Research Article

The Montreal Cognitive Assessment (MoCA) in Multiple Sclerosis: Relation to Clinical Features

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Abstract

Background: The Montreal Cognitive Assessment (MoCA) is quickly becoming the most common clinical screen for cognitive impairment. Cognitive impairment is a frequent symptom of multiple sclerosis (MS) and can be difficult to detect in routine evaluation. Although specific screening measures have been studied and established for use in MS, MS cognitive screening tools may not be implemented in a general neurology setting.

Method: The present study sought to characterize the use of the Montreal Cognitive Assessment (MoCA) a brief measure employed in general neurologic practice for the detection of cognitive impairment in MS. The MoCA, along with other clinical measures, was administered to consecutively-recruited outpatients diagnosed with MS (N=259) to describe the findings and determine the frequency of detection of impairment. A subgroup (n=28) was also administered the oral version of the Symbol Digit Modalities Test (SDMT) as a measure of information processing speed.

Results: Participants' mean age was 45.8 ± 13.3 years and were diagnosed with relapsing-remitting MS (66%), secondary-progressive MS (18%), primary progressive MS (10%), clinically isolated syndrome (6%) or radiologically isolated syndrome (<1%). Median EDSS score was 2.5. A total of 41% of the sample scored in the impaired MoCA range (cutoff score of 26) with a mean of 25.86 ±2.92 points. EDSS was the clinical variable that most strongly predicted MoCA score. The combined SDMT and MoCA score led to the strongest prediction of EDSS score.

Conclusion: In an outpatient setting where MS-specific cognitive screening is not implemented, the MoCA can be a helpful to identify those MS patients who warrant full neuropsychological evaluation.

Keywords: Multiple sclerosis; Montreal assessment of cognition; Cognitive impairment; Clinical features

Introduction

The Montreal Cognitive Assessment (MoCA) is quickly becoming the most commonly-used screen for cognitive impairment for clinicians. It is an alternative to the mini-mental status exam (MMSE) that provides a broader and more sensitive screen of cognitive functioning [1,2]. Similar to the MMSE, the MoCA is a one-page test, which can be administered in five to ten minutes or less. It assesses more cognitive domains than the MMSE, including short-term memory, visuospatial abilities, executive functions, attention, concentration, working memory, language and orientation [3]. Its sensitivity in detecting MCI is 90%, while that of the MMSE is only 18% [4,2]. More recently, studies have sought to provide population-based norms more specific for age and educational attainment [5]. However, the universal cut-off score of 26 is generally used by clinicians and for most studies.

Multiple studies have found that the MoCA is more sensitive than the MMSE for patients with neurodegenerative disorders including Parkinson's disease, early (pre-motor stages) of Huntington's chorea and those with cerebrovascular disease. These patients usually score normally on the MMSE but fall below normal range on the MoCA [3,6-9].An extensive list of diseases for which the MoCA has been used as an assessment tool can be found on the MoCA website, www.mocatest.org [1].

Cognitive impairment occurs in approximately 43-65% of adults with multiple sclerosis (MS) [10,11]. However, it is often considered an "invisible" symptom of the disease that can go undetected without direct examination [12]. While those with more severe disease are at greatest risk [11,13-15], all patients are vulnerable. Cognitive deficits are found even among patients with "benign" disease [16] as well as those at a very early disease stage (i.e., clinically isolated syndrome or CIS and radiologically isolated syndrome or RIS) [17,18].

Unfortunately, screening for cognitive impairment may not be included in the routine clinical assessment of the MS patient. The most commonly-used cognitive screening instrument for the general neurologist, the Mini-Mental State Exam (MMSE), has a ceiling effect for those with milder deficits (e.g. patients with mild cognitive impairment or MCI often score in the normal range [2,8,4]) and therefore is not sensitive enough for use in MS. Instead, deficits in MS are often found only with more extensive neuropsychological testing [13,19].

