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Memory and Executive Dysfunction Predict Complex Activities of Daily Living Impairment in Amnestic Multi-Domain Mild Cognitive Impairment

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Abstract.
Background: Specific cognitive alterations could be one of the predictors that lead to the complex activities of daily living (CADL) impairment in mild cognitive impairment (MCI) and, hence, help to explain the continuum between MCI and dementia.
Objective: We aimed to reevaluate the existing uncertainty regarding the impact of memory and executive functions on CADL in patients with MCI.
Methods: Caregivers of 161 patients with amnestic multi-domain MCI and of 150 patients with incipient Alzheimer's disease as well as 100 age-, sex-, and education-matched controls, completed the *Interview for Deterioration in Daily Living Activities in Dementia*, a suitable instrument for the description and discrimination of CADL. In addition, all patients and controls were assessed with a neuropsychological battery to measure explicit memory and executive functions performance.
Results: Multiple regression analyses showed that in the group of patients with amnestic multi-domain MCI, 67.4% of the variability of the CADL impairment was explained by worse performance on executive functions tests ($p < 0.0001$) and 41.8% by different explicit memory components impairment ($p < 0.0001$). Further, in patients with incipient AD, 44.0% of the variability of CADL impairment was explained by worse performance on executive functions tests ($p < 0.0001$) and 39.9% by different explicit memory components worsening ($p < 0.0001$).

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Conclusions: Memory and executive functions alterations impact similarly on the CADL in both amnestic multi-domain MCI and incipient Alzheimer's disease. Given the continuum that exists between both conditions, we conclude that CADL impairment may be an important early step in the evolution towards Alzheimer's disease from amnestic multi-domain MCI.

Keywords: Alzheimer's disease, amnestic multi-domain MCI, complex activities of daily living, executive functions, memory function

INTRODUCTION

Mild cognitive impairment (MCI) is a clinical entity that increases the risk of dementia [1]. There are different types of MCI, notably single-domain and multi-domain subtypes, showing the later a greater risk of evolution toward Alzheimer's disease (AD) than other subtypes [1]. Several studies have established that the border between MCI and AD should be based on whether the activities of daily living are affected or not [2, 3]. In contrast, although the simpler "normal" activities of daily living/instrumental activities of daily living are not affected, some researchers have highlighted that patients with MCI might seem to experience subtle changes in higher or "complex" instrumental activities of daily living [4, 5]. However, it is not well known, which predictors might explain decline in complex instrumental activities of daily living impairment in patients with MCI.

Only a few small studies have explored the relationship between cognitive functioning and complex activities of daily living (CADL) in mildly impaired subjects who may or may not qualify for a diagnosis of incipient dementia [6–13]. Some researchers have found that specific cognitive alterations could be one of the predictors that lead to the CADL impairment in MCI and, hence, help to explain the continuum between MCI and dementia [6–13]. Among the cognitive domains that might be predictors of alteration of some CADL in MCI are impairment of memory [14] and impairment in executive functions [7, 10–13].

We aimed to reevaluate the existing uncertainty regarding the impact of memory and executive functions on CADL in patients with MCI. Towards this purpose, we recruited a large sample of patients with amnestic multi-domain MCI and incipient AD with the aim to explain the functional alteration of the CADL through the memory and executive functions in MCI.

METHODS

Standard protocol approvals, registrations, and patient consents

All the participants included in the study gave their written informed consent after full explanation of the procedure. The study, which was conducted in accordance with the principles of the Helsinki declaration of 1975, was approved by the ethical standards committee on human experimentation at the Salamanca University Hospital (Salamanca). Written (signed) informed consent was obtained from all enrollees.

Participants

Patients with amnestic multi-domain MCI and incipient AD were consecutively recruited from September 2012 to January 2014 from the Memory and Dementing Disorders clinic at the Salamanca University Hospital in Salamanca (Spain), a public hospital, which covers an area of more than 300,000 inhabitants. One neurologist with expertise in dementing disorders (J.C.) examined these patients, with the aid of senior neuropsychologists (R.G.-G.-P). Diagnoses of dementia and MCI were assigned after a detailed clinical and mental status examination, using the Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV-TR criteria [15] and Winblad criteria [16], respectively. Amnestic multi-domain MCI was defined as impairment on at least 1.5 SD below normative expectations on a test of memory and at least one other cognitive domain impairment, according to Winblad criteria [16]. Patients with incipient AD (possible or probable AD) were diagnosed according to the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association diagnostic criteria [17], and had to score one (i.e., mild dementia) on the Clinical Dementia Rating [18]. Inclusion

criteria were: 1) 65 years and older at the time of the recruitment; 2) Spanish as maternal tongue; and 3) at least they should have primary studies. Patients with history of epilepsy, head injury, major psychiatric disorders or who were receiving medications with central nervous system effects (anxiolytics, stimulants, antipsychotics, antidepressants, antihistamines, or antiepileptics drugs) that could interfere with cognitive performance, were excluded.

Patients were 1 : 1 frequency matched with a group of controls. Frequency-matching was based on age, sex, and years of education. Controls were recruited among the patients who came to the neurological clinics for reasons other than cognitive problems (e.g., headache, dizziness). Each control underwent a standardized neurological examination performed by one neurologist (J.C.) with the aid of a senior neuropsychologist (R.G.-G.-P) to further rule out dementia using DSM–IV-TR criteria [15] or MCI, using Winblad criteria [16]. The exclusion criteria were the same as before.

Procedure

During recruitment, participants were told that the purpose of the study was to complete a testing battery to assess neuropsychological status. After the study had been described to participants, informed consent to participate was obtained. Clinical characteristics were obtained from review of records from their dementia neurological care or from their records (in the case of controls) with their consent.

All participants underwent an initial screening cognitive assessment and then a more detailed neuropsychological assessment covering the domains of memory and executive functions (see below).

Global cognitive performance was evaluated with the Spanish version of the Mini-Mental State Examination (MMSE) (higher scores indicate better cognitive performance) [19]. The clock drawing test was also performed on verbal command following these instructions: "I want you to draw a clock with all the numbers on it. Make it large and draw the hands at ten past eleven". The clock drawing test was scored on a 0–10 scale according to the criteria previously published by our group [20].

Explicit memory was evaluated with three tests. First, the Hopkins Verbal Learning Test, which consists of remembering a list of 12 words that the examiner reads to the participant through an immediate and delayed free recall, a memory with immediate and delayed semantic facilitation, and an acknowledgment [21]. Second, the subscale of memory of the Dementia Rating Scale-2 (DRS-2) [22]. Through different tasks, this subscale measures the memory by means of verbal and non-verbal items presented for the evaluation of aspects of orientation, delayed verbal free recall, verbal recognition, and immediate visual recognition [22]. Finally, the Rey-Osterrieth Complex Figure Test, which evaluates superior functions such as visual-spatial memory, was used [23]. The application of the test is divided into two moments [23]. The first test is characterized by requesting the copy of the figure [23]. The second test is characterized by requesting the reproduction of the memory figure, around 20 min after the second moment of memory reproduction [23].

Executive abilities were evaluated with a series of tests. First, participants underwent the Trail-Making Test (TMT), a measure of visuomotor coordination in which subjects must connect circles in one form (A) on the basis of a simple rule of consecutive numbers and, in the second form (B), by alternating between numerical and alphabetical sