresponding to an average time for the establishment of diagnosis of 2.47 ± 3.82 years. These patients had a mean disease duration of 10.39 ± 6.55 years, EDSS median of 2.0 (mean=2.50±1.42), approximately 86% had a Relapsing-Remitting and 14% a Secondary Progressive disease course subtype. Table 2 summarizes the cognitive features of subgroups, taking into account the results of the neuropsychological assessment battery compiled for this study.

(Insert Table 1 about here)

(Insert Table 2 about here)

As mentioned above, the control participants were matched for gender, age, and educational level with the MS patients. Because of this, there were no gender differences between the two groups ($\chi^2_{(1)}$=0.000, p=1.0). Likewise, no statistically significant differences were found based on age ($t_{(115)}$=0.798, p=0.427) or educational level ($t_{(178)}$=1.282, p=0.202).

Psychometric Properties

The internal consistency of the MoCA was estimated using Cronbach's α. In the total sample (N=118), we found a Cronbach's α of 0.65. This coefficient was also computed for the MS group (n=59), where the respective value was 0.61. A more detailed analysis revealed that there was no improvement regarding the Cronbach's α value with the exclusion of any item of the scale.

As indicators of convergent validity, we found statistically significant correlation coefficients between the MoCA total scores and the scores in the neuropsychological battery assessment instruments, with coefficient values ranging between 0.35 and 0.59 (p<0.01) in the total sample and between 0.31 and 0.62 (p<0.01) in the MS group, as presented on table 3.

(Insert Table 3 about here)

In the MS group, we also analyzed the correlations between each MoCA item and the MoCA cognitive domains, between MoCA cognitive domains, and between each MoCA cognitive domain and the MoCA total score. All of the items showed a stronger correlation with their respective domains than with any other domain. In addition, we found a significant positive correlation between each cognitive domain and the total score of the scale, ranging from 0.43 to 0.63 (p<0.01). Furthermore, each domain showed stronger correlations with the MoCA total score than with any other domain, which illustrates the discriminative power of the MoCA cognitive domains.

Influence factors on MoCA performance

Considering only the MS group, we did not find any statistically significant differences in MoCA scores between gender groups ($t_{(57)}$=0.579, p=0.565) and age groups [3 subgroups were considered: < 30 years, 30-40 years and > 40 years ($F_{(2,58)}$ =2,036, p=0.140)]. Education, defined as years of schooling successfully completed, was the sociodemographic variable with the greatest influence on MoCA results, with higher performances in the more educated groups [3 subgroups were considered: Primary to Middle (< 9 years of schooling), High (10-12 years of schooling) and University (>12 years of schooling); ($F_{(2,58)}$=4.705, p=0.013)].

The MoCA total score showed statistical significant correlation (p<0.01) with the educational level (r=0.33), MFIS (r=-0.39) and TeLPI (r=0.44), whereas no significant coefficients were founded with age and BDI scores.

To examine the contributions of age, education level, BDI, MFIS and TeLPI scores in explaining the variance in MoCA scores, an MLR analysis was performed using the *Enter* method. This analysis resulted in a significant regression model

($F_{(1,58)}$=6.740, p<0.001) in which all variables together explain 33% of total variance in the MoCA scores (Adjusted R^2=0.331). Table 4 presents the significance of each factor in the regression model, the Tolerance and VIF values and partial correlations.

(Insert Table 4 about here)

Group Differences

The MS patients were classified as cognitively intact or cognitively impaired according to their performance in the comprehensive neuropsychological assessment battery compiled for this study, excluding the MoCA. In this study sample, approximately 56% (n=33) of all MS patients showed cognitive impairment, while 44% (n=26) had a normal global cognitive performance, according to the above criteria.

A comparison of all three groups: cognitively impaired MS group, cognitively intact MS group and control group – showed the existence of statistically significant differences between the groups ($F_{(1,118)}$=11.962, p<0.001, η_p^2=0.175) in the MoCA total scores as well as in several domains: short-term memory ($F_{(1,118)}$=11.200, p<0.001, η_p^2=0.178), executive functions ($F_{(1,118)}$=3.502, p=0.033, η_p^2=0.058), and temporal and spatial orientation domains ($F_{(1,118)}$=5.091, p=0.008, η_p^2=0.083), controlling for the effect of covariates age and educational level [since statistically significant differences were observed in mean age ($F_{(2,117)}$=4.210, p=0.017) and mean educational level ($F_{(2,117)}$=7.011, p=0.001) between the groups but no gender differences ($\chi^2_{(2)}$=1.060, p=0.588)].