The Symbol Digit Modalities Test (SDMT), a measure of information processing included in both of these MS-specific batteries, is considered to be the most sensitive single neuropsychological measure in MS and is increasingly included as an outcome in clinical trials [20-23].However, the SDMT assesses only information processing (via rapidly matching numbers to abstract symbols using a key), and therefore does not screen for other domains that may be affected (e.g., memory).

When combined with the learning score from the verbal list-learning task, the California Verbal Learning Test (CVLT) [24], visual learning task and the Brief Visuomotor Integration Test- Revised (BVMT-R) [25] represent the Brief International Cognitive Assessment in MS or BICAMS [26,19].The BICAMS was developed through an international effort of leading experts to establish a brief, reliable and sensitive screen to be used in MS. It is easily administered with normative data automatically calculated through the BICAMS website **www.bicams.net**.

While the BICAMS is the established approach for screening for cognitive impairment in MS, the general neurologist or practitioner may still continue to employ a more broadly applicable measure such as the MoCA. In addition to its generalizability, the MoCA is also briefer to administer and easier to score than the BICAMS with a single value cut point to determine impairment.

In a small study of 41 individuals with MS who underwent testing with the MoCA and more extensive neuropsychological battery, the cognitively intact group (n=27) (defined by their performance on the neuropsychological battery) had a significantly better mean MoCA score than that of the impaired group (n=14) [27].

Here, to further characterize the use of the MoCA for screening of MS-related cognitive impairment, we evaluated MoCA performances in a large and consecutively-recruited sample of adults with MS seen at our outpatient clinic. Participants underwent neurologic examination, routine collection of biometric data and were then administered the MoCA along with measures of fatigue and depression. A subgroup of patients were administered the oral version of the SDMT as an additional cognitive measure.

Methods

Participants

This study was approved by the Stony Brook Institutional Review Board.MS participants were consecutively-recruited outpatients presenting for neurological evaluation at the MS Comprehensive Care Center at Stony Brook Medicine. Individuals were recruited between December 2009 and July 2012 and also between December 2012 and July 2013. An additional sample was recruited between November 2012 and May 2013.Participants had to meet criteria for MS, CIS or RIS as diagnosed by a neurologist (LBK) [28] with no other primary neurological, psychiatric or medical disorder judged to influence cognition. All participants had to be age 18 years or older and fluent in English in order to complete the measures.

Procedures

Following their routine clinical visit, participants who agreed to complete the study and signed consent had demographic and clinical information recorded including age, gender, education, body mass index (BMI), MS subtype, disease onset and EDSS (administered by examining neurologist).

The MoCA [1,2] was administered by a trained research assistant. The MoCA consists of 30 items divided into the domains of attention (5 points, 3 items: identifying a target in a series, digits forward and backward and serial subtraction), language (5 points, 3 items: naming, sentence repetition and categorical verbal fluency), memory (5 points, 3-trial recall of 3 items with short-term delayed recall); visuospatial (4 points, 2 items: clock drawing, cube copy), executive (4 points, 3 items: alternating trails, categorical verbal fluency, verbal abstraction) and orientation (6 points, assessment of orientation to time and place).Score is a total of the points earned; an additional point was given for having 12 years or less of education. For individuals whose upper extremity function was too impaired to hold a pencil (n=5), the items alternating trails, cube copy and clock drawing were not administered and instead given full credit (representing a total of five points).

A subgroup of participants were also administered the oral version of the SDMT. The SDMT has a key at the top of the page with numbers and symbols; participants are required to refer to the key to correctly decode several lines of symbols. After completing sample items correctly, participants are timed for 90 seconds and the total number correct is their raw score. Following the Rao adaption from the Brief Repeatable Battery for MS [29], the oral condition (answers provided verbally) was used to limit the influence of motor slowing.To adjust for effects of age, raw scores were converted to z-scores based on published normative data [20]Cognitive impairment is defined by scores falling more than one standard deviation below the mean.

