ORIGINAL ARTICLE

Mild cognitive impairment: cognitive screening or neuropsychological assessment?

Comprometimento cognitivo leve: rastreio cognitivo ou avaliação neuropsicológica?

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Abstract

***Objective**: To describe the neuropsychological profile of mild cognitive impairment subtypes (amnestic, non-amnestic and multiple-domain) of a clinical sample. We further address the diagnostic properties of the Mini-Mental State Examination and the Cambridge Cognitive Examination for the identification of the different mild cognitive impairment subtypes in clinical practice. **Method:** Cross-sectional clinical and neuropsychological evaluation of 249 elderly patients attending a memory clinic at a university hospital in Sao Paulo, Brazil. **Results:** The performance of patients with mild cognitive impairment was heterogeneous across the different subtests of the neuropsychological battery, with a trend towards an overall worse performance for amnestic (particularly multiple domain) mild cognitive impairment as compared to non-amnestic subtypes. Screening tests for dementia (Mini-Mental State Examination and Cambridge Cognitive Examination) adequately discriminated cases of mild Alzheimer's disease from controls, but they were not accurate to discriminate patients with mild cognitive impairment (all subtypes) from control subjects. **Conclusions:** The discrimination of mild cognitive impairment subtypes was possible only with the aid of a comprehensive neuropsychological assessment. It is necessary to develop new strategies for mild cognitive impairment screening in clinical practice.*

***Descriptors**: Cognition disorder; Alzheimer disease; Neuropsychological tests; Diagnosis; Dementia*

Resumo

***Objetivo:** Descrever o perfil neuropsicológico dos subtipos de comprometimento cognitivo leve, amnéstico, não-amnéstico e múltiplos domínios, de uma amostra clínica. Além disto, avaliou-se as propriedades diagnósticas do Mini-exame do Estado Mental e do* Cambridge Cognitive Examination *na identificação dos diferentes subtipos de comprometimento cognitivo leve na prática clínica. **Método:** Avaliação clínica e neuropsicológica transversal de 249 idosos em uma clínica de memória de um hospital universitário em São Paulo, Brasil. **Resultados:** Testes de rastreio para demência (Mini-exame do Estado Mental e* Cambridge Cognitive Examination*) identificam corretamente casos de doença de Alzheimer leve, mas não apresentam boa acurácia para diferenciar os diversos subtipos de comprometimento cognitivo leve. A performance dos sujeitos portadores de comprometimento cognitivo leve foi heterogênea nos diferentes testes da bateria neuropsicológica, com uma tendência a uma pior performance global nos pacientes com o subtipo amnéstico (especialmente os com envolvimento de múltiplos domínios cognitivos) em relação ao comprometimento cognitivo leve não-amnéstico. **Conclusões:** A discriminação dos diferentes subtipos de comprometimento cognitivo leve foi possível somente a partir de uma avaliação neuropsicológica detalhada. Desta maneira, é necessário o desenvolvimento de novas estratégias de rastreio para esta condição na prática clínica.*

***Descritores:** Transtornos cognitivos; Doença de Alzheimer; Testes neuropsicológicos; Diagnóstico; Demência*

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Introduction

On clinical grounds, a current attempt to identify individuals at risk of developing Alzheimer's disease (AD), or at least to characterize the cognitive manifestations of the disease at pre-clinical stages, relies on the diagnosis of mild cognitive impairment (MCI).[1] The diagnostic criteria for MCI subsume the presence of subjective memory complaints, preferably corroborated by a close informant, and documented by an abnormal performance on cognitive tests, adjusted for age and education. These deficits must have no, or minimal, impact on global intellectual functioning and on the ability to perform activities of daily living, and the patient should not have evidence of dementia.[2] A recent meta-analysis showed that patients with MCI evolve to dementia at rates of approximately 10% per year.[3] Boyle et al. showed that patients with MCI had a 6.7 higher risk to progress to dementia.[4] Such estimates are supported by other studies on early predictors of dementia.[5,6] Nevertheless, these estimates show a great variability, from 5 to 40% per year,[3] according to the setting where the studies were carried out (clinical versus population-based studies).

