Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment

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ABSTRACT

Background: Previous studies have reported an association between executive dysfunction and the ability to perform activities of daily living (ADL)s among older adults. This study aims to examine the association between executive functions and functional status in a cross-section of older adults with varying degrees of cognitive impairment.

Methods: 89 individuals (mean age 73.8 years) were recruited at a memory clinic in São Paulo, Brazil. Subjects underwent evaluation, and were allocated into three diagnostic groups according to cognitive status: normal controls (NC, n = 32), mild cognitive impairment (MCI, n = 31) and mild Alzheimer's disease (AD, n = 26). Executive functions were assessed with the 25-item Executive Interview (EXIT25), and functional status was measured with the Direct Assessment of Functional Status test (DAFS-R).

Results: Significantly different total DAFS-R scores were observed across the three diagnostic groups. Patients with AD performed significantly worse in EXIT25 compared with subjects without dementia, and no significant differences were detected between NC and MCI patients. We found a robust negative correlation between the DAFS-R and the EXIT25 scores (r = –0.872, p < 0.001). Linear regression analyses suggested a significant influence of the EXIT-25 and the CAMCOG on the DAFS-R scores.

Conclusion: Executive dysfunction and decline in general measures of cognitive functioning are associated with a lower ability to undertake instrumental ADLs. MCI patients showed worse functional status than NC subjects. MCI patients may show subtle changes in functional status that may only be captured by objective measures of ADLs.

Key words: executive function, functional status, DAFS-R, EXIT25, mild cognitive impairment, Alzheimer's disease

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Introduction

Cognitive impairment has been implicated as a risk factor for loss of autonomy and dependence, and the magnitude of this risk may vary depending on how well and how quickly the subject can perform simple everyday tasks (Gill *et al.*, 1995). To date, the concept of mild cognitive impairment (MCI) is the best attempt to characterize the transitional phase between healthy cognitive aging and the initial stages of dementia (Petersen and Negash, 2008), in spite of the unquestionable etiological and prognostic heterogeneity of this categorization. According to the current diagnostic criteria (Petersen and Negash, 2008), patients with MCI, as opposed to those with dementia, have normal global cognitive functioning, which renders the ability to perform activities of daily living (ADL) unimpaired. Nevertheless, subtle difficulties illustrated by slowing and hesitation in the management of complex ADL tasks may indicate some degree of dysfunction that might be detected by sensitive screening.

The relationship between cognitive impairment and functional competence has been documented by several studies (Teri *et al.*, 1988; Perry and Hodges, 2000). The functional assessment of older subjects is usually based on their ability to perform basic (BADL) and instrumental (IADL) activities of daily living. The former category refers to the ability to complete simple functions such as eating, bathing, grooming and getting dressed, whereas the term IADL comprises more complex activities required for independent living, such as the preparation of meals, shopping, managing finances and using the telephone or public transportation (Lindeboom *et al.*, 2003). Even mild degrees of cognitive deterioration may have negative effects on the ability to perform complex IADL (Perneczky *et al.*, 2006; Farias *et al.*, 2006). This observation has encouraged some authors to propose the inclusion of IADL deficits in the diagnostic criteria for MCI, in order to improve the prediction of the risk of conversion to dementia (Peres *et al.*, 2006).

Although the completion of IADL requires competent memory, it involves executive functions (EF) as well. EF are complex cognitive abilities that enable an individual to perform tasks that includes planning, problem solving, anticipation of possible outcomes, and inhibition of irrelevant processing (Lezak *et al.*, 2004). A few studies have proposed that the impairment on EF is a key factor that underlies poor functional achievement (Cahn-Weiner *et al.*, 2000; van Hooren *et al.*, 2005; Royall *et al.*, 2005). Disturbances in EF are also associated with the higher needs for care and a more rapid progression to dementia (Mann *et al.*, 1992). Executive dysfunction may be even more strongly associated with functional impairment than are deficits in memory, language, visuospatial skills, and psychomotor speed (Bell-McGinty *et al.*, 2002; Cahn-Weiner *et al.*, 2002) and may, at least for some AD patients, precede overt memory decline (Binetti *et al.*, 1996). Royall *et al.* (2005) further suggested that the conversion from amnestic MCI to dementia subsumes a concurrent impairment in EF. This observation is in agreement with Rozzini *et al.* (2007), who provided evidence that the conversion from MCI to AD upon a follow-up of one year is associated with worsening scores on EF and functional status (FS), which is independent of memory deterioration. In a recent review by the Committee on Research