As an additional characterization of the sample, participants also completed self-reported measures of fatigue and mood: the Fatigue Severity Scale (FSS) [30] and the Center for Epidemiologic Studies Depression Scale (CES-D) [31] were administered. The FSS is a nine-item scale with each score rated from 1 to 7, to represent the degree to which fatigue interferes with daily life. The scores were averaged across items to range from 1 (minimum fatigue) to 7 (maximum fatigue) [30].The CES-D is a screening instrument with 20 items rated from 1 to 4 according to the degree of recent experience of depressed mood and other symptoms of depression, with scores ranging from 0 to 60 and a cutoff of 16 to indicate possible depression [31].

Sample Characteristics

Demographic and clinical features: A total of 259 patients participated in the study. As shown in Table 1, our sample was composed of 180 females (69.5%) and 79 males (30.5%).The average age was 45.8 ±13.34 years. The average educational attainment was 14.63 ± 2.41 years. A total of 168 (65.6%) were diagnosed with relapsing-remitting MS (RRMS), 25 (9.7 %) with primary progressive MS (PPMS), 47 (18.1%) with secondary progressive MS (SPMS), 15 (5.8%) with CIS and 1 (0.4%) with RIS. Three participants could not be classified due to insufficient data. For the full sample, the median Expanded Disability Status Scale or EDSS score was 2.5, with a range of 0 to 8.5.As would be expected, age was significantly associated with greater neurologic disability as measured by the EDSS (r=0.43, p<0.001).Also shown in Table 1, the sample as a whole was in the overweight range with a mean BMI of 27.8 ± 6.4.EDSS was not related to weight (r=-0.25, p=0.71) and the proportion of those who were normal weight, overweight or obese (using standard cutoffs [32]) did not significantly differ between the MS diagnostic subtypes χ^2 (6, N=192)=9.29, p=0.16 [33].

Age and Education M (SD)	
Age	45.8 (13.3)
Education Years	14.6 (2.4)
Gender – n (%)	
Women	180 (69.5)
Men	79 (30.5)
MS Subtype – n (%)	
RRMS	168 (64.9)
PPMS	25 (9.7)
SPMS	47 (18.1)
CIS	15 (5.8)
RIS	1 (0.4)
EDSS	
Median	2.5
Range	0 to 8.5
M (SD)	3.0 ±2.8
Biometrics	
Height (m): M (SD)	1.7 (0.1)
Weight (kg): M (SD)	77.3 (19.1)
BMI (kg/m2): M (SD)	27.8 (6.4)
Systolic BP: M (SD)	125.3 (14.5)
Diastolic BP: M (SD)	78.3 (8.8)
Pulse Rate: M (SD)	79.6 (12.6)

Table 1: Demographic and clinical features of the sample

Results

MoCA

The mean MoCA score for the sample was 25.86 ± 2.92 points, just below the impairment cutoff of 26.Of the total sample, 40% (n=103) scored in the impaired range: 33% (n=56) of those with RRMS, 55% (n= 26) of those with SPMS, 56% (n=14) of those with PPMS and 38% (n=16) of those with CIS or RIS (Figure 1).

Neither level of fatigue nor depressive symptoms strongly predicted lower MoCA scores (with FSS, r=-0.18; with CES-D, r=-0.14). Linear multiple regression was used to determine whether age, BMI, EDSS, fatigue (FSS) and mood (CES-D) predicted MoCA scores. The total variance of the model as a whole to explain variance in MoCA scores was only 7.7%, but significant $F_{(5, 223)}$=3.71, p=0.003.Of the demographic and clinical features, only EDSS was uniquely predictive of MoCA scores, beta=-0.20, p=0.009.As shown in Figure 3, those scoring in the impaired MoCA score range had slightly higher proportions of those with older age (greater than 40 years; 37% vs. 25%), depression (CES-D score greater than 15; 43% vs. 38%), fatigue

