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Original Research Article

The Memory Alteration Test Discriminates between Cognitively Healthy Status, Mild Cognitive Impairment and Alzheimer's Disease

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Key Words

Dementia · Differential diagnosis · Memory alteration test

Abstract

Background/Aims: Dementia is a worldwide public health problem and there are several diagnostic tools for its assessment. The aim of this study was to evaluate the performance of the Memory Alteration Test (M@T) to discriminate between patients with early Alzheimer's disease (AD), patients with amnesic mild cognitive impairment (a-MCI), and subjects with a cognitively healthy status (CHS). **Methods:** The discriminative validity was assessed in a sample of 90 patients with AD, 45 patients with a-MCI, and 180 subjects with CHS. Clinical, functional, and cognitive studies were independently performed in a blinded fashion and the gold standard diagnosis was established by consensus on the basis of these results. The test performance was assessed by means of a receiver operating characteristic curve analysis as area under the curve (AUC). **Results:** M@T mean scores were 17.7 (SD = 5.7) in AD, 30.8 (SD = 2.3) in a-MCI, and 44.5 (SD = 3.1) in CHS. A cutoff score of 37 points had a sensitivity of 98.3% and a specificity of 97.8% to differentiate a-MCI from CHS (AUC = 0.999). A cutoff score of 27 points had a sensitivity of 100% and a specificity of 98.9% to differentiate mild AD from a-MCI and from CHS (AUC = 1.000). **Conclusions:** The M@T had a high performance in the discrimination between early AD, a-MCI and CHS.

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Introduction

Dementia is a worldwide public health problem. In Latin America, the prevalence of dementia in people older than 60 years is about 8.5% [1–7]. Alzheimer's disease (AD) is the main cause of dementia around the world.

Mild cognitive impairment (MCI) occurs in nearly 9% of community-dwelling elderly in Latin American countries [8, 9]. Amnesic MCI (a-MCI) is a clinical entity recognized as a risk factor for AD [10], with a conversion rate to dementia of 4–25% per year [10–12], and represents a transition stage between normal cognition and mild AD [13, 14]. Thus, a-MCI could be an AD precursor.

Currently, there are several diagnostic tools for assessing dementia [15–23], but the sensitivity for the early detection of dementia is very low [24]. Furthermore, the majority of tests are complex and need highly trained personnel and specialized equipment [25], which is not usually available at primary care level. Because of this, a-MCI and mild AD are often unrecognized in primary care centers [25]. Therefore, there is a need to develop a memory screening test oriented to the general practitioners that allows them to differentiate a-MCI and mild AD patients from normal cognitive controls, and that is easily applicable in daily practice in primary care centers.

The Memory Alteration Test (M@T), which is a brief and simple memory screening test, could be performed at primary care level. It has shown a good diagnostic performance in other studies. Thus, it arises as a promising alternative for the detection of early cognitive impairment by general practitioners [26].

The aim of this study was to assess the validity of the M@T for discriminating between subjects with a cognitively healthy status (CHS) and patients with a-MCI and mild AD.

Materials and Methods

Design of the Study

This study assesses the performance of the M@T as a diagnostic test. As a gold standard, consensus diagnosis by a neurologist and a neuropsychologist was used. Both the M@T and the gold standard were systematically and independently assessed in all consecutive eligible patients.

Population and Sample

All participants gave their informed consent. We included patients older than 60 years, with Spanish as their native language, with at least 6 years of education, who were consecutively enrolled during the period between April 2010 and December 2012. We excluded those subjects with structural and/or functional deficits (visual or auditory deficits), since they affect the performance of the cognitive tests, subjects with a history of diseases associated with secondary cognitive impairment [e.g. cerebrovascular diseases, hypothyroidism, infections of the central nervous system (HIV or syphilis), severe encephalic traumatism, and subdural hematoma], subjects with a history of conditions associated with secondary cognitive impairment (e.g. B₁₂ vitamin deficiency, chronic hepatopathy or nephropathy, and addiction or abuse of substances), as well as subjects with a score >4 on the Hachinski scale (which suggests an underlying cerebrovascular deficit).

This study included three groups: a-MCI, AD, and CHS. The a-MCI and AD groups were formed using the diagnostic criteria by Petersen et al. [27] and NINCDS-ADRDA [28], respectively. In the AD group, we only included patients with early and moderate dementia according to the Global Deterioration Scale (GDS-4 and GDS-5, respectively). The CHS group consisted

of patients without memory complaints, and none of these patients met the diagnostic criteria for a-MCI or AD based on a clinical interview and neuropsychological testing including memory, language, and executive functions.