Although the original diagnostic criteria for MCI emphasized the importance of memory impairment, more recently the MCI classification was expanded to encompass other cognitive domains, such as executive functioning and language, allowing the diagnosis of single and multiple-domain amnestic or non-amnestic MCI. In view of different neuropsychological profile, these subtypes were hypothesized to be associated with distinct outcomes.[7] Whereas single-domain amnestic MCI may be a pre-dementia stage of AD, multiple-domain MCI may be a precursor of both AD or vascular dementia, and single domain non-amnestic MCI may be found in the prodromal phases of frontotemporal dementia, vascular dementia, dementia with Lewy bodies, or even depressive disorders.[8]

There are many unclear points with respect to the prognostic relevance of the MCI concept. Despite the evidence that poses MCI patients at a higher risk for converting to dementia, it is noteworthy that the current diagnostic criteria still yield a too heterogeneous group. Many of the patients fulfilling MCI criteria will remain stable or even resume normal cognitive functioning on follow-up.[9,10] In such cases, there is no additional risk for dementia given the diagnosis of MCI.[11] In addition, recent long-term, longitudinal studies failed to demonstrate that the classification according to MCI subtypes at baseline predicted distinct dementia outcomes.[12,13] There are many potential reasons to explain such discrepant results in the literature, such as the unclear definition and quantification of cognitive "impairment" and of "minor" deficits in activities of daily living, the lack of standardized assessment tools across the various analyses, and different diagnostic conceptualization of the MCI diagnostic criteria.[14,15] The development of biomarker technology, including CSF Aβ42 and Tau levels,[16] and *in vivo* amyloid-β imaging with *Positron Emission Tomography* (PET),[17] is likely to shed some light to this diagnostic impasse.

Despite its clinical relevance, the diagnosis of MCI and its subtypes relies on comprehensive neuropsychological assessment. Thus, the identification of these subjects may be difficult in clinical practice, since this diagnostic procedure is not thoroughly available. In addition, few studies have addressed routinely used cognitive screening tests for dementia in the identification of MCI subjects. Ravaglia et al. showed that the combination of the Mini-Mental State Examination (MMSE) and the Clock Drawing Test (CDT) in the assessment of patients with suspected multiple-domain MCI increased the diagnostic sensitivity from the 40-50% range (either test alone, respectively) to 75%; however, in other MCI subtypes, the sensitivity of this intervention was much lower.[18] Similarly, Tang-Way et al. found that the bedside screening test "Short Test of Mental Status" (STMS), which covers a broader range of cognitive abilities than the MMSE, is more accurate in the identification of MCI.[19] However, the sensitivity and specificity of the tests used in the aforementioned studies were lower than 80%, which renders both tests unsuitable for screening purposes. On the other hand, Diniz et al. showed that the qualitative analysis of the performance of subjects in the subitems of the MMSE may help distinguish the MCI subtypes in clinical practice.[20]

The aim of the present study is to characterize the performance of MCI subtypes patients in a comprehensive battery as compared to the performance of healthy subjects and patients with AD. We further evaluate the diagnostic properties of cognitive screening tests routinely used in clinical practice (the MMSE and the Cambridge Cognitive Examination - CAMCOG) to discriminate the MCI subtypes from Alzheimer's disease patients and controls subjects.

Method

1. Patients

Two hundred and forty-nine patients (75% female) were assessed at the Memory Clinic of the Institute of Psychiatry, University of Sao Paulo, Brazil, between December 2001 and May 2007 (mean age: 71.2 ± 7.9 years; mean educational level: 10.5 ± 5.9 years). In addition to the spontaneous demand for memory assessment, patients were also referred from other clinics due to suspected cognitive decline. In order to include cognitively unimpaired controls, relatives or acquaintances of patients, as well as volunteers from other sources, were invited to participate in the study. All subjects of this study signed their informed consent prior to enrolment. This study was approved by local Ethical Committee (process number 1053/02) and was performed in accordance with the Helsinki Declaration.

2. Clinical and neuropsychological assessment

Patients and controls were examined by an expert multidisciplinary team, including geriatric psychiatrists, neurologists, geriatricians and neuropsychologists. Mental state examination was performed with the Brazilian version of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) semi-structured interview,[21,22] which yields scores for the CAMCOG, the Abbreviated Mental Test (AMT),[23] the MMSE,[24] and the Hachinski Ischemic Score, which assesses vascular pathology of the brain.[25] The Clock Drawing Test, which is part of the CAMCOG schedule, was additionally scored accordingly to Sunderland's guidelines.[26] The 21-item Hamilton Depression Scale (HAM-D)[27] was administered to rule out depressive symptomatology.

