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Profiles of functional deficits in mild cognitive impairment and dementia: benefits from objective measurement

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Abstract

The magnitude of functional impairment that may indicate the threshold between MCI and incipient Alzheimer's disease (AD) has not been clearly defined. The objective was to examine the pattern of functional impairment in the continuum MCI-AD. Eighty-nine older adults (32 cognitively unimpaired, 31 MCI, and 26 AD patients) were examined with the Brazilian version of the Direct Assessment of Functional Status (DAFS-BR) at a university-based memory clinic. MCI patients were sub-divided according to the progression to AD upon follow-up, and had baseline cognitive, functional and biological variables analyzed. MCI patients displayed mild deficits in functional abilities, with intermediate scores as compared to controls and AD. The DAFS-BR items that differentiated MCI from controls involved the ability to deal with finances and shopping skills. At baseline, scores obtained by MCI patients who converted to AD were not significantly different from scores of nonconverters. The magnitude of functional deficits was associated with AD-like pathological findings in the CSF. In conclusion, MCI patients present with early functional changes in complex, instrumental abilities that require the integrity of memory and executive functions. The objective measurement of the functional state may help identify older adults with increased risk of developing dementia in the MCI-AD continuum. (*JINS*, 2010, *16*, 297–305.)

Keywords: Neuropsychology, Activities of daily living, Mild cognitive impairment, Alzheimer's disease, Dementia, CSF biomarkers

INTRODUCTION

Previous studies suggested that individuals with mild cognitive impairment (MCI) display functional changes that are not present in healthy older adults (Ritchie, Artero, & Touchon, 2001; Tabert et al., 2002; Wadley et al., 2007). The characterization of the conversion from MCI to incipient dementia requires functional deficits to be severe enough to impair the ability to independently undertake activities of the daily living (ADLs). Nevertheless, this diagnosis usually relies on the subjective appraisal of the ability to perform ADLs, rather than on objective measurements of functionality. The objective, longitudinal assessment of functional status in patients with MCI may be important to characterize subtle functional changes that evolve in this process, in which case instrumental abilities are prone to be affected earlier in this continuum. Despite this pivotal relevance, the magnitude and the pattern of functional impairment that thresholds the diagnosis of dementia are still imprecise (Petersen, 2007).

Functional abilities are frequently measured by IADL inventories which investigate the preservation of daily tasks associated to particular cognitive abilities (Artero, Touchon, & Ritchie, 2001; Cahn-Weiner et al., 2007; Farias, Mungas, Reed, Harvey, Cahn-Weiner, & Decarli, 2006), especially memory (Schmitter-Edgecombe, Woo, & Greeley, 2009) and executive functions (Boyle, Malloy, Salloway, Cahn-Weiner, Cohen, & Cummings, 2003; Pereira, Yassuda, Oliveira, & Forlenza, 2008; Rozzini et al., 2007). Most studies have focused on the cognitive profile of MCI patients (Barberger-Gateau, Fabrigoule, Rouch, Letenneur, & Dartigues, 1999), yet, only a few have investigated the pattern of

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functional changes in these patients (Barberger-Gateau, Fabrigoule, Amieva, Helmer, & Dartigues, 2002).

IADLs have been described as a complex range of activities which facilitate independent living. They include financial management, food preparation, telephone use, medication management, driving or traveling, housekeeping and shopping (Jefferson, Paul, Ozonoff, & Cohen, 2006). Four IADLs, in particular—telephone use, use of means of transportation, responsibility for medication intake, and handling of finances—are strong predictors of incident dementia and are strongly associated with cognitive performance (Barberger-Gateau, Dartigues, & Letenneur, 1993; Martin et al., 2008).

There are still doubts as to which domains of everyday function are most likely affected in MCI, and to what degree (Nygard, 2003). In an initial attempt to determine which functional limitation is most commonly reported among patients with MCI, a recent study found that these patients are inefficient and imprecise when performing a broad array of tasks (Giovannetti et al., 2008). In a cross-sectional study of patients with different degrees of cognitive impairment, the earliest IADLs to deteriorate were the ability to deal with finances, to prepare meals, housekeeping, and shopping, suggesting increased vulnerability to cognitive decline for such tasks, while telephone use was less susceptible to cognitive change (Jefferson et al., 2006). In another study, changes in four target IADLs (telephone use, transportation, medication intake, and finances) in healthy elders along 10 years preceded the clinical diagnosis of dementia (Péres et al., 2008). They concluded that subjects who developed dementia performed worse in IADLs, especially handling finances. These adults had poorer functional status and a faster trajectory of change over time.

In the present study, we investigated, with the aid of objective measures, the ability to perform basic and instrumental activities of the daily living in elderly patients with varying degrees of cognitive impairment (AD, MCI, and cognitively unimpaired older adults). Cross-sectional data (including cognitive and biological variables) were obtained for patients and controls, and longitudinal data (cognitive outcome) were provided for the sub-sample of patients with MCI to address the profile of functional deficits that are likely to occur in continuum MCI-AD.

Considering that subjective ADL measures suffer different sources of biases, such as the informant's ability to notice and report subtle changes in patients' daily activities, we chose to investigate the usefulness of an objective measure to identify functional deficits and contribute to the diagnosis of MCI and AD. We chose to use the Brazilian version of the Direct Assessment of Functional Status (DAFS-BR) because it assesses a broad range of daily activities and it offers scalability within each domain. Additionally, it offers the clinician the opportunity to observe the patient as he/she performs simulated daily tasks and the strategies (or lack thereof) chosen to accomplish goals or to correct the course of performance.

We predicted that the objective assessment of ADL would have higher accuracy to detect functional deficits in MCI patients than instruments based on subjective appraisals. We hypothesized that MCI patients would show deficits in the complex tasks of DAFS-BR, and that MCI patients with higher functional deficits at baseline and those who converted to mild AD in longitudinal re-assessments would show a biomarker pattern consistent with the one presented by AD patients.

METHODS

Participants

Eighty nine older adults (26 AD, 31 MCI, and 32 healthy controls) who are regularly followed-up at the Psychogeriatric Unit of the Institute of Psychiatry, University of São Paulo, Brazil, were assessed at baseline. Participants were originally recruited from community sources (community centers, newspaper, and radio ads), when a study on memory and aging was advertised. The sample also included participants who spontaneously sought medical attention related to memory complaints, or who were referred from other hospital units for assessment of suspected cognitive decline. Most of this clinical sample was therefore composed of older adults who were concerned about possible cognitive decline. Participant origin was not nestled into any diagnostic group, that is, NC, MCI, and AD patients came from different sources. Yet, participant origin has not been included as a variable in our database, therefore, it was not possible to objectively determine whether specific sources have contributed differently to each diagnostic group. All subjects signed an informed consent before enrolment. This study was approved by local Ethical Committee and was performed in accordance to the Helsinki Declaration. This sample has been described in previous articles (Diniz, Nunes, et al., 2008). The sample was predominantly female (75% of controls, 74% of MCI, and 58% of AD), with a mean age of 73.8 years (± 6.7) and mean years of education was 10.3 (± 6.0). AD patients were older than controls and MCI (77.9 ± 6.0; 71.6 ± 5.6; and 72.6 ± 7.0 years of age respectively; $p = .001$), although the difference between the latter two groups was not significant ($p = .915$; *post-hoc* Tukey test). The current sample did not comprise illiterates; although controls were slightly more educated than MCI and AD (13.2 ± 6.0; 8.5 ± 5.5; 8.8 ± 5.5 years of formal schooling; $p = .002$), all subjects in the sample had finished at least elementary school.

Clinical and Neuropsychological Assessments

A detailed description of the recruitment strategy, and clinical and neuropsychological evaluation protocols of this cohort has been published elsewhere (Diniz, Nunes, et al., 2008). In brief, patients were examined by clinicians specialized in the evaluation of dementing disorders, including geriatric psychiatrists, neurologists, and neuropsychologists. The Brazilian version of the CAMDEX (Cambridge Mental Disorders of the Elderly Examination) (Roth et al., 1986), which yields scores for the Cambridge Cognitive Test (CAMCOG) and the Mini-Mental State Examination (MMSE) (Folstein,

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Folstein, & McHugh, 1975), was administered to each patient. The Clock Drawing Test, which is also part of the CAMCOG, was additionally scored accordingly to Sunderland's guidelines (Sunderland, Hill Mellow, Gundersheimer, Newhouse, & Grafman, 1989). The Brazilian version of the CAMCOG has shown adequate psychometric and diagnostic properties to detect dementia and mild cognitive impairment (Nunes et al., 2008). The Hachinski Score (Hachinski et al., 1975), which is also derived from the CAMDEX interview, and the 21-item Hamilton Depression Scale (HAM-D) (Hamilton, 1960) were administered to all patients and controls, and scores indicated that subjects recruited for this study had no evidence of cerebrovascular disease and of depressive symptoms (HAM-D: controls, 0.0; MCI, 3.0 ± 0.5; AD, 2.1 ± 0.6).

Neuropsychological examinations were conducted by trained psychologists on a different day and included the following tests administered in the order they are presented: the Short Cognitive Test (SKT) (Erzigkeit, 1991, Flaks et al., 2006), the Fuld Object-Memory Evaluation (FOME) (Fuld, 1980), Verbal Fluency fruit category (Radanovic et al., 2009), the Trail Making Test (TMT) A and B (Army Individual Test Battery et al., 1944), the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary and Block Design tests (Wechsler, 1981), and the Rivermead Behavioural Memory Test, second edition (RBMT-II) (Oliveira and Schimidt, 1999).

To assess executive functions, we used the Executive Interview (EXIT-25), which is a structured, clinical assessment that incorporates multiple tasks that address executive functions. It comprises 25 items that assess verbal fluency, design fluency, frontal release signs, motor/impulsive control, and imitation behavior. The total score ranged from 0 to 50, higher scores being indicative of greater impairment. Scores of 15 or higher suggest a clinically significant impairment of EF (Royall, Mahurin, & Gray, 1992).

Clinical Diagnosis

Consensus diagnoses were established at expert multi-disciplinary meetings, taking into account clinical, neuropsychological, laboratorial, and neuroimaging data. Participants were classified as normal controls (NC), mild cognitive impairment (MCI), and Alzheimer's disease (AD). Alzheimer's disease was diagnosed according to the NINCDS–ADRDA criteria (McKhann et al., 1984). Diagnosis of MCI was made according to the Mayo Clinic criteria (Petersen et al., 2001): (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. For diagnostic purposes, we understood minimal impairment as deficits that did not undermine independent living.

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, syphilis tests. Neuroimaging studies (CT scans or MRI) were completed according to clinical judgment.

Assessment of Functional State

The objective functional assessment was carried out by two trained psychologists with the Brazilian version of the Direct Assessment of Functional Status, DAFS-BR (Loewenstein, Amigo, & Duara, 1989; Pereira et al., 2008). The DAFS-BR is a standardized measure of performance in six domains of daily functioning. Each domain is composed by several specific tasks that simulate real life activities. The domains are: 1. "time orientation" - orientation to time and the ability to tell time; 2. "communication skills" - ability to use the telephone and prepare a letter for mailing; 3. "dealing with finances" - identify and count currency, write a check, balance a checkbook and make change for a purchase; 4. "shopping skills" - shopping from memory – verbal recall of six grocery items from memory selection of the six items from a total of twenty-one items, and selection of other four items using a written list; 5. "grooming skills" - ability to remove the top of a toothpaste tube; put the toothpaste on the toothbrush, turn the water on and off, brush teeth, wash hands, and comb hair; 6. "eating skills" - demonstrate the motor activity involved in cutting a steak, taking a bite of the steak, eating soup, pouring water into the glass from the pitcher; and drinking water. The six domains have varying numbers of items differing, therefore, in score range – "time orientation", 16 points; "communication skills", 15 points; "dealing with finances", 32 points; "shopping skills", 20 points; "grooming skills", 13 points; and "eating skills", 10 points. Administration of this test requires approximately 25 min for each subject (Loewenstein et al., 1989; Loewenstein & Bates, 2006). DAFS-BR has been the focus of previous studies addressing its psychometric characteristics (Pereira, Forlenza, Oliveira, Diniz, & Yassuda, submitted), and its association with global cognitive performance and executive dysfunction (Pereira et al., 2008). The professionals who administered the DAFS-BR were not aware of the diagnostic status, and the scores on this assessment were not taken into account to reach consensus diagnoses.

Subjective assessment of functional impairment was based on the scores of the Informant Questionnaire of Cognitive Disorders of the Elderly (IQCODE) (Abreu, Nunes, Diniz, & Forlenza, 2008; Jorm & Jacomb, 1989), which is a subjective measurement of functional state based on the information provided by a proxy caregiver, and on the Blessed Dementia Scale (BDS) (Blessed, Tomlinson, & Roth, 1968), which is a by-product of the CAMDEX interview and consists in an informant-based, 11-item scale with scores ranging from 0 to 17, higher scores indicating a worse performance on basic abilities of the daily living (household tasks, dealing with money, grooming) and memory-related skills (orientation, comprehension, and short-term memory). Clinicians also took into account caregivers' and patients' reports on

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ADLs. IQCODE scores were taken into consideration for consensus diagnoses.

Cerebrospinal Fluid Samples

A subsample of 19 MCI patients consented to undergo lumbar puncture for cerebrospinal fluid (CSF) sampling and biomarker analysis. CSF samples were taken by lumbar puncture in the L3/L4 or L4/L5 inter-vertebral space, with a 23-gauge needle and using polypropylene tubes, in morning period. A total of 12–15 ml of CSF was collected and, then, centrifuged at 3200 g for 10 min at 4ºC. After centrifugation, the samples were separated in 0.5-ml aliquots and immediately frozen at −80ºC until analysis, without being thaw and refrozen. The CSF biomarkers Total Tau (T-Tau), Phospho-Tau_{181} (P-Tau) and Amyloid $\beta_{1\text{-}42}$ (Aβ42) were analyzed in duplicates with the INNo-Bia AlzBio3 assay (Innogenetics, Ghent, Belgium), a multiplex microsphere-based Luminex xMAP platform that allows simultaneous analysis of these biomarkers. After prewetting of the filter plate with a wash buffer, a suspension of microsphere carrying the corresponding capturing antibodies (AT120, AT270, and 4D7A3 for T-Tau, P-Tau, and Aβ1-42, respectively) was added to the plate. A mixture of biotinylated detection monoclonal antibodies designed to detect specifically one of the capturing antibodies (HT7 for t-Tau and P-Tau and 3D6 for $A\beta_{1\text{-}42}$) and 75 µl of CSF or standards were added to the plate and incubated overnight in the dark. Next, the plate was washed and a detection conjugate (phycoerythrin-labeled streptavidin) was added and incubated for 1 h at room temperature. The plate was washed, and after the addition of a reading solution (phosphate buffer saline), the assay was analyzed on a Luminex 100 IS platform (Luminex, Austin, TX). Standard curves were constructed for each biomarker using a sigmoidal curve fitting method, and the mean fluorescence values for the duplicate CSF samples were used to determine the concentration of T-Tau, P-Tau, and Aβ1-42.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS version 14.0). The means for socio-demographic and clinical variables for the three groups were compared by means of ANOVAs, and two-by-two comparisons were done with *post-hoc* Tukey tests. Parametric tests were used because these values displayed normal distribution. Pearson analyses were carried out to address the correlation between the scores for DAFS-BR and IQCODE, and the scores on DAFS-BR, EXIT-25 and memory tests (Rivermead Behavioral Memory Test and Fuld Object Memory Evaluation) with the CSF biomarkers ($A\beta_{42}$, P-Tau, and T-Tau). Receiver Operator Curve (ROC) analyses and Hanley and McNeil tests were done to assess the accuracy of DAFS-BR and IQCODE to discriminate between the different diagnostic groups.

RESULTS

Demographic information for the 89 participants of the study is presented in Table 1. There was a small but significant difference between the groups in age (AD were significantly older) and education (NC were significantly more educated).

Patients with AD were significantly more impaired than those with MCI and NC in global cognitive and functional measures, as observed in the total scores of MMSE, CAMCOG, IQCODE, and DAFS-BR (Table 1). Patients with MCI had a mild but significantly worse performance than NC in these tests except for the MMSE. We found a significant negative correlation between DAFS-BR and IQCODE scores ($r = -0.61$; $p < .001$, lower scores in DAFS-BR and higher scores in IQCODE mean worse performance), and a strong positive correlation between the DAFS-BR scores and the MMSE ($r = 0.81$; $p < .001$) and CAMCOG ($r = 0.87$; $p < .001$).

Significant differences were observed in the scores of the DAFS-BR sub-domains "dealing with finances" and "shopping skills" across all three groups (Table 2). These groups did not differ significantly in "grooming skills" and "eating skills". Compared with MCI and NC, AD patients were more impaired in the following DAFS-BR subscales: "dealing with finances", "shopping skills", "time orientation", and "communication skills". In these last two tasks, MCI and NC had equivalent performance. ROC analyses were carried out for DAFS-BR and the IQCODE to examine which in-

Table 1. Mean test scores (SD) for normal controls (NC) and patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD)