MS Group *versus* Control Group

A comparative analysis between the clinical and control groups revealed statistically significant differences in the MoCA total scores ($t_{(116)}$=3.768, p<0.001,

d=0.69), with a lower performance for the MS patients (25.03±2.51; control group: 26.76±2.44). With regard to the subscores in MoCA cognitive domains, the two groups showed statistically significant differences in the executive functions ($t_{(116)}$=2.710, p=0.008), language ($t_{(116)}$=2.338, p=0.021), and short-term memory domains ($t_{(116)}$=3.813, p<0.001).

Cognitively Impaired MS *versus* Cognitively Intact MS

The MS subgroups, showed statistically significant differences in mean age [$t_{(57)}$=3.358, p=0.001; with the cognitively intact patients being younger (33.77±6.92) than the cognitively impaired patients (39.91±7.03)] and mean educational level [$t_{(57)}$=3.765, p<0.001; with the cognitively intact patients presenting a higher educational level (15.15±2.91) than the cognitively impaired patients (11.70±4.13)]. Controlling for the effect of these variables, no statistically significant differences were found in average age of onset, average age at diagnosis, average time taken to establish a diagnosis, the mean disease duration, the physical disability measured by the EDSS or the depressive symptomatology as measured by the BDI. Regarding the measure of fatigue, cognitively impaired MS patients presented significantly higher MFIS total scores ($F_{(1,55)}$=9.363, p=0.003, η_p^2=0.145).

Controlling for the effect of covariates (age and educational level), we found statistically significant differences in the MoCA total scores ($F_{(1,55)}$=15.229, p<0.001, η_p^2=0.217) between the cognitively intact (26.58±1.82) and cognitively impaired MS group (23.70±2.31); and regarding the MoCA cognitive domain subscores the two groups showed statistically significant differences in the executive functions ($F_{(1,55)}$=4.321, p=0.042, η_p^2=0.073), visuospatial ($F_{(1,55)}$=5.749, p=0.020, η_p^2=0.095),

short-term memory ($F_{(1,55)}$=8.354, p=0.005, η_p^2=0.132) and temporal and spatial orientation domains ($F_{(1,55)}$=4.045, p=0.049, η_p^2=0.069).

Cognitively Impaired MS *versus* Control Group

There were statistically significant differences between groups in the MoCA total scores ($F_{(1,88)}$=21.939, p<0.001, η_p^2=0.200) as well as in several domains: short-term memory ($F_{(1,88)}$=22.189, p<0.001, η_p^2=0.201), executive functions ($F_{(1,88)}$=6.187, p=0.015, η_p^2=0.066), and temporal and spatial orientation domains ($F_{(1,88)}$=7.471, p=0.008, η_p^2=0.078), considering the control for the effect of covariates (age and educational level).

Cognitively Intact MS *versus* Control Group

A comparative analysis between the cognitively intact MS patient group and the control group revealed no statistically significant differences in MoCA total scores ($F_{(1,81)}$=1.757, p=0.189) or in any of the MoCA's cognitive domains, considering the control for the effect of covariates (age and educational level).

Cut-off Points and Diagnostic Validity

Several ROC curve analyses were conducted to evaluate the diagnostic validity of MoCA total score in discriminating between: (i) cognitively impaired MS group and cognitively intact MS group; (ii) cognitively impaired MS group and control group; and (iii) cognitively impaired MS group and unimpaired group (comprising the control group and the cognitively intact MS group).

Additionally we investigated an EM-MoCA-Subscore which includes scores of executive functions, visuospatial, short-term memory and temporal and spatial

orientation domains, with a range from 0 to 19 points. We found statistically significant differences in the EM-MoCA-Subscore ($F_{(1,55)}$=21.458, p<0.001, η_p^2=0.281) between the cognitively intact (16.62±1.17) and cognitively impaired MS group (14.21±1.82), considering the control for the effect of covariates (age and educational level). ROC curve analyses were computed to investigate the diagnostic accuracy of EM-MoCA-Subscore in discriminating between: (i) cognitively impaired MS group and cognitively intact MS group; (ii) cognitively impaired MS group and control group; and (iii) cognitively impaired MS group and unimpaired group (comprising the control group and the cognitively intact MS group).