(FSS score of four or greater; 68% vs. 59%) and overweight or obese BMIs (70% vs. 62%).
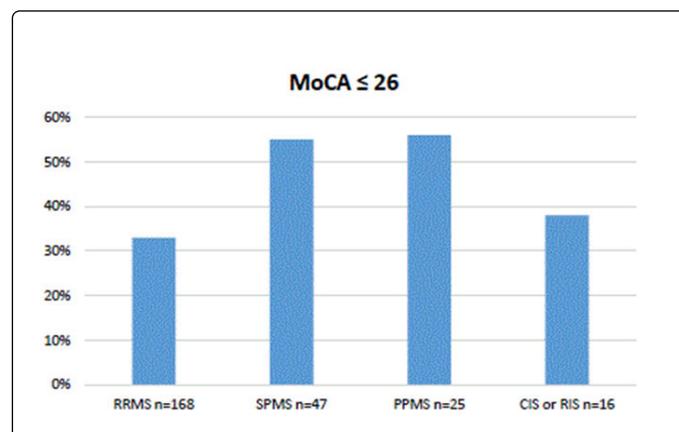

Figure 1: Frequency of MoCA impairment across MS subtypes. Lower MoCA scores were predicted by greater neurologic disability as measured by the EDSS, (r=-0.25, p<0.001).Age and years of education were not related to MoCA score (r=0.13, r=-0.92, respectively). As shown in Figure 2, proportion of MoCA impairment increased across EDSS tertile of severity
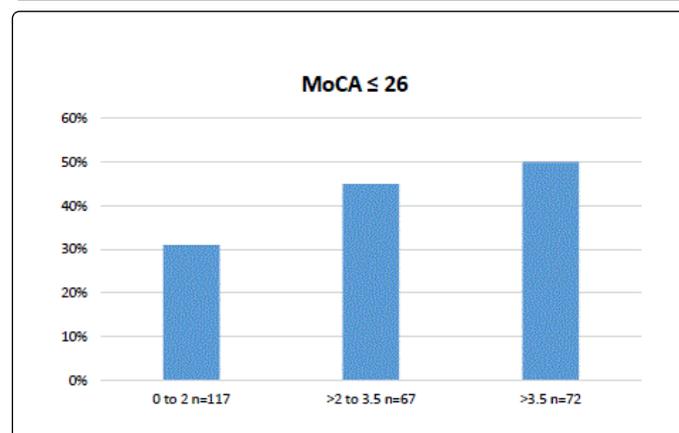

Figure 2: Frequency of MoCA impairment across EDSS score tertiles

Overall, the memory subtest was the most sensitive MoCA item, with 83% of the sample having at least one error. Following memory, the items most frequently not receiving full credit were sentence repetition (29%), serial subtraction (28%), cube copy (28%), clock drawing (26%), fluency (22%), abstraction (18%), trails (15%), digit span (11%), naming (11%), orientation (6%) and the sustained attention item (5%).Comparing those impaired and non-impaired (below or above the cut-off score), no one item or domain distinguishes the two groups. Instead, more than one-fourth of the impaired group had a performance error on memory, fluency, abstraction, serial subtraction, sentence repetition and cube drawing. Both the RRMS (n=168) and combined progressive group (n=72) had the same general pattern of error rates (i.e., both groups made the most errors on the memory test).However, the progressive group