Trained neuropsychologists administered neuropsychological examinations to all study participants. The neuropsychological battery included tests for *episodic memory*: the Rivermead Behavioural Memory Test (RBMT),[28,29] and the Fuld Object-Memory Evaluation (FOME), memory subscale of the Short Cognitive Test (SKT);[30-32] *language*: verbal fluency (category: fruit); *attention and psychomotor speedy*: Trail Making Test A (TMT A), and attention subscale of the SKT; *executive function*: Trail Making Test B (TMT B);[33] *pre-morbid IQ*: Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary and Block Design tests.[34] Evidence of functional decline was based on the scores of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),[35] and on all available evidence of difficulties in the performance of basic and instrumental activities of daily living, as reported by a close relative or caregiver, and on the patient's self-

report. The neuropsychological evaluation was the "gold standard" for the distinction of the present cognitive status, i.e. dementia vs. MCI vs. cognitively unimpaired subjects.

Laboratory tests were carried out for every patient to rule out potentially reversible causes of cognitive impairment, including: thyroid function, complete blood count, blood chemistry, folic acid and vitamin B12, blood lipid profile, and syphilis tests. Neuroimaging studies (CT scans or MRI) were completed according to clinical judgment.

3. Diagnosis

Consensus diagnosis was reached at expert multidisciplinary meetings, taking into account clinical, neuropsychological, laboratorial, and neuroimaging data. Alzheimer's disease was diagnosed according to the NINCDS-ADRDA criteria.[36] The MCI diagnosis was made according to the following criteria: 1) subjective cognitive complain, preferably corroborated by an informant; 2) objective impairment in the performance on the cognitive tests of the assessment battery, but not severe enough to reach dementia diagnosis; 3) preserved global intellectual function; 4) preserved or minimal impairments in activities of daily living 5) not demented. MCI patients were further allocated into three different subcategories, according to the pattern of impairment on neuropsychological evaluation: a) amnestic (aMCI), if the evidence of impairment resulted from abnormal performance in memory tests only (e.g.: RBMT and/or FOME); b) non-amnestic (naMCI) in the presence of impairment in any single cognitive domain but memory; and c) multiple domain (mdMCI), if there was objective impairment in two or more cognitive domains including memory. Subjects without evidence of cognitive impairment were included in the control group.

4. Statistical analysis

We performed Pearson's Chi-square analysis to assess for differences in the distribution of gender among different diagnostic groups. Kolmogorov-Smirnov tests were done to assess for the normality of the distribution for each continuous variable. As these analyses showed that all variables had normal or near-normal distribution, we decided to carry out parametric statistical tests for all analyses. We carried out univariate analysis of variance (ANOVA) to assess mean differences for sociodemographic data, clinical variables, and scores on cognitive and neuropsychological tests among the diagnostic groups. If differences on sociodemographic or clinical variables known to influence cognitive performance were statistically significant among diagnostic groups in univariate analysis, we carried out multivariate analyses to control for the influence of these potential confounding variables on the scores of cognitive and neuropsychological tests. In addition, we carried out Bonferroni analyses for multiple comparisons to address mean differences in the scores of cognitive and neuropsychological tests between each diagnostic group. Receive Operator Characteristics (ROC) analyses were done to compare the diagnostic performance of the MMSE and the CAMCOG to identify MCI subtype cases in comparison to the gold standard neuropsychological evaluation. As the mean age of all diagnostic groups was higher than 8 years of schooling, we decided not to stratify the patients into different educational stratum to increase statistical power. All statistical analyses were performed using SPSS v14.0 for Windows (SPSS Inc., Chicago, IL) and α was set at 5%.

Results

Table 1 illustrates sociodemographic characteristics of patients according to diagnostic groups. Seventy-three patients had mild to moderate AD (29%), 51 had multiple domains MCI (21%), 25 had amnestic MCI (10%), 11 had non-amnestic MCI (5%). Eighty-nine subjects were regarded cognitively unimpaired (controls, 35%). There was no difference in the distribution of diagnosis between genders. Univariate analysis of variance did not show statistical difference in the scores of HAM-D 21 (F 1.42, d.f. (4,244), $p = 0.227$). On the other hand, patients with AD were older, less educated, and had higher scores on the HIS than MCI and controls (Table 1 and 2).

Multivariate analyses with diagnosis as the independent variable, and age, educational level, and the scores on the HIS as covariates to control for their confounding effect on the scores of clinical and neuropsychological tests showed that AD patients had worse performance in all cognitive tests as compared to MCI and controls. MCI patients (all subtypes) and normal controls had a similar overall performance on screening tests for dementia, such as the MMSE and the CDT. Patients with either amnestic- or non-amnestic MCI, but not with multiple-domain MCI, achieved similar mean scores on the CAMCOG test as compared to controls (Table 2).