of the American Neuropsychiatry Association, an expert panel suggested that measures of executive functions are strong correlates of functional capacities, particularly involving medical or financial decision-making (Royall *et al.*, 2007).

The objective assessment of FS is not a routine procedure in the evaluation of cognitive impairment and dementia. The assessment of functionality usually relies on the subjective appraisal of a relative or caregiver, or even on the patient's judgment about him or herself. For this reason, most instruments designed to assess the FS indirectly may be influenced by the informant's personality, mood and cognitive state, yielding biased information that can both minimize or maximize the actual deficits (Loewenstein *et al.*, 2001). The purpose of the present study is to examine the association between EF and FS by means of an objective assessment schedule in a sample of Brazilian older adults with different levels of cognitive impairment (MCI and mild AD), as compared to healthy controls.

Methods

Patients and controls were recruited from community sources, including patients with spontaneous demand for assessment due to memory complaints, invitation of community-dwelling elderly through radio advertisements, health lectures for seniors, and referral from other clinics for the assessment of suspected cognitive decline at a university-based memory clinic (Institute of Psychiatry, University of São Paulo). Eighty-nine subjects (70% women) were enrolled for the current sub-study. Mean age was 73.8 ± 6.7 years, ranging from 59 to 89 years, and mean education was 10.3 ± 6.0 years of education, ranging from 1 to 26 years of formal education.

Patients were examined by clinicians specialized in the evaluation of dementing disorders, including geriatric psychiatrists, neurologists, geriatricians and neuropsychologists. Mental state examination was performed with the Brazilian version of the Cambridge Examination for Mental Disorders in the Elderly (CAMDEX) semi-structured interview which yields scores for the Cambridge Cognitive Test (CAMCOG) (Roth *et al.*, 1986); the Mini-mental State Examination (MMSE) (Folstein *et al.*, 1975) and the Hachinski Ischemic Score (Hachinski *et al.*, 1975). The Clock Drawing Test, which is part of the CAMCOG schedule, was additionally scored accordingly to Sunderland's guidelines (Sunderland *et al.*, 1989). The Brazilian version of the CAMCOG has shown adequate psychometric and diagnostic properties (Bottino *et al.*, 1999; Nunes *et al.*, 2008). The 21-item Hamilton Depression Scale (HAM-D) was administered to rule out depressive symptomatology (Hamilton, 1960). Neuropsychological examinations were conducted by trained psychologists and included the Rivermead Behavioural Memory Test (RBMT) (Wilson *et al.*, 1985; Oliveira and Schmidt, 1999; Yassuda *et al.*, 2006), the Fuld Object-Memory Evaluation (FOME) (Fuld, 1980; Diniz *et al.*, 2007), Verbal Fluency (category: fruit; Diniz *et al.*, 2007), the Trail-Making Test (TMT) A and B (Army Individual Test Battery, 1944; Diniz *et al.*, 2007), the Short Cognitive Test

(SKT) (Erzigkeit, 1991; Flaks *et al*., 2006) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary and Block Design tests (Wechsler, 1981). The following scores were of interest in the clinical evaluation of patients: for the RBMT, profile and screening scores; for the FOME, the sum of the five consecutive immediate recalls of 10 objects, and the 30-minute delayed recall; for verbal fluency, the total number of generated fruits; for the TMT, the seconds required to complete each trail; for the SKT the total and the attention and memory scores.

Evidence of functional decline was based on the scores of the Informant Questionnaire of Cognitive Disorders of the Elderly (IQCODE) (Jorm and Jacomb, 1989) and on the Blessed Dementia Scale (BDS) (Blessed *et al.*, 1968). Clinicians also took into account caregivers' and patients' reports on ADL limitations. 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.

Consensus diagnoses were reached by the expert multidisciplinary team, taking into account clinical, neuropsychological, and laboratorial and neuroimaging data. Dementia was diagnosed according to DSM-IV criteria (American Psychiatric Association, 1994). AD was diagnosed according to the NINCDS–ADRDA criteria (McKhann *et al.*, 1994). Diagnosis of MCI was made according to the Petersen's (2004) criteria: (1) subjective cognitive complaint, 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; and (4) preserved or minimal impairments in activities of daily living. In Brazil, some cognitive instruments suitable for dementia diagnosis have had their applicability and psychometric properties evaluated; however, almost none has normative data for older adults. Therefore, evaluating criterion 2 was particularly challenging, due to the lack of Brazilian norms for the selected instruments. Objective test results were compared with international norms; however, clinical judgment taking into account patients' educational and occupational backgrounds and our extensive experience with the instruments were used to determine whether performance was below normal parameters.

The MCI patients were classified into three different sub-types according to the pattern of cognitive impairment: (1) amnestic (aMCI) if there was only objective impairment in one or more of the memory tests (e.g. RBMT or FULD); (2) non-amnestic (naMCI) if there was objective impairment on one cognitive domain, except memory; and (3) multiple domain (mdMCI) if there was objective impairment in two or more cognitive domains. Subjects without evidence of cognitive impairment were regarded as normal controls (NC), although some reported memory complaints.

In the studied sample 32 subjects were cognitively unimpaired (NC), 26 had AD, and 31 had evidence of MCI. Of these, 22% had a neuropsychological

profile compatible with the diagnosis of single-domain amnestic MCI, 62.5% multiple-domain amnestic MCI, and 15.5% non-amnestic MCI. To test if the sample size of each diagnostic group (NC, AD, MCI) was adequate to provide reliable comparisons, power analysis was performed for each diagnostic group pair assuming p = 0.05, and revealed power $(1-\beta)$ of at least 74%, i.e. a probability of type II error of 26%.

To assess FS, participants completed the revised version of Direct Assessment of Functional Status Scale (DAFS-R) (Loewenstein *et al.*, 1989). The DAFS-R schedule evaluates the behavioral competence in tasks that simulate ADL. Seven ADL domains are objectively tested: time orientation, communication skills, ability to deal with finances, shopping, grooming, eating and transportation. Each DAFS-R domain or sub-domains have different score ranges (higher scores indicating better performance), and cut-off scores separating normal from impaired functioning have been established by Loewenstein and Bates (2006). Time orientation includes "telling time" (score ranging from 0 to 8; cut-off: 4) and "orientation to date" (range: 0–8; cut-off: 4). Communication skills include "using the telephone" (range: 0–9; cut-off: 6) and "writing a letter" (range: 0–6; cut-off: 4). The ability to deal with finances is assessed by "identification of currency" (range: 0–7; cut-off: 6), "counting currency" (range: 0–4; cut-off: 2), "writing a check" (range: 0–5; cut-off: 3), "balancing a check-book" (range: 0–8; cut-off: 2) and "finding change for a purchase" (range: 0–8; cut-off: 0). Shopping skills are tested by the ability to "recall a shopping list from memory" (range: 0–6; cut-off: 2), to "recognize shopping list items from memory" (range: 0–6; cut-off: 3), to "choose shopping items with the aid of a written list" (range: 0–8; cut-off: 8). Grooming skills are scored from 0 to 13 (cut-off: 10) and eating skills from 0 to 10 (cut-off: 8). Transportation skills are assessed by the ability to name and respond to road signs (range:0–13; cut-off: 12). For the current study, the latter item was not included in the analysis, because a large proportion of subjects were non-drivers and would thus have more difficulty interpreting road signs.

To assess EF, patients were submitted to the Executive Interview (EXIT25), which is a bedside, 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 ranges from 0 to 50, higher scores being indicative of greater impairment. Scores of 15 or higher suggest a clinically significant impairment of EF (Royall *et al.*, 1992).