All AUC values, optimal cut-off points (according to the Youden index) and respective sensitivity, specificity, PPV, NPV, and accuracy values are presented in the Table 5.

Discussion

To date, there have been few validation studies of the MoCA for the detection of cognitive impairment in MS patients (Abraham & Rege, 2012; Aksoy et al., 2013; Danegais et al., 2013; Kaur, Kumar & Singh 2013). Although these studies consensually pointed out the usefulness and validity of the instrument, none of them fully examined the discriminative validity of the test, nor was the diagnostic accuracy of the MoCA to detect CD in MS using cut-off points clearly defined. Thus, the aim of the present study was to carry out a deeper and more consistent investigation of the utility of the MoCA's Portuguese version to screen for CD in MS patients. For this purpose, several analyses were conducted in order to examine the psychometric properties of the MoCA, the influence of sociodemographic variables on its performance and the

cognitive performances of MS patients, and to determine the optimal cut-off point for detecting cognitive impairment in these patients and the respective diagnostic accuracy.

The results of this study indicate that the MoCA is a psychometrically valid screening instrument for the detection of MS-related cognitive impairment. The MoCA displayed adequate overall psychometric characteristics when used to assess MS patients, as indicated by good indicators of convergent validity. Our results showed coefficient alpha for the MoCA slightly lower than 0.70, which can lead to question whether it has an acceptable reliability. Although the Cronbach's alpha is the most commonly used measure of internal consistency, psychometricians have pointed out limitations of coefficient alpha as a measure of reliability, as well as recurrent misinterpretations. In this context, it should be noted that higher reliability may indicate undue narrowness of content or item redundancy that can limit predictive utility (according to attenuation paradox: Loevinger, 1954). For this reason, some authors disputed the view that alpha should necessarily be above .70 (e.g., Schmitt, 1996) and others cautioned against alphas greater than .90 (e.g., Streiner, 2003).

Additionally, the significant positive correlation coefficients found between each item and its respective cognitive domain (all of the items were more strongly correlated with their own respective domain than with any other) and between cognitive domains and the MoCA total score (each cognitive domain was more strongly correlated with the MoCA total score than with any other domain) support both the MoCA's construct-related validity and the discriminative power of the cognitive domains. These results are congruent with previous studies conducted with the MoCA in the Portuguese population (Freitas, Simões, Marôco et al., 2012).

The MLR analyses highlighted the significant influence of MFIS and TeLPI scores on MoCA performance in MS patients, reflecting the positive impact of

premorbid intelligence and the negative impact of fatigue on cognitive functioning of MS patients. In contrast, age, education level and BDI had no significant contribution to the regression model. The premorbid intelligence, along with age and education, has been identified as a major predictor of cognitive performance in screening tests such as MMSE scores (Christensen & Jorm, 1992; Star & Lonie, 2007). More specifically, Alves and collaborators (2013) demonstrated that premorbid intelligence influences the MMSE and the MoCA scores in both cognitively healthy participants and patients with cognitive impairment (mild cognitive impairment and Alzheimer disease), and proposed that a premorbid intelligence measure should be considered to ensure correct interpretation of scores.

In this study, the prevalence of cognitive impairment in patients with MS was 56%, and although the reported frequency of cognitive impairment in MS varies widely, our findings are in line with studies describing a high prevalence (Amato et al., 2006). Moreover, it is also noteworthy that cognitively impaired MS patients presented similar age of onset, age at diagnosis, time taken to establish a diagnosis, disease duration, physical disability measured by the EDSS and depressive symptomatology as measured by the BDI compared to cognitively intact MS patients, suggesting that cognitive dysfunction may occur in all disease stages and be dissociated from physical disability. Finally, patients with cognitive impairment presented higher scores for fatigue, as measured by the MFIS. Fatigue is a prominent symptom in MS and its relation with cognitive impairment is still a matter of debate. While some studies indicated that fatigue can impair cognitive functioning in MS (Krupp et al., 2000), others revealed that there is no direct association between fatigue and actual cognitive performance (Parmenter et al., 2003). Moreover, the nature of this potential association remains unknown. It may be hypothesized that either cognitive dysfunction causes fatigue by

producing activation of compensatory pathways or fatigue contributes to a poorer performance in cognitive tasks.