MCI is defined by Petersen et al. [11] as impairment of at least one cognitive function, normal activities of daily living and absence of dementia. This diagnostic entity can be divided into nonamnestic MCI and a-MCI [10], which is characterized by memory complaints (usually confirmed by an informant), objective memory impairment adjusted for age and education, and preserved general cognitive function [27].

Participants for the a-MCI and AD groups were enrolled among the patients who visited the neurology consulting room in the 'Clínica Internacional'. Participants for the CHS group were enrolled among the patients who visited the internal medicine (in the 'Clínica Internacional' or 'hospital militar central') or the preventive medicine consulting room (in the 'Clínica Internacional').

Procedures

All patients were evaluated using the same tests: the Mini Mental State Examination (MMSE) [15], the Pfeffer Functional Activities Questionnaire [29], and a standardized neuropsychological assessment battery [30] including tests for delayed recall, immediate recall, intrusion errors, and recognition memory. The GDS was administered only to patients with a diagnosis of AD.

Memory Alteration Test

The M@T is a screening test with high discriminative properties for a-MCI and early AD among the general primary care population aged ≥ 60 years [26]. The maximum score on the M@T is 50. One point is given for each correct answer and there are a maximum and minimum of 50 and 40 questions, respectively, depending on the subject's success in free recall. All questions are oral and have only one possible answer. There are 5 subtests: encoding (5 points), orientation (10 points), semantic (15 points), free recall (10 points) and cued recall (10 points) [26].

Statistical Analysis

The discriminative validity of the M@T was assessed by calculating the sensitivity and specificity of the M@T for discriminating a-MCI and early AD from CHS subjects.

The χ^2 and Mann-Whitney tests for pairs of groups (a-MCI vs. CHS and AD vs. CHS) were used to compare demographic and neuropsychological scores between the groups. The influence of demographic variables on the association between diagnosis and M@T was studied by logistic regression analysis.

Receiver operating characteristic (ROC) curves were used in order to calculate the sensitivity and specificity of the M@T and MMSE. As both the M@T and MMSE are continuous variables, we sought to assess their diagnostic performance for different threshold values. For this, we estimated the area under the curve (AUC) for the ROC curves for the M@T (global and by subtests) and MMSE. The cutoff points for sensitivity and specificity were based on the highest diagnostic accuracy (proportion of correct diagnoses). All analyses were performed by using STATA 12.0 (Stata Corporation, College Station, Tex., USA).

Ethical Aspects

This study was authorized by the Investigation and Teaching Unit of the 'Clínica Internacional'. The present study was approved by the Ethics Committee of the 'Universidad Privada San Martín de Porres'.

Table 1. Demographic characteristics and test scores in 315 subjects attended at the neurology consulting room of the 'Clínica Internacional'

	Groups			p value (AD vs. MCI)	p value (MCI vs. CHS)
	AD (n = 90)	MCI (n = 45)	CHS (n = 180)		
Female, n (%)	58 (64.44)	30 (66.67)	113 (62.78)	0.798*	0.628*
Age, years	74.16±3.73	71.09±4.20	69.97±4.04	0.0000**	0.0995**
Education, years	6.56±2.87	6.49±2.73	6.99±3.15	0.8974**	0.3247**
MMSE score	19.43±2.66	26.80±1.08	28.47±1.23	0.0000**	0.0000**
M@T global score	17.61±5.71	30.84±2.29	44.51±3.07	0.0000**	0.0000**

Data are presented as mean ± standard deviation unless indicated otherwise. * p value for the χ^2 test. ** p value for the Student test.

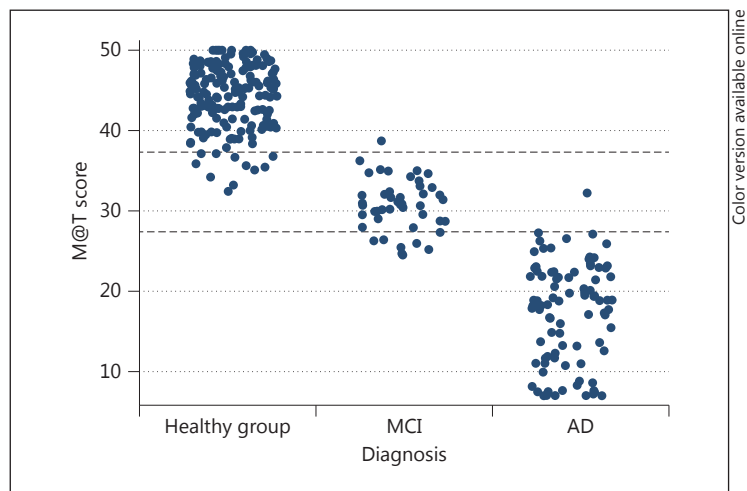


Fig. 1. M@T scores according to the diagnosis in 315 subjects attended at the neurology consulting room of the 'Clínica Internacional'.