For cognitively unimpaired patients, the examination of EF and FS took approximately 45 minutes, whereas patients with cognitive impairment required 60 to 75 minutes to complete the assessment using both scales.

The SPSS 14.0 was used to compile and analyze the database for this study. One-way analyses of variance were carried out to compare means from three diagnostic groups for EXIT25 and DAFS-R scores, because scores followed a normal distribution. The confounding effect of age and education level was controlled for by analyses of co-variance (ANCOVA). Pair-wise comparisons were carried out with Bonferroni post-hoc tests. Pearson correlation scores were calculated to assess the relation between EF and FS, and the relation

between these instruments and age and education. Regression analysis was performed in order to identify which variables were most predictive of everyday functional changes. DAFS-R was used as the dependent variable, while age, education, gender, EXIT25 and CAMCOG scores, were included in the model as independent variables.

Results

Demographic characteristics of patients in the sample are presented in Table 1, along with the total scores on the MMSE and the CAMCOG. The proportion of men and women in each diagnostic group was statistically equivalent (p = 0.29). There were significant differences between NC, MCI and AD with respect to age (p = 0.001) and years of schooling (p = 0.002), AD patients being older than MCI and NC, and NC more educated than AD and MCI. As expected, the scores on cognitive screening tests (MMSE and CAMCOG) were significantly lower in the AD group (p < 0.001), and the latter test further differentiated MCI from NC (p < 0.001).

The total DAFS-R and EXIT25 scores for patients (AD and MCI) and controls (NC) are also displayed in Table 1. Analyses of covariance (ANCOVA) controlling for age and education indicated that the DAFS-R and EXIT25 scores were significantly different among the diagnostic groups (p < 0.001 and p < 0.001 respectively). Pair-wise comparisons indicated that the three diagnostic groups were significantly different for DAFS-R, with NC showing higher performance than MCI and AD (p = 0.009 and p < 0.001 respectively), and MCI higher than AD (p < 0.001). For EXIT25 there were no significant differences between NC and MCI (p = 0.29); however, AD patients had worse scores than patients with no dementia (p < 0.001 for comparisons with NC and MCI).

Pearson's correlations showed a robust negative association between the DAFS-R and the EXIT25 total scores (r = −0.87, p < 0.001) (Figure 1). Pearson's correlation coefficients further indicated that the scores on these scales

Table 1. Demographic characteristics, scores on cognitive screening tests (MMSE and CAMCOG), and total DAFS-R and EXIT25 scores of patients in the sample

	N C	M C I	A D	p
Gender (female/total)	24/32	23/31	15/26	0.28
Age, years (mean ± SD)	71.6 (5.6)	72.6 (7.0)	**77.9 (6.0)**	0.001*
Education, years (mean ± SD)	**13.2 (6.0)**	8.5 (5.5)	8.8 (5.5)	0.002*
MMSE (mean ± SD)	28.7 (1.6)	27.3 (2.4)	**20.4 (6.0)**	<0.001*
CAMCOG (mean ± SD)	**97.8 (5.5)**	**87.6 (9.2)**	**64.2 (17.5)**	<0.001*
DAFS-R (mean ± SD)	**98.0 (5.7)**	**87.6 (7.4)**	**61.4 (15.9)**	<0.001#
EXIT25 (mean ± SD)	7.0 (4.0)	10.1 (4.1)	**19.9 (5.2)**	<0.001#