The analyses of group differences highlight the MoCA's discriminative capacity. In fact, total scores were able to efficiently distinguish: (i) all three groups: cognitively impaired MS group, cognitively intact MS group and control group; (ii) the clinical from the control group, (iii) the cognitively intact from the cognitively impaired MS patients, and (iv) the cognitively impaired MS patients from the control group, with large effect sizes according to Cohen (1988). Furthermore, when we analyzed the MoCA's cognitive domains, statistically significant differences were systematically observed in the executive functions and memory domains in all above subgroups' comparisons established. These findings are convergent with findings that have been reported in the literature (Abraham & Rege, 2012; Aksoy et al., 2013), with one exception: in the current study, no differences were found in the attention domain. Overall, the cognitively impaired MS patients showed a statistically significant poor performance in the executive functions, visuospatial, short-term memory and orientation domains when compared with cognitively intact MS patients, and statistically significant lower scores in the executive functions, short-term memory and orientation domains than the healthy control subjects. On the other hand, when comparing the cognitively intact MS patient group with the control group, we did not find any statistically significant differences in MoCA total scores or any of the MoCA's cognitive domains, suggesting a similar cognitive performance.

Regarding the results obtained with the comprehensive and holistic battery of tests used in this study, there were significant differences between the cognitive profiles of the MS patients and those of the healthy control subjects. As expected, premorbid

intelligence levels were comparable, and in addition similar performances were observed in the VFT and RAPM tests. Concerning other neuropsychological measures of the battery, the MS group showed a statistically significant lower performance than the control group in all instruments. Since the performances on these instruments were used to classify the cognitive state of MS patients as cognitively intact or cognitively impaired, it is not methodologically correct to compare the performances of the MS subgroups in the comprehensive neuropsychological assessment battery.

Several ROC curve analyses were conducted to evaluate the diagnostic validity of MoCA total score and EM-MoCA-Subscore in discriminating between: (i) cognitively impaired MS group and cognitively intact MS group; (ii) cognitively impaired MS group and control group; and (iii) cognitively impaired MS group and unimpaired group (comprising the control group and the cognitively intact MS group). The optimal cut-off point for the MoCA total score for identifying CD in MS patients, allowing maximum sensitivity and specificity, was below 26 points. For example, between the cognitively impaired and intact MS patients it showed good sensitivity (76%), specificity (73%), PPV (78%), NPV (70%) and classification accuracy (75%). These diagnostic accuracy parameters are improved with the EM-MoCA-Subscore which only includes the MoCA's cognitive domains with more discriminative power between the cognitively impaired MS patients and unimpaired participants (executive functions, visuospatial, short-term memory and temporal and spatial orientation domains), thus enhancing their sensitivity to cognitive impairment. Considering this EM-MoCA-Subscore it was possible to observe an increase of discriminative capacity between the cognitively intact and cognitively impaired MS patients, as indicated by the higher effect size (MoCA total scores: η_p^2 = 0.217 and EM-MoCA-Subscore: η_p^2 = 0.281) and AUC of ROC curves (MoCA total scores: AUC = 0.837, 95% CI = 0.736 -

0.937; EM-MoCA-Subscore: AUC = 0.871, 95% CI = 0.784 - 0.958). For a maximum possible score of 19 points, the optimal cut-off point for the EM-MoCA-Subscore for identifying CD in MS patients, according to the Youden index, was below 17 points (Sensitivity = 94%; Specificity = 62%; PPV = 76%; NPV = 89%; Classification Accuracy = 80%). These results suggest that the effectiveness of MoCA, particularly the EM-MoCA-Subscore, as a screen for cognitive impairment in MS is roughly equal to that of other recognized screening tests. For instance, SDMT revealed a sensitivity of 82%, specificity of 60%, PPV of 71%, and NPV of 73%, for a cut-off of 55 (Parmenter, Weinstock-Guttman, Garg, Munschauer & Benedict, 2007).