In comparison to controls, patients with single-domain non-amnestic MCI had mostly evidence of executive dysfunction, as depicted by the worse scores on the Trail B test. Multiple-domain MCI patients had, in addition to the memory impairment, significant deficits in praxis and executive functions. Interestingly, these patients had a performance somewhat similar to that of AD patients, at least in some of the cognitive tests in this battery (e.g., the Trail B and WAIS-R block design test), but had, by definition, no evidence of significant functional impairment (Table 2). Figure 1 shows the ROC analysis showing the best cutoff point, with its respective sensitivity and specificity, and Area under the Curve (*AUC*), for the MMSE and the CAMCOG according to each diagnostic category versus controls. Our results showed that the MMSE had poor diagnostic performance to discriminate between all MCI subtypes from controls. On the other hand, the CAMCOG showed a slightly better discriminative power to identify the MCI subtypes from controls, especially the multiple-domain MCI (sensitivity, 85%; specificity, 75%). Both the MMSE and the CAMCOG had good diagnostic performance to discriminate between Alzheimer's disease patients and control subjects.

Discussion

The most common MCI subtype in this cohort was multiple-domain amnestic MCI, corresponding to approximately two thirds of the MCI patients. Single-domain amnestic MCI occurred in

Table 1 – Sociodemographic variables according to diagnosis

	Controls	Amnestic MCI	Non-amnestic MCI	Multiple-domain MCI	AD	p
N (M/W)	89 (21/68)	25 (10/15)	11 (1/10)	51 (10/41)	73 (22/51)	0.184
Age (years)*	67.8 ± 6.1	72.3 ± 6.6	67.8 ± 4.8	70.2 ± 6.5	75.80 ± 7.9	< 0.001
Educational attainment (years) *	13.4 ± 5.8	10.8 ± 5.2	9.63 ± 6.6	8.5 ± 4.4	8.1 ± 5.4	< 0.001

** mean ± standard deviation. M: Men; W: Women; MCI: Mild Cognitive Impairment; AD: Alzheimer's disease*

Table 2 - Scores on the cognitive screening tests, neuropsychological tests, the HAM-D 21, and the HIS from the clinical and neuropsychological battery according to diagnosis

	Control	Amnestic MCI	Non-amnestic MCI	Multiple-domain MCI	AD	F	P
Cognitive screening tests							
MMSE*	28.2 ± 1.8	26.40 ± 3.0	27.7 ± 1.8	26.5 ± 2.4	19.9 ± 4.7	48.4	<0 .001
CAMCOG[&]	96.4 ± 5.5	90.1 ± 8.4	91.3 ± 5.3	86.6 ± 8.4	65.9 ± 15.3	60.2	< 0.001
IQCODE*	3.15 ± 0.15	3.32 ± 0,37	3.25 ± 0.16	3.34 ± 0.37	3.81 ± 0.51	34.9	< 0.001
CDT*	8.9 ± 1.8	8.6 ± 1.4	6.6 ± 2.5	7.5 ± 1.9	5.3 ± 2.7	18.0	< 0.001
AMT*	9.5 ± 0.8	9.0 ± 1.0	9.3 ± 1.1	9.0 ± 0.9	6.6 ± 2.1	29.1	< 0.001
HIS[#]	0.9 ± 1.6	0.9 ± 1.4	1.0 ± .8	1.3 ± 1.3	2.1 ± 1.88	6.6	< 0.001
HAM-D 21[#]	1.3 ± 2.4	2.2 ± 2.7	0.8 ± 1.4	1.5 ± 2.1	1.9 ± 2.4	1.4	0.227
Neuropsychological tests							
RBMT screening score†	10.3 ± 1.7	7.1 ± 1.5‡	9.7 ± 2.0	7.2 ± 2.0†	2.5 ± 2.2	100.3	< 0.001
- Profile score†	21.7 ± 2.5	17.4 ± 2.3‡	21.0 ± 2.2	16.7 ± 3.6	6.7 ± 4.6	125.7	< 0.001
FOME total recall*	44.0 ± 3.1	41.1 ± 5.7	42.5 ± 2.7	38.3 ± 6.4	20.9 ± 9.6	92.6	< 0.001
- Delayed recall*	9.3 ± 0.8	8.7 ± 1.2	8.2 ± 1.1	8.4 ± 1.5	3.4 ± 2.5	105.9	< 0.001
Verbal fluency*	14.6 ± 3.1	12.6 ± 3,5	13.9 ± 3.0	11.4 ± 2.5	9.9 ± 2.6	16.2	< 0.001
Trail A (seconds)‡	47.8 ± 17.3	61.6 ± 25.6	78.7 ± 24.4	92.4 ± 47.3	118.7 ± 51.2	19.6	< 0.001
Trail B (seconds) ‡	114.6 ± 50.3	135.7 ± 54.7	227.5 ± 83.1	223.2 ± 64.3	274.6 ± 56.4	53.3	< 0.001
SKT total scaled score&	2.3 ± 2.7	3.3 ± 2.8	3.1 ± 2.5	5.4 ± 3.4	11.4 ± 3.9	55.7	< 0.001
WAIS-R vocabulary††	56.0 ± 9.3	45.1 ± 10.9	49.3 ± 12.0	41.5 ± 11.4	39.3 ± 10.2	14.6	< 0.001
- Block design‡	22.6 ± 7.8	21.6 ± 6.5	18.5 ± 6.0	15.4 ± 6.9	10.6 ± 6.6	15.7	< 0.001