NC = normal controls; MCI = mild cognitive impairment; AD Alzheimer's disease; MMSE = Mini-mental Status Examination; CAMCOG = Cambridge Cognitive Test; EXIT25 = 25-item Executive Interview; DAFS-R = Direct Assessment of Functional Status test* = one-way ANOVA, # = ANCOVA Bold type indicates scores yielding significant differences compared to other diagnostic groups.
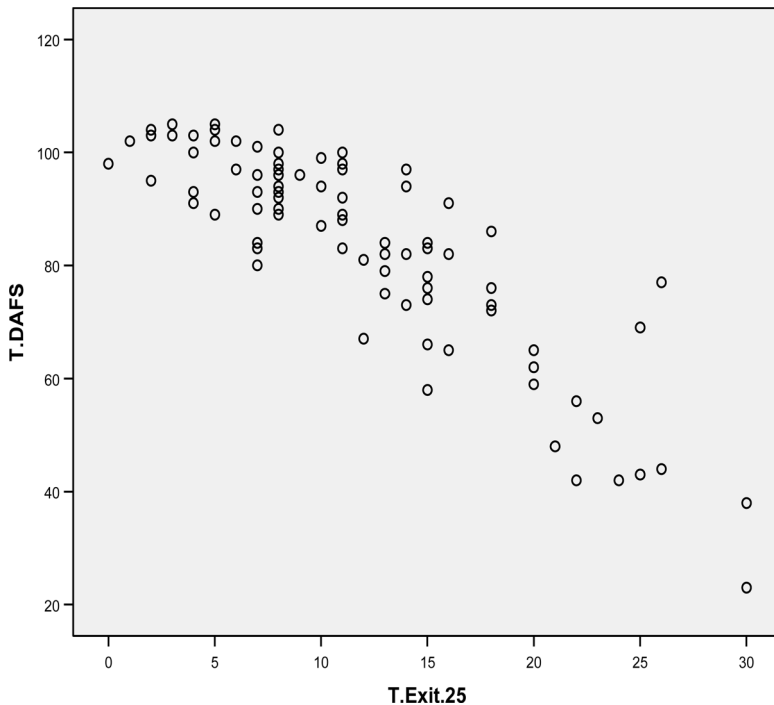
Figure 1. Pearson's correlation between the EXIT25 and the DAFS-R total score for patients in the sample, irrespective of diagnostic status

were moderately but significantly correlated with age (DAFS-R: $r = -0.47$, $p < 0.001$; EXIT25: $r = 0.49$, $p < 0.001$) and education (DAFS-R: $r = 0.36$ $p < 0.001$; EXIT25: $r = -0.39$, $p < 0.001$). Correlations between DAFS-R and EXIT25 scores were also significant in each diagnostic sub-group: for NC ($r = -0.707$; $p < 0.001$), MCI ($r = -0.513$; $p < 0.001$) and AD ($r = -0.744$; $p < 0.001$), although of smaller magnitude for the MCI group. This finding seems to reflect higher variance in scores for this group.

Table 2 presents results for the regression analysis, indicating that changes in CAMCOG and EXIT25 scores predict changes in DAFS-R scores. In addition, our results suggest the association between EXIT25 and DAFS-R is almost three times stronger than the association between the CAMCOG and DAFS-R.

Discussion

In the current study we examined the association between executive functions and functional status, as documented by the EXIT25 and the DAFS-R scores, in three groups of older adults with different levels of cognitive performance. Correlation and linear regression analysis showed that subjects who score higher in EXIT25 tend to have a worse performance in DAFS-R. Our data, in agreement with the available literature, suggest that executive dysfunction

Table 2. Results of regression analyses of DAFS-R as the dependent variable, and age, education, gender, EXIT25 and CAMCOG scores in the model as independent variables

	β	S E	p
Intercept	63.656	13.342	<0.001
Gender	1.232	1.839	0.06
Age, years	−0.064	0.139	0.64
Education, years	−0.305	0.159	0.060
EXIT25	−1.323	0.204	<0.001
CAMCOG	0.513	0.083	<0.001

DAFS-R = Direct Assessment of Functional Status test; β = standardized coefficient; SE = standardized error; EXIT25 = 25-item Executive Interview; CAMCOG = Cambridge Cognitive Test.

exerts a negative impact on the ability to perform activities of daily living, stronger than general cognitive deficits (Cahn-Weiner *et al.*, 2002; Bell-McGinty *et al.*, 2002; van Hooren *et al.*, 2006). To our knowledge, this is the first study to demonstrate this relation using an objective, performance-based assessment of ADLs. In agreement with a growing body of studies (Farias *et al.*, 2006; Perneczky *et al.*, 2006), our results also indicate that MCI patients (who do not meet FS impairment criteria based on subjective reports of FS) may reveal deficits in ADL when performance-based measures are used.