In our opinion, the strengths of the current study include 1) the homogeneity of the samples in terms of group size, gender, age and educational level, which allowed for a clearer analysis and minimized the influence of individual and methodological variables; 2) the above-mentioned rigorous methodological procedures, which included the previous well-validated clinical diagnosis of the MS group by a multidisciplinary team using standard criteria and based on a full investigation; 3) the subdivision of the MS group into cognitively intact or cognitively impaired patients, according to their performance in the comprehensive neuropsychological assessment battery, and considering strict criteria for classification; 4) the well-characterized control group, composed of cognitively healthy adult members of the community; and 5) the reduction of inter-rater variability due to all participants being assessed by the same psychologist with expertise in neuropsychological assessment. However, some limitations and caveats of the current study must be addressed: 1) the small sample size; 2) the diagnostic utility must be understood in the context of a matched case-control study design and the inherent heterogeneity to MS; 3) the fatigue is a common symptom in MS patients that may influence the cognitive performance during the

neuropsychological assessment; 4) although the final version of the Portuguese MoCA emerged as the result of a rigorous process that followed the methodological guidelines for cultural adaptation studies, and maximum equivalence between the original instrument and the final version of the Portuguese MoCA was sought (Freitas et al., 2010), caution should be exercised in generalizing these results to other target populations; and 5) there are no other validation studies with which the results of our research can be compared, namely at the levels of diagnostic accuracy of the MoCA total score and respective cut-off point; at this level and in relation to the EM-MoCA-Subscore corroborative studies are needed in future studies.

In conclusion, the present validation study produced several findings that demonstrate that the MoCA is a psychometrically valid and sensitive instrument to identify the MS-related cognitive impairment. The MoCA is a widely accepted tool requiring no specialist equipment or specialist expertise, which makes it an alternative screening method eventually more easy to use in everyday practice given its widespread use and international recognition and acceptance. However, the MoCA, like the other screening instruments, is not a substitute for a more comprehensive assessment and should be used to identify patients who may benefit from a more thorough assessment or need treatment. The multidimensional structure of the MoCA and its potential to firstly identify impaired cognitive domains can be useful in a context of cognitive inter-patient variability insofar as it provides information that may be relevant for planning a more comprehensive neuropsychological assessment. Finally, we propose the use of the EM-MoCA-Subscore for identifying the MS-related cognitive impairment, which can reduce administration time for cognitive screening in clinical settings and potentiate the discriminative power.

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Table 1. *Sociodemographic characteristics of the total sample and subgroups*

	MS Group	**MS Intact Group**	**MS Impaired Group**	**Control Group**	**Total Sample**
n / N	59	26	33	59	118
Gender F (%)	39 (66.1)	19 (73.1)	20 (60.6)	39 (66.1)	78 (66.1)
Age					
M ± SD	37.20 ± 7.58	33.77 ± 6.92	39.91 ± 7.03	36.03 ± 9.52	36.62 ± 8.59
[Min.-Max.]	[22-54]	[22-53]	[28-54]	[21-55]	[21-55]
Education					
M ± SD	13.22 ± 4.01	15.15 ± 2.91	11.70 ± 4.13	14.12 ± 3.86	13.67 ± 3.94
[Min.-Max.]	[4-19]	[8-19]	[4-19]	[6-21]	[4-21]

Note. F = feminine gender; M = mean; SD = standard deviation; Min. = minimum value; Max. = maximum value.

Table 2. *Cognitive characteristics of the subgroups*

Measure	**Control Group**	**MS Group**	**MS Intact Group**	**MS Impaired Group**	**Control vs. MS**	**Control Group vs. MS Impaired vs. MS Intact**
Symbol Digit Modalities Test, Rao adaptation (SDMT)	56.34 ± 9.67 [32;74]	47.10 ± 12.09 [19;74]	55.00 ± 7.73 [44;74]	40.88 ± 11.30 [19;63]	$t_{(116)}$=4.583, p<0.001 d=0.84	$F_{(1,118)}$=20.326, p<0.001, η_p^2=0.265
Paced Auditory Serial Addition Test, Rao adaptation (PASAT)	39.79 ± 12.31 [3;59]	31.85 ± 15.77 [1;60]	39.73 ± 11.90 [14;60]	25.64 ± 15.82 [1;53]	$t_{(116)}$=3.040, p=0.003 d=0.56	$F_{(1,118)}$=9.560, p<0.001, η_p^2=0.146
Brief Visuospatial Memory Test-Revised						
Total	26.31 ± 4.46	21.61 ± 8.12	28.65 ± 4.23	16.06 ± 5.78	$t_{(116)}$=3.893,	$F_{(1,118)}$=48.250,