made significantly more errors on both the orientation and serial subtraction items (p=0.004 and p=0.001, respectively).
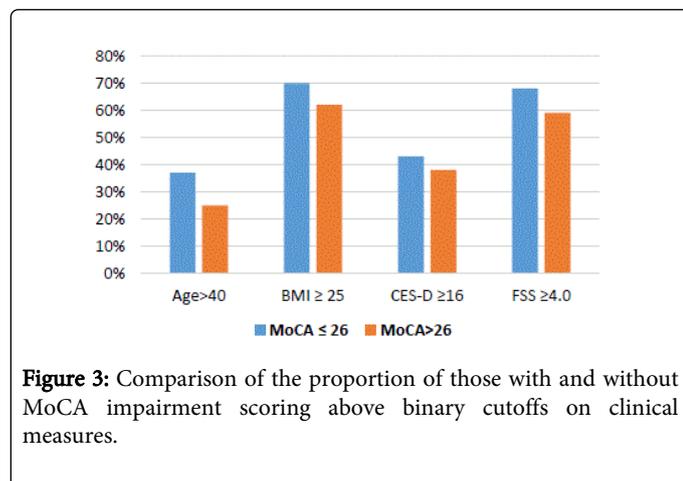

Figure 3: Comparison of the proportion of those with and without MoCA impairment scoring above binary cutoffs on clinical measures.

SDMT

A subgroup of participants enrolled in the study (n=28) were administered the SDMT as well as the MoCA. This subset included ten men and 19 women, ranging in age from 19 to 74 years with a mean of 40.53 ±12.93.Twenty-five of the 28 participants were diagnosed with RRMS, two with PPMS and one with RIS. This was the same rate of impairment found with the MoCA scores in this subgroup, also with 61% scoring in the impaired range. In this smaller subgroup, MoCA scores ranged from 21 to 30 with a mean of 24.57 ± 2.54, similar to the larger sample. However, the overall rate of impairment was higher than the larger group, with 61% versus 40% with MoCA scores below 26.The higher impairment rate for the SDMT may reflect the overall slowed processing speed in this group following disease progression, while the MoCA reflects cognitive functioning more broadly across domains of language, memory, visuospatial, executive and orientation, so it can be considered a measure that is wider in scope of cognitive functioning.

The subgroup participants' SDMT z scores ranged from -2.91 to 0.88, with a mean of-1.15 ± 0.94, also with the 61% falling into the impaired range (more than one standard deviation below the normative means). Despite the finding of the same rate of impairment in the sample with each measure, there was not consistent overlap with impairment on both measures, as 12 of the 28 participants met impairment on either the MoCA or SDMT alone. The MoCA total and SDMT z scores were not correlated (r=0.02, p=0.92), further suggesting that each measures a separate aspect of cognitive function.

Fatigue and Depression

Forty-percent of MS participants had elevations in depressive symptoms. This may reflect, in part, overlap of somatic disease-related symptoms with items measuring depression, but this is similar to the rate reported in other studies [34] and represents a high rate of potential clinical concern. Mean CES-D scores for the full sample fell just under the cutoff of 16 for significant levels of depressive symptoms (15.55 ±12.33) and 40% of the sample scored in the clinical range, indicating a high rate of at least mild depression. The sample as a whole reported moderate levels of fatigue, with a mean FSS score of

4.32 ± 1.73 and 62% with a clinical significant score of four or greater. Fatigue and mood were strongly correlated (r=0.50, p<0.001) and both correlated with EDSS (r=0.33, p<0.001 for FSS and r=0.15, p=0.24 for CES-D).When mood was controlled for, the relation between EDSS and FSS remained (r=0.30, p<0.001).

Factors Associated with Neurologic Disability

Binary logistic regression was performed to determine which demographic and clinical features were most predictive of either higher or lower neurologic disability, based on a binary EDSS cutoff of scores 3.0 or less vs. greater than 3.0. The model containing age, BMI, mood (CES-D), fatigue (FSS) and MoCA score distinguished those with high and low disability, χ^2(5, N=229)=71.68, p<0.001 and explained between 26.9 and 30% of the variance with correct classification of 72.1% of the participants. However, fatigue was the most predictive (beta=0.43, p<0.001) followed by MoCA score (beta=-0.18, p=0.003) and were the only two variables that held uniquely significant contributions to the model.