	Controls ($n = 32$)	MCI ($n = 31$)	AD ($n = 26$)	p*
DAFS-BR (0–106)	98.0 (5.7)	87.6 (7.4)	61.4 (15.9)	<.001
EXIT-25 (0–50)	6.9 (4.1)	10.7 (4.8)	19.8 (5.2)	<.001
CAMCOG (0–107)	97.8 (5.7)	87.6 (9.2)	64.2 (17.5)	<.001
MMSE (0–30)	28.8 (1.5)#	27.3 (2.3)#	19.5 (5.5)	<.001
IQCODE (0–5)	3.1 (0.3)	3.4 (0.3)	3.8 (0.7)	<.001
BDS (0–17)	0.0#	0.9 (0.2)#	4.5 (0.5)	<.001

Note. *One-way analysis of variance. #Not significantly different upon *post-hoc* Tukey test. DAFS-BR = Direct Assessment of Functional Status, Brazilian version; EXIT-25 = 25 item Executive Interview; CAMCOG = Cambridge Cognitive Test; MMSE = Mini-Mental State Examination; IQcode = Informant-based Questionnaire of Cognitive Decline; BDS = Blessed Dementia Scale. Higher scores for EXIT-25 and IQCODE indicate worse performance.

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Table 2. Mean DAFS-BR sub-items scores (SD) for normal controls (NC) and patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD)

DAFS-BR sub-items (maximum score)	Controls (n = 32)	MCI (n = 31)	AD (n = 26)	p
Time orientation (0–16):	15.2 (2.7)	15.6 (1.0)	9.7 (4.8)[#]	<.001
Communication skills (0–15):	14.1 (2.5)	13.6 (1.4)	9.6 (3.3)[#]	<.001
Dealing with finances (0–32):	27.4 (4.5)	21.3 (5.3)[£]	13.8 (6.5)[#]	<.001
Shopping skills (0–20):	16.6 (1.2)	14.5 (2.3)[£]	7.1 (2.9)[#]	<.001
Grooming skills (0–13):	12.6 (2.0)	12.7 (0.7)	11.1 (2.8)[#]	.007
Eating skills (0–10):	10.0 (0.0)	10.0 (0.0)	9.9 (0.5)[#]	.014

Note. The p values refer to analyses of variance. *Post-hoc* Tukey test for pairwise comparisons between DAFS-BR sub-scores: [#]AD significantly different from controls and MCI; [£]MCI significantly different from controls. DAFS-BR = Direct Assessment of Functional Status, Brazilian version.

strument had better accuracy to discriminate the three groups. Results presented in Table 3 indicate that the DAFS-BR total score separated controls from AD and MCI from AD with better accuracy than the IQCODE (Hanley and McNeil test: Control *vs*. MCI; z = 1.39; p = .1; Control *vs*. AD; z = 2.2; p = .02; MCI *vs*. AD, z = 3.4; p = .001).)

As to MCI sub-types, the sample was composed of eight amnestic single domain, 18 amnestic multiple domain, and five non-amnestic multiple domain patients. MCI sub-types were compared on DAFS-BR performance with the Kruskal-Wallis test, due to lack of normal distribution within groups, and no significant differences were detected for the total score and for its subscales (p > .15 for all comparisons).

Patients with MCI had at least one routine re-assessment after the administration of baseline DAFS-BR (minimum interval 1 year). Eight patients with MCI (20.5%) progressed to AD upon follow-up (MCI-AD) and 23 were stable over time (MCI-S). Among converters (MCI-AD), the mean interval between baseline assessment and the conversion from MCI to AD was of 15.7 (±3.7) months, whereas those who maintained the MCI status (MCI-S) had been longitudinally assessed for 17.1 (±4.1) months. These patients did not display statistically significant differences with respect to age, years of education, global cognitive function (MMSE and CAMCOG scores), and IQCODE scores (ANOVA with Tukey test for pairwise comparisons). Also, no significant differences were observed in the DAFS-BR scores obtained by patients with MCI-AD and MCI-S (Table 4). Considering the whole sample sub-divided into four diagnostic groups (i.e., MCI group split according to conversion status), statistically significant differences in the DAFS-BR scores were observed between NC, MCI-S, MCI-AD, and AD (ANOVA; F = 72.2; df = 3; p < .001). The scores on the EXIT-25 showed a similar pattern as the one shown by the DAFS-BR scores, except for the lack of statistically significant differences between NC and MCI-S (Table 4)..

In the sub-group of patients with MCI who had samples available for the analysis AD biomarkers (n = 19), the CSF concentrations of $A\beta_{42}$, total Tau and phospho-Tau did not correlate either with the total DAFS-BR or EXIT-25 scores at baseline; nevertheless we found significant negative correlations between the scores in two DAFS-BR sub-domains, namely "shopping skills" and "dealing with finances", the CSF concentrations of phospho-Tau (r = −0.63; p = .002 for both sub-scores) and of total Tau (r = −0.56; p = .005 and r = −0.52; p = .01, respectively). The profile score of the RBMT showed a positive correlation with CSF $A\beta_{42}$ (r = 0.416; p = .04), and negative correlation with CSF P-Tau (r = −0.484; p = .02) and CSF T-Tau (r = −0.468; p = .02). No significant correlation between screening scores of the RMBT and total and delayed recall scores of the FOME were found.

We further dichotomized the MCI group according to the degree of functional impairment, by using the median DAFS-BR score (88.5 points) and the median EXIT-25 score (11 points) as a cutoff, lower and higher scores, respectively, indicating more severe impairment. In the subgroup with greater functional impairment (n = 7), mean CSF concentrations of total Tau and phospho-Tau were significantly higher than in patients with less severe impairment. (Table 5). No

Table 3. Diagnostic accuracy of DAFS-BR and IQCODE

	DAFS		IQCODE	
	AUC ± SE [$CI_{95\%}$]	p	AUC ± SE [$CI_{95\%}$]	p
Control vs. MCI	0.873 ± 0.044 [0.78 – 0.96]	<0.001	0.769 ± 0.062 [0.649 – 0.889]	<0.001
Control vs. AD	0.998 ± 0.003 [0.992 – 1.000]	<0.001	0.848 ± 0.075 [0.701 – 0.995]	<0.001
MCI vs. AD	0.961 ± 0.022 [0.916 – 1.000]	<0.001	0.734 ± 0.078 [0.543 – 0.926]	0.01

Note. Hanley and McNeil test: Control vs. MCI, z = 1.39, p = 0.1; Control vs. AD, z = 2.2, p = 0.02; MCI vs. AD, z = 3.4, p = 0.001. AUC = area under the curve. SE = Standard error; DAFS = Direct Assessment of Functional Status; IQCODE = Informant Based Questionnaire of Cognitive Decline in the Elderly; MCI = mild cognitive impairment; AD = Alzheimer's disease.

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Table 4. Cognitive and functional test scores in distinct diagnostic groups (patients with MCI sub-divided according to conversion status)

	Controls (n = 32) Mean ± SD	MCI-S (n = 23) Mean ± SD	MCI-AD (n = 8) Mean ± SD	AD (n = 26) Mean ± SD	p
IQCODE	3.1 ± 0.3	3.3 ± 0.3	3.7 ± 0.3	3.8 ± 0.7	<0.001*
CAMCOG	97.8 ± 5.7	88.3 ± 9.0	84.5 ± 9.3	62.9 ± 16.8	<0.001*
DAFS-BR	98.0 ± 6.0	89.0 ± 7.0	82.0 ± 8.0	60.0 ± 15.0	<0.001*
EXIT-25	7.0 ± 4.0	10.0 ± 4.0	14 ± 6.0	20.0 ± 5.0	<0.001*

Note. *One-way analysis of variance; Tukey *post-hoc* test: DAFS-BR: Control vs. MCI-S, $p = 0.002$; Control vs. MCI-AD, $p < 0.001$; MCI-S vs. MCI-AD, $p = 0.3$; MCI-S and MCI-AD vs. AD, $p < 0.001$; Control vs. AD, $p < 0.001$; EXIT-25: Control vs. MCI-S, $p = 0.09$; Control vs. MCI-AD, $p < 0.001$; MCI-S vs. MCI-AD, $p = 0.08$; MCI-S vs. AD, $p < 0.001$; MCI-AD vs. AD, $p < 0.01$; Control vs. AD, $p < 0.001$. MCI-AD = MCI patients who progressed to AD upon follow-up; MCI-S = MCI patients who retained the MCI diagnosis upon follow-up; AD = Alzheimer's disease; DAFS-BR = Direct Assessment of Functional Status, Brazilian version; EXIT-25 = Executive Interview, 25 items; IQcode = Informant-based Questionnaire of Cognitive Decline; CAMCOG = Cambridge Cognitive Test.

statistically significant differences in CSF biomarker concentrations were depicted when MCI patients were sub-divided according to median EXIT-25 scores.