Learning (BVMT-R-TL)	[17;34]	[3;35]	[19;35]	[3;28]	p<0.001 d=0.72	p<0.001, η_p^2=0.461
Delayed Recall (BVMT-R-DR)	10.49 ± 1.65 [6;12]	8.59 ± 2.94 [1;12]	11.12 ± 1.11 [7;12]	6.61 ± 2.34 [1;11]	$t_{(116)}$=4.319, p<0.001 d=0.80	$F_{(1,118)}$=50.782, p<0.001, η_p^2=0.473
California Verbal Learning Test (CVLT)						
Total Learning (CVLT-TL)	61.73 ± 6.72 [45;78]	54.78 ± 10.22 [19;75]	61.77 ± 6.27 [47;75]	49.27 ± 9.36 [19;72]	$t_{(116)}$=4.364, p<0.001 d=0.81	$F_{(1,118)}$=25.422, p<0.001, η_p^2=0.310
Delayed Recall (CVLT-DR)	14.02 ± 1.29 [11;16]	12.05 ± 3.03 [3;16]	14.27 ± 1.73 [9;16]	10.30 ± 2.66 [3;16]	$t_{(116)}$=4.590, p<0.001 d=0.85	$F_{(1,118)}$=41.477, p<0.001, η_p^2=0.423

Judgment of Line Orientation Test (JLOT)	25.44 ± 3.65 [14;30]	23.56 ± 4.78 [13;30]	25.69 ± 2.81 [19;30]	21.88 ± 5.34 [13;30]	$t_{(116)}$=2.403, p=0.018 d=0.44	$F_{(1,118)}$=6.305, p=0.003, η_p^2=0.100
Stroop Test					$t_{(116)}$=4.257, p<0.001 d=0.78	$F_{(1,118)}$=10.150, p<0.001, η_p^2=0.152
Color (ST-C)	56.80 ± 8.35 [43;82]	69.54 ± 21.43 [45;199]	63.31 ± 10.06 [45;85]	74.45 ± 26.39 [46;199]		
Color -Word (ST-CW)	120.10 ± 20.76 [82;176]	143.00 ± 40.09 [93;271]	121.15 ± 18.11 [93;170]	160.21 ± 44.31 [99;271]	$t_{(116)}$=3.896, p<0.001 d=0.72	$F_{(1,118)}$=19.144, p<0.001, η_p^2=0.253
Trail Making Test A (TMT-A)	38.32 ± 13.36 [16;74]	46.63 ± 30.59 [22; 128]	42.46 ± 16.43 [24;83]	49.91 ± 23.07 [22;128]	$t_{(116)}$=2.600, p=0.011 d=0.35	$F_{(1,118)}$=2.743, p=0.069, η_p^2=0.046
Trail Making Test B (TMT-B)	82.49 ± 32.16 [43;237]	125.78 ± 66.17 [49;369]	98.46 ± 46.81 [49;281]	147.30 ± 71.69 [64;369]	$t_{(116)}$=4.519, p<0.001 d=0.83	$F_{(1,118)}$=12.545, p<0.001, η_p^2=0.182
Verbal Fluency Test (VFT)	7.37 ± 2.71 [0;13]	7.03 ± 2.77 [2;13]	8.19 ± 2.74 [2;12]	6.12 ± 2.47 [2;13]	$t_{(116)}$= 0.672, p=0.503 d=0.12	$F_{(1,118)}$=2.688, p=0.072, η_p^2=0.045

Raven's Advanced Progressive Matrices (RAPM)	11.44 ± 0.86 [8;12]	11.02 ± 1.54 [5;12]	11.77 ± 0.51 [10;12]	10.42 ± 1.80 [5;12]	$t_{(116)}$=1.850, p=0.068 d=0.34	$F_{(1,118)}$=6.685, p=0.002, η_p^2=0.106
Irregular Word Reading Test (TeLPI)	39.83 ± 3.34 [30;45]	38.73 ± 5.41 [20;46]	40.42 ± 4.57 [28;46]	37.39 ± 5.71 [20;44]	$t_{(116)}$=1.324, p=0.189 d=0.25	$F_{(1,118)}$=1.369, p=0.259, η_p^2=0.024