Discussion

The MoCA was administered to a large group of consecutively-recruited MS outpatients. Overall, 40% scored in the impaired range. Those with greater neurologic disability, older age, higher BMI, greater fatigue, more elevated depressive symptoms and progressive subtypes were more likely to have impaired scores. However, even among those with the lowest EDSS scores, there was still 31% impairment. This rate of impairment is at the lower end of the range of expected rates of impairment in an MS sample when using full neuropsychological testing batteries [10,14].

While there are psychometric limitations for the interpretation of sub-item analyses [35], the memory test (three-item learning across three trials with short delay recall) was by far the most sensitive to impairment. Otherwise, no one test or domain was consistently impaired for the group as a whole or for those with total scores in the impaired range. Those with progressive subtypes were more likely to make errors on orientation questions and serial subtraction than those with RRMS.

In the subset with SDMT scores, there was not strong overlap between impairment on the SDMT and MoCA impairment. Instead, the SDMT and the MoCA may have unique contributions as a screen for detecting cognitive impairment in MS. Because the SDMT measures processing speed, a domain not specifically measured by the MoCA, it would be expected that the addition of this test would strengthen the MoCA's predictive value. The SDMT can be administered in less than five minutes, so it adds very little time to MoCA administration.

Among the demographic and clinical variables, EDSS was a uniquely significant predictor of MoCA scores. Fatigue was the most predictive of higher EDSS scores, followed by MoCA score.

The availability of MoCA scores of a large group of patients with other neurological disorders provides an opportunity to compare MS to different conditions. The mean MoCA of 25.86 ± 2.92 in our sample was similar to a smaller sample of individuals with MS [27], 26.02± 2.30 and is in the same range as other neurologic disorders associated with mild cognitive impairment including REM Sleep Behavior Disorder[34] (n=38, 24.34 ± 3.50), or early Parkinson's disease [7] (n=100, 24.9 ±3.1), but is considerably higher than individuals with

brain metastasis [36](n=40, 20.53 ± - 5.15), cerebral small vessel disease [37] (n=40, 19.2 ± 4.2), Huntington's disease [9](n=53, 21 ±4.4) or Alzheimer's disease [3](n=321,13.0 4 ±6.05)[4,7-9,27,36-39].

This study has several limitations. First, data from a comprehensive neuropsychological battery or from a cognitive screen that has been established for use in MS such as the BICAMS were not available. Therefore, the accuracy of MoCA detection of cognitive impairment could not be confirmed in reference to a clinical standard. Second, unfortunately SDMT datawere not available for only a subset of participants. SDMTs administered to the full sample would have clarified the suggested utility of using both measures for screening. A third consideration is our choice to use the single cutoff score for impairment [31] rather than reference studies providing normative data for age and educational bands [5].The single cutoff score was intended for use for clinical bedside screening, similar to that with the MMSE and has been employed for the majority of studies in other disorders. Further, in our sample, age was only weakly related to MoCA scores and years of education were unrelated. A demographically matched and locally recruited healthy control group would provide the most accurate comparisons. Finally, the study would have been strengthened by additional clinical data including disease duration, use of disease modifying therapies and brain neuroimaging findings to better understand the relation between MoCA performance and MS disease status.

In sum, these findings characterize the MoCA in the largest consecutively-recruited sample size of MS patients to date and the first study to link MoCA to additional clinical measures. MoCA scores were in the impaired range for a large proportion of our sample and were associated with demographic and clinical features associated with greater disease severity. There is indication that the MoCA combined with the SDMT would provide the best brief screen for the clinician. Future studies are needed to directly compare the utility of the MoCA in comparison to the recommended MS-specific screens such as the BICAMS. Instead, for the general clinician, the MoCA is likely to be most useful in identifying those MS patients who may be at risk for cognitive impairment and warrant referral for full neuropsychological evaluation.

Acknowledgement

Ethical standards

This study was approved by the Stony Brook Institutional Review Board. All participants gave their informed consent prior to their inclusion in the study.

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