Scores displayed as unadjusted mean ± standard deviation.
Bonferroni analysis for multiple comparisons:
** controls = MCI subtypes > AD; & controls = aMCI, naMCI > mdMCI > AD; † controls = naMCI >aMCI > mdMCI> AD; ‡ controls = aMCI, naMCI > mdMCI = AD; ††controls > aMCI > naMCI, mdMCI = AD.*
MMSE: Mini-Mental State Examination; CAMCOG: Cambridge Cognitive Examination; AMT: Abbreviated Mental Test; CDT: Clock Drawing Test; IQCODE: Informant Questionnaire of Cognitive Decline in the Elderly; HIS: Hachinski Ischemic Score; HAM-D 21: Hamilton Depression Scale 21 items. RBMT: Rivermead Behavioural Memory Test; FOME: Fuld Object-Memory Evaluation; SKT: Short Cognitive Test; WAIS-R: Wechsler Adult Intelligence Scale-Revised; aMCI: Amnestic Mild Cognitive Impairment; naMCI: Non-Amnestic Mild Cognitive Impairment; mdMCI: Multiple-Domain Mild Cognitive Impairment; AD: Alzheimer's Disease.

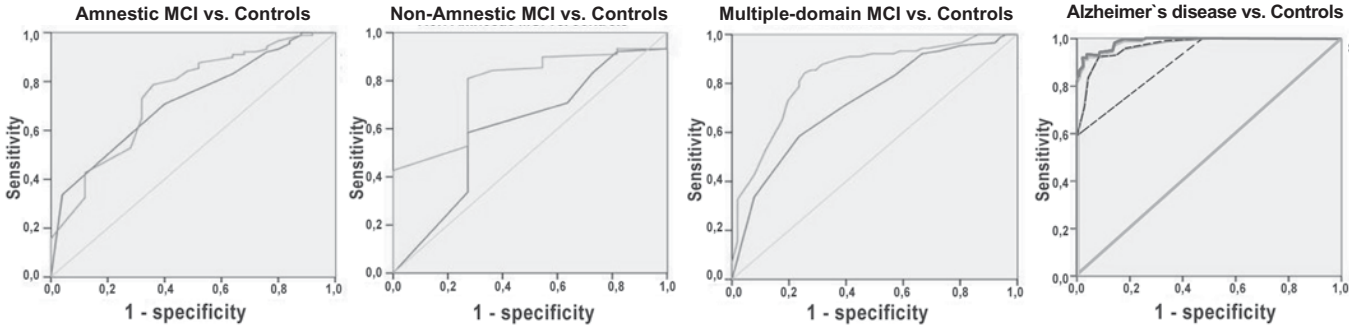
approximately 25% of the subjects, and non-amnestic MCI was the least frequent diagnosis. These results are in accordance with recent population and clinical studies.[37]

We showed that commonly used test for clinical assessment of dementia, i.e. the MMSE and the CAMCOG, had moderate accuracy for the identification of MCI subtypes in comparison to controls, as shown by the ROC analysis. These results were somewhat expected since these instruments were designed for the diagnosis of full-blown dementia syndromes, and, thus, show a ceiling effect when assessing subjects with less severe cognitive impairment, such as MCI.[37] However, the CAMCOG displayed a better diagnostic performance profile in the identification of multiple-domain MCI patients than for the other subtypes. These results are in line with those reported by Ravaglia et al.[18] As currently used cognitive screening tools do not have a high accuracy in the identification of most MCI patients, the development of cognitive screening tests primarily designed for the discrimination of such cases, e.g.: the Montreal Cognitive Assessment (MoCA), might help to overcome this issue.[38] Hence, in the current practice, the identification of MCI (and its subtypes) still relies upon a comprehensive neuropsychological evaluation. The cutoff values reported herein should be viewed with caution, since these patients were assessed in a tertiary clinical memory and their educational background may not reflect the educational background of most Brazilian older individuals. Therefore, these results should be replicated in other clinical settings and populations.