Results

Three hundred and fifteen patients were obtained from the Unit of Cognitive Impairment and Dementia Prevention of the 'Clínica Internacional' in Lima. Forty-five and ninety of them met the criteria for a-MCI and early AD, respectively.

Our data did not show significant differences among the groups when adjusted for sex, age, and education (table 1). This is critical because age and education are considered to have an influence on cognitive performance, being evaluated by the cognitive tests applied in this study. Thus, we expect that our results are not confounded by these two factors.

According to both cognitive tests applied (MMSE and M@T), the cognitive performance of patients with early AD is significantly worse than that of patients with a-MCI (table 1). The scatter plot shows that the M@T had a good overall discriminability between early AD, a-MCI and CHS (fig. 1).

Discriminative Validity of the M@T

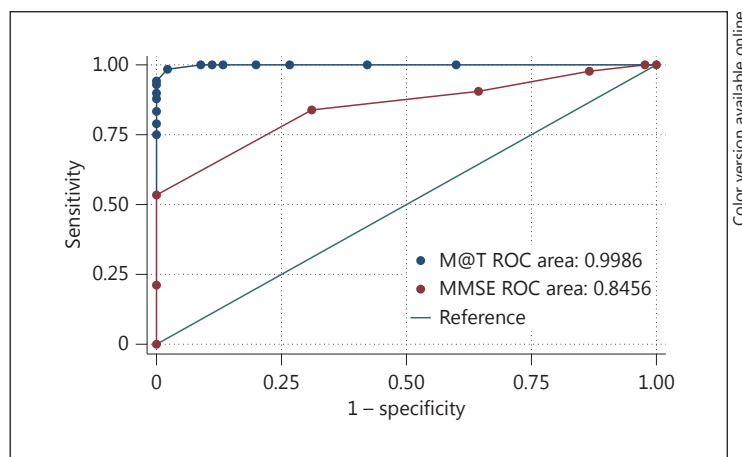
The performance assessments of the cognitive tests are summarized in table 2. Using the M@T, a score of 27 provided the optimal cutoff score for discriminating between early AD

Table 2. Cutoff points and diagnostic utility of the M@T and MMSE to discriminate between AD, MCI and CHS groups, in 315 subjects attended at the neurology consulting room of the 'Clínica Internacional'

	Distinction between patients with MCI and healthy subjects		Distinction between patients with AD and healthy subjects		Discrimination between patients with AD and patients with MCI	
	M@T	MMSE	M@T	MMSE	M@T	MMSE
Optimal cutoff point ^a	≥37	≥28	≥27	≥24	≥27	≥24
Sensitivity, %	98.33	83.89	100.00	100.00	100.00	100.00
Specificity, %	97.78	68.89	98.89	96.67	98.89	96.67
Correctly classified, %	98.22	80.89	99.63	98.89	99.26	97.78
AUC	0.9986 ^b	0.8456	1.0000	1.0000	1.0000	0.9996

^a Cutoff point simultaneously based both on the sensitivity and specificity to obtain a maximum percentage of correctly classified. ^b Significant difference with regard to the MMSE, $p < 0.05$. Our gold standard was the final diagnosis achieved by means of the application of the diagnostic protocol for cognitive impairment.

Fig. 2. ROC curve for the discrimination between MCI and CHS subjects by means of the application of the M@T in comparison to the MMSE in 225 subjects attended at the neurology consulting room of the 'Clínica Internacional'.



and a-MCI (sensitivity 100%; specificity 98.9%), whereas a score of 37 provided the optimal cutoff score for discriminating between a-MCI and CHS (sensitivity 98.3%; specificity 97.8%).

There were no statistical differences between the MMSE and M@T for the discrimination between early AD and a-MCI. However, the M@T was significantly better than the MMSE ($AUC_{M@T} = 0.9986$ vs. $AUC_{MMSE} = 0.8456$, $p < 0.05$) for the discrimination between a-MCI and CHS (fig. 2).

Item Analysis of the M@T

The results for the M@T subtests in the early AD, a-MCI and CHS groups are summarized in table 3. The only subtest with acceptable precision to discriminate between early AD and a-MCI was the orientation subtest ($AUC = 0.8043$). All other items showed an AUC below 0.80, and the cued recall subtest did not show discriminatory capacity ($AUC = 0.5$).

Otherwise, the free recall subtest was the most accurate subtest for discriminating between a-MCI and CHS ($AUC = 0.9947$). The encoding, orientation, and semantic subtests showed a high discriminability between a-MCI and CHS ($AUC > 0.80$). Finally, the cued recall subtest did not show discriminatory capacity ($AUC = 0.5$).

Table 3. Neuropsychological results of the M@T subtests in 315 subjects attended at the neurology consulting room of the 'Clínica Internacional'

	Groups			AUC (AD vs. MCI)	AUC (MCI vs. CHS)
	AD (n = 90)	MCI (n = 45)	CHS (n = 180)		
M@T _{encoding}	5.76 ± 1.98	6.71 ± 0.79	8.57 ± 0.78	0.6311	0.9379
M@T _{orientation}	2.52 ± 1.21	3.84 ± 0.74	4.72 ± 0.45	0.8043	0.8105
M@T _{semantic}	6.58 ± 2.30	12.42 ± 0.69	13.59 ± 1.04	0.5000	0.8282
M@T _{free recall}	0.99 ± 0.74	2.13 ± 1.58	8.39 ± 1.17	0.7267	0.9947
M@T _{cued recall}	1.77 ± 0.96	5.73 ± 0.78	9.23 ± 0.80	0.5000	0.5000

Data are presented as mean ± standard deviation.

Discussion

This study showed a high precision of the M@T to discriminate between early AD, a-MCI and CHS. We found high performance values (AUC ≥ 0.99), sensitivity (≥ 98%), and specificity (≥ 97%) when the M@T was applied in our sample. These findings are consistent with those previously reported by other studies [26, 31, 32].

The cutoff score of the M@T varies according to the diagnosis suspected. When the M@T was applied using a cutoff score of 37 points, we found a sensitivity of 98.3% and a specificity of 97.8% for the diagnosis of a-MCI (AUC = 0.999). This performance is higher than observed in previous studies [26, 31, 32].

Furthermore, we found a sensitivity of 100% and a specificity of 98.9% to differentiate between early AD and CHS and to differentiate between a-MCI and early AD when the M@T was applied using a cutoff score of 27 points, which is less than previously reported by Rami et al. [26, 31] (cutoff score = 28). We used this cutoff score because it provided the best correctly classified percentage in our sample of patients.

Considering the M@T assessment (global and by subtests) for discriminating between early AD and a-MCI, the M@T AUC_{global} is higher than the M@T AUC_{subtests}. This suggests that the combination of subtests to discriminate between these conditions is more accurate than using the subtests alone. On the other hand, the M@T AUC_{global} is practically equal to the M@T AUC_{recall} for discriminating between a-MCI and CHS, suggesting that this subtest is as accurate as using the full test.

Furthermore, the AUC values for the cued recall subtest (AUC = 0.5) showed that, in our sample, this subtest was irrelevant for the discrimination between early AD and a-MCI and between a-MCI and CHS. This suggests that this subtest may be removed for the not illiterate populations, thereby reducing the application time of the M@T. This possibility should be further assessed by considering the results of the study by Carnero-Pardo et al. [32], which showed that the M@T requires a longer application time compared to other short cognitive tests (Eurotest and Phototest), being more expensive and less efficient.

The MMSE is used worldwide as a screening test for dementia, particularly at primary care centers, but its sensitivity and specificity is low for a-MCI and mild AD [24, 33]. This is related to the fact that memory impairment is often the earliest feature of AD, and global cognitive scales present low sensitivity and specificity for detecting a-MCI and very mild AD. Indeed, in our sample, the MMSE showed a low performance for discriminating between early AD, a-MCI and CHS.

The present study has the following limitations. We only took into consideration the analysis of the M@T by subtests. However, a closer analysis (by items) could evaluate whether a combination of less items is as or more accurate than the application of all items. Otherwise, the M@T was designed to screen a-MCI and typical AD, and it evaluates temporal orientation and different types of memory (episodic, textual, and semantic). Therefore, its utility in atypical AD presentations or other dementias (in which language or frontal functions may be the earliest manifestation) is uncertain.

In conclusion, the M@T is a reliable, brief, and simple test with high precision for discriminating between early AD, a-MCI and CHS. Thus, it is a valuable tool for easy and early cognitive impairment detection at the primary care setting.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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