Note. Results are presented as mean ± standard deviation and additionally are provided the range of the results [minimum value; maximum value]. Possible ranges of scores: MoCA = [0;30], SDMT = [0;110], PASAT = [0;60], BVMT-R-TL = [0;36], BVMT-R-DR = [0;12], CVLT-TL = [0;80],CVLT-DR = [0;16], JLOT = [0;30], ST-C (time) = [0;∞[, ST-CW (time) = [0;∞[, TMT-A (time) = [0;∞[, TMT-B (time) = [0;∞[, VFT (60’ Animals) = [0;∞[, RAPM = [0;12], TeLPI (raw scores) = [0;46]. The comparisons of all three groups considered the control of covariates age and educational level.

Table 3. *Correlation coefficients between the MoCA and the neuropsychological battery assessment instruments*

	MoCA Total Scores	
	MS Group	**Total Sample**
Symbol Digit Modalities Test, Rao adaptation (SDMT)	0.61	0.50
Paced Auditory Serial Addition Test, Rao adaptation (PASAT)	0.58	0.53
Brief Visuospatial Memory Test-Revised		
Total Learning (BVMT-R-TL)	0.50	0.50
Delayed Recall (BVMT-R-DR)	0.52	0.54
California Verbal Learning Test (CVLT)		
Total Learning (CVLT-TL)	0.50	0.53
Delayed Recall (CVLT-DR)	0.45	0.45
Judgment of Line Orientation Test (JLOT)	0.54	0.53
Stroop Test		
Color (ST-C)	-0.37	-0.35
Color -Word	-0.54	-0.43

(ST-CW)		
Trail Making Test A (TMT-A)	-0.31	-0.38
Trail Making Test B (TMT-B)	-0.54	-0.56
Verbal Fluency Test (VFT)	0.42	0.37
Raven's Advanced Progressive Matrices (RAPM)	0.62	0.52
Irregular Word Reading Test (TeLPI)	0.44	0.46
Number of impaired scores on the battery assessment instruments	0.62	0.59

Note. All correlation coefficients are significant at the 0.01 level. The criterion for impaired score on the neuropsychological battery assessment instruments was $z < -1.5$.

Table 4. *Regression Model*

	Contribution to the Model	Tolerance	VIF	Partial Correlations
Age	*ß*=-0.126, *t*=1.171, *p*=0.247	0.956	1.047	-1.59
Education	*ß*=0.127, *t*=1.038, *p*=0.304	0.768	1.303	0.141
BDI	*ß*=0.152, *t*=1.086, *p*=0.282	0.588	1.699	0.148
MFIS	*ß*=-0.454, *t*=3.242, *p*=0.002	0.589	1.697	-0.407
TeLPI	*ß*=0.363, *t*=3.000, *p*=0.004	0.790	1.266	0.381

Table 5. *Cut-off Points and Diagnostic Validity*

	Groups	AUCs	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
MoCA Total Score	Impaired MS vs Intact MS	0.837 (CI=0.736-0.937)	< 26	76	73	78	70	75
	Impaired MS vs Control	0.833 (CI=0.751-0.914)	< 26	76	59	66	70	68
	Impaired MS vs Unimpaired	0.834 (CI=0.760-0.907)	< 26	76	77	56	89	76
EM-MoCA-Subscore	Impaired MS vs Intact MS	0.871 (CI=0.784-0.958)	<17	94	87	76	97	89
	Impaired MS vs Control	0.844 (CI=0.767-0.921)	<17	94	41	57	89	65
	Impaired MS vs Unimpaired	0.852 (CI=0.783-0.922)	<17	94	52	49	95	66

Note. MoCA: Montreal Cognitive Assessment (maximum score = 30); EM-MoCA-Subscore: composed by executive functions, visuospatial,

short-term memory and orientation domains (maximum score = 19); Unimpaired group comprise the Control group and the Intact MS group; AUC: area under the operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value.

Sensitivity, Specificity, PPV, NPV, and Classification Accuracy values were expressed in percentage.

Cut-off values indicate the minimum score required for absence of signal.