DISCUSSION

The present data confirm the notion that patients with MCI may have subtle functional deficits affecting the ability to perform instrumental activities of the daily living. This finding is in agreement with previous studies reporting instrumental deficits in patients with MCI (Artero et al., 2001; Kim, Lee, Cheong, Eom, Oh, & Hong, 2009; Tabert et al., 2002). Functional impairment in patients with MCI is less severe than that observed in patients who already fulfill the diagnostic criteria for mild dementia, but correlates with the magnitude of global cognitive impairment, as shown by the strong correlation with total CAMCOG scores and executive dysfunction (Pereira et al., 2008). We have recently suggested that, along this continuum, the onset of executive dysfunction, in addition to existing amnestic deficits, may accompany the progression of functional impairment, until the functional loss becomes severe enough to fulfill the diagnostic criteria for dementia (Forlenza, Diniz, Nunes, Memoria, Yassuda, & Gattaz, 2009). We further showed that in the present study total DAFS-BR scores had higher accuracy than the IQCODE to discriminate the diagnostic groups, providing additional evidence of the benefit of objective measurement of functional abilities over the self-reported or informant-based reported functional impairment in these subjects.

One might argue that the MCI patients that participated in this study should be regarded as already demented, in view of their subtle instrumental deficits. However, the cross-sectional analysis of the DAFS-BR scores showed that patients with MCI still perform significantly better than those with mild AD. In addition, this difference persists irrespectively of the conversion status of patients with MCI, because both MCI-S and MCI-AD patients had significant better performance than patients diagnosed with mild AD, and no significant differences were found between them. Additional information evaluated in consensus meetings, such as cognitive performance, IQCODE scores, and patients' and relatives' reports on ADL, were also inconsistent with mild AD. Thus we are confident that the MCI patients included in this analysis were not misclassified at baseline. In addition, the longitudinal analysis showed that the DAFS-BR scores did not predict the conversion from MCI to AD, albeit this analysis may have been underpowered by the small number of patients MCI who actually progressed to dementia. Further studies with larger samples should be carried out to address this question more appropriately.

According to Fillenbaum (1985), the assessment of instrumental activities of the daily living by instruments addressing the ability to deal with finances, to use the telephone, and

Table 5. CSF biomarkers according to the magnitude of functional impairment and executive dysfunction (MCI group dichotomized according to median DAFS-BR and EXIT-25 scores)

AD biomarkers Mean ± SD	Functional state			Executive function		
	DAFS-BR > 88.5 (n = 12)	DAFS-BR < 88.5 (n = 7)	p*	EXIT-25 < 11 (n = 13)	EXIT-25 > 11 (n = 6)	p*
β-amyloid$_{42}$ (pg/mL)	467.1 ± 156.5	345.6 ± 80.1	0.07	451.3 ± 165.1	364.2 ± 56.3	0.3
Phospho-Tau$_{181}$ (pg/mL)	44.8 ± 14.8	84.8 ± 43.3	0.01	49.7 ± 14.6	80.1 ± 52.7	0.3
Total Tau (pg/mL)	74.2 ± 23.8	138.3 ± 78.2	0.03	79.6 ± 23.1	135.1 ± 90.6	0.2

Note. *Student t test analysis. DAFS-BR = Direct Assessment of Functional Status, Brazilian version; EXIT-25 = Executive Interview, 25 items. Median DAFS-BR score: 88.5 (lower scores indicative of greater impairment); Median EXIT-25 score: 11 (higher scores indicative of greater impairment); data restricted to those MCI patients which had baseline CSF analysis available (n = 19). CSF = cerebrospinal fluid.

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to manage medication has been shown to bear the highest correlation with global cognitive function in older adults. Okonkwo, Wadley, Griffith, Ball, and Marson (2006) further showed a positive correlation between cognitive functions and the ability to deal with finances in patients with MCI. They found that attention and executive functions are involved in the selective response to stimuli, self-monitoring, and temporary integration of information which are essential to dealing with finances. Given that these sub-components of executive functions are highly susceptible to interference while performing instrumental activities, these functional domains may be more sensitive to subtle degrees of cognitive impairment (as observed in MCI patients). As a consequence of that, these domains may be more susceptible to the changes that evolve in patients with MCI, as observed in the present study.

Our findings are also in agreement with Griffith et al. (2003), who reported that the objective assessment of the ability to manage finances can differentiate healthy controls from patients with MCI and AD. In the study above, patients with MCI were impaired in a range of financial abilities such as conceptual knowledge of finances, transactions involving cash, management of bank statements and payment of bills.