In the current sample, EXIT25 and DAFS-R scores were modestly influenced by age and education. Since age and education differences observed in the comparison groups were controlled for in the statistical analysis of variance as co-variables, and were included in the regression analysis model, we understand that the putative age and education biases do not jeopardize the actual indication of an important effect of impaired executive function on the performance on the DAFS-R.

Few studies have tried to differentiate healthy older adults from MCI and AD on the basis of the objective assessment of ADL and executive functions (Perneczy *et al.*, 2006). Most researchers have emphasized the importance of testing memory, language and visuospatial skills, overlooking the need for an objective assessment of functional impairment (De Bettignies *et al.*, 1990; Loewenstein *et al.*, 2001, Argüelles *et al.*, 2001). Loewenstein *et al.* (2006) examined the cognitive profiles of individuals with varying degrees of impairment, including patients clinically diagnosed as MCI, having neurobiological evidence of prodromal AD or vascular cognitive impairment, and patients with AD dementia, as compared to healthy controls. The authors found that both MCI groups had, in addition to poorer global cognitive performance, lower scores on measures of executive functions. These results are consistent with the notion that it is not only memory that is impaired in preclinical AD (Backman *et al.*, 2004).

In the current study, as expected, patients with AD were significantly more impaired than those with MCI and controls in cognitive and functional measures. EXIT25 raw scores suggest that MCI patients have worse executive abilities than

NC; however, when age and education effects are controlled for, MCI and NC scores do not reach statistical difference in this sample. These changes, although not within statistically significant limits, illustrate a similar tendency to that observed among patients with mild AD.

The present results suggest that the DAFS-R can differentiate patients with dementia, MCI and normal controls on the basis of functional impairment. Although the diagnostic criteria for MCI subsume functional preservation, the current findings suggest that MCI patients may already have difficulties performing ADLs. Interestingly, although the DAFS-R and the EXIT25 scores were strongly correlated, only the DAFS-R differentiated MCI from controls in this sample. This may be due to the fact that the DAFS-R "shopping skills" sub-domain is in fact a memory task, rendering the test more sensitive to the deficits presented by patients with amnestic MCI. In the current study, most of the MCI patients (84.5%) were classified as single- and multiple-domain amnestic MCI. We thus speculate that analysis of DAFS-R sub-domains across distinct MCI sub-types may reveal different patterns of functional impairment. For instance, multiple-domain MCI may be associated with a higher degree of executive dysfunctions with stronger impact on functional status (Tabert *et al.*, 2006).

The present study has some important limitations that need to be addressed. The study design was cross-sectional and the proposed hypothesis could be more appropriately tested in longitudinal designs. In addition, the studied sample was derived from a memory clinic which might introduce particular biases and yield results that may not be generalized to other populations. Although power analyses indicated adequate sample size, results should be replicated in larger samples. Future studies should also evaluate the independent contribution of other cognitive functions to FS impairment, such as memory, perception and motor control. A final limitation relates to the fact that executive dysfunction was documented by cognitive measures only, and corresponding frontal lobe atrophy was not confirmed by imaging data.

Despite these limitations, this study supports the notion that executive dysfunction is strongly associated with impairment in ADLs, that MCI patients may already show FS deficits which may be missed by subjective reports, and that performance-based measures of functional status may help identify patients at risk for cognitive decline beyond age-related changes. We hypothesize that a gradual reduction in DAFS-R illustrates the progressive functional changes that take place along the conversion from MCI to AD.

Conflict of interest

None.

Description of authors' roles

F. S. Pereira formulated the research questions and undertook data collection and the data analysis. M. S. Yassuda helped formulate the research questions and

the study design, and undertook data analyses. A. M. Oliveira was involved in the data collection, and O. V. Forlenza helped formulate the research questions and study design, and was involved in writing the paper.

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