In the current sample, the amnestic MCI subjects had a global cognitive performance (as measured by the CAMCOG) worse than non-amnestic MCI did. This may be due in part to the fact that such memory impairment may result from milder disturbances on other cognitive domains. In addition, single domain (either amnestic or non-amnestic) MCI subjects had a better global cognitive performance than multiple-domain MCI subjects did. In the latter group, the performance on memory and executive function tasks was worse than of the single domain counterparts.

The abnormal performance of multiple-domain MCI patients in certain tests, such as the WAIS-R block design and Trail B, was comparable to that of mild AD patients. This result may suggest that, as the cognitive deficits spread to more than one cognitive domain, particularly affecting executive functions, there is a progressive deterioration of global cognitive performance towards the clinical threshold of dementia, thus indicating that at least a subset of MCI patients may progress from aMCI to mdMCI prior to the conversion to AD. Additionally, aMCI patients (either single or multiple-domain) had a worse performance on the RBMT, along with a relatively preserved performance on the FOME. This result may be due to the different ability of these two tests to identify memory deficits in MCI patients, because the RBMT assesses different memory subsystems, such as prospective memory, episodic memory, visual and verbal memory, whereas, the FOME assesses only visual episodic memory, or perhaps, the two tests are differently affected by the education bias.

Taken together, the current results on the performance of mdMCI and aMCI on distinct neuropsychological tests reinforce a recent debate raised in the literature regarding the usefulness of MCI concept.[14] Although there seems to be a continuum between



		Amnestic MCI	p	Non-amnestic MCI	p	Multiple-domain MCI	p	Alzheimer's disease	p
MMSE	Cutoff	27/28		27/28		27/28		24/25	
	Sens./Spec.	71%/60%		71%/36%		71%/61%		96%/83%	
	AUC	0.719 ± .05	< 0.001	0.599 ± 0.09	< 0.001	0.728 ± 0.04	< 0.001	0.970 ± 0.01	< 0.001
CAMCOG	Cutoff	94/95		94/95		91/92		85/86	
	Sens./Spec.	79%/64%		78%/72%		85%/75%		92%/96%	
	AUC	0.743 ± .05	< 0.001	0.776 ± 0.06	< 0.001	0.837 ± 0.03	< 0.001	0.986 ± 0.01	< 0.001

Results from the AUC displayed as Area ± standard error.
Sens. = Sensitivity; Spec. = Specificity

Figure 1 – Receiver Operator Characteristics (ROC) analysis and respective cutoff points, sensitivity and specificity, AUC values for the MMSE and the CAMCOG scores (diagnostic groups *vs.* controls)

normal aging, MCI and dementia on a subgroup of patients, the current diagnostic criteria for MCI still yields a highly heterogeneous group, which jeopardizes its prognostic relevance. This may be a result from the lack of a clear definition of normal vs. pathological cognitive impairment or decline. In addition, in view of the intra-group heterogeneity of performance on neuropsychological tests that assess the same cognitive domains (e.g., the performance on the RBMT different from the FOME), we believe that the establishment of a concise but comprehensive cognitive assessment battery would be welcome to standardize the assessment for MCI across different populations. Follow-up studies of this cohort are underway in order to confirm present results, the stability and validity of the MCI concept, and the conversion rates and prognostic value of the MCI patients.

In conclusion, the discrimination of MCI from normal aging is a difficult task in clinical settings, and requires an extensive cognitive assessment. A more accurate characterization of cognitive changes in normal and pathological aging, a more precise conceptualization of MCI, and definition of core neuropsychological tests in the assessment of patients with suspected cognitive decline is needed in order to clarify these important aspects of the transition from healthy aging to dementia.

Disclosures

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: IPqFMUSP = Instituto de Psiquiatria, Faculdade de Medicina, Universidade de São Paulo; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Cientifico e Tecnológico; ABADHS = Associação Beneficente Alzira Denise Hertzog da Silva.
For more information, see Instructions for authors.

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