The analysis of the interaction between functional impairment and CSF biomarkers, illustrating the underlying AD pathology in a sub-set of patients with MCI, provides additional insights into the nature of the association between functional deficits and the development of dementia. Because of the small number of subjects in these sub-categories, we understand that these findings are preliminary and need replication in larger samples. Nevertheless, based on the available findings, we hypothesize that patients with more severe impairment (i.e., DAFS-BR scores below the median value of 88.5 in the current sample), although not demented, have a pattern of CSF biomarkers which is similar to that found in patients with AD and in patients with MCI who further progress to AD, that is, high CSF concentrations of total Tau and phospho-Tau (Diniz, Pinto Júnior & Forlenza, 2008; Sunderland et al., 2003). Also, CSF concentrations of these biomarkers were shown to be correlated with worse performance in two of the DAFS-BR sub-scores, namely "shopping skills" and "dealing with finances", and with the RBMT profile scores. Our findings are compatible with the recent study published by Nordlund et al. (2008) indicating that MCI patients displaying the AD biomarker signature in the CSF have more severe episodic memory and speed/attention deficits.

We understand that the objective assessment of instrumental abilities of the daily living through the DAFS-BR may enhance the identification of subtle dysfunction in patients with MCI. This hypothesis is supported by data presented in this study indicating that DAFS-BR has higher accuracy than the IQCODE to identify MCI patients. The objective assessment of functional status is not a routine procedure in the evaluation of patients with suspected cognitive impairment; rather, it usually relies on the subjective appraisal of a relative or caregiver, or even on the patient's judgment about him or herself, rendering this information imprecise and subject to several sources of bias, including the informant's personality, mood and cognitive state (Loewenstein et al., 2001).

Subjective evaluations may be based on a single question about a domain and, therefore, may not assess performance competence reliably. In case of medication use, for example, a single question may ignore the multidimensional nature of the task which involves remembering to take medication, taking the correct dosage, and understanding the label (Allaire, Gamaldo, Ayotte, Sims, & Whitfield, 2009). In addition, the objective assessment of functional impairment is critical for the characterization of mild functional disability. Older adults with MCI present functional losses that may not be detected by the clinician when based solely on informant's reports (Wadley, Okonkwo, Crowe, & Ross-Meadows, 2008). Allaire et al. (2009), for instance, did not find significant differences between elderly subjects with and without MCI, when the assessment was based on the subjective appraisal of informants; yet, they found significant differences between MCI and controls in objective measurements of the ability to deal with medication, finances, nutrition, and food preparation. DAFS-BR "dealing with finances" subscale contributes with 32 points for the total score and allows for the grading of impairment within this domain, which may be missed by informants' assessments.

Although DAFS-BR assesses a varied and relevant range of ADL and allows scalability, it is faced with certain limitations. First, some domains, essential to independent living, such as medication management, transportation use, and food preparation are not included in it. On the other hand, "grooming" and "eating skills" are basic not instrumental ADL, therefore, they do not contribute to the diagnosis of MCI. Finally, some of the activities proposed may be influenced by gender (men may have less grocery shopping experience than women who may be less experienced with financial issues) or suffer education biases in tasks such as balancing a checkbook. Cultural factors may also influence its scores. DAFS-BR scores may need to be interpreted in light of such potential biases.

Acknowledging the fact that MCI patients already present a small degree of functional impairment, these findings raise the complex issue of setting new boundaries between MCI and the dementia. Rather than the magnitude of deficits in one given skill, we hypothesize that functional impairment is determined by the inability to compensate for such deficits, which may result from the cumulative effect of mild deficits in several critical functions. In such case, an array of mild deficits affecting the resistance to interference may lead to more relevant functional impairment than a more robust decline in one given function. The survival of the MCI concept a useful nosological entity will depend upon clearer definitions of acceptable functional deficits in this diagnosis. One possible solution to this issue will be the proposal of cutoff scores for objective ADL measures (Forlenza & Chiu, 2008).

In conclusion, considering that functional impairment is a core aspect to distinguish MCI from the early stages of dementia, and that the ability to perform instrumental

functions depends on preserved cognition (Sabbagh et al., 2007), we propose that the objective assessment of functional state may provide important insights into the patients' ability to manage daily life challenges. Such information may guide certain clinical judgments, ranging from the early diagnosis of AD and other dementias (given the characterization of MCI), to the longitudinal outcome, and the decision to intervene with anti-dementia drugs and/or clinical rehabilitation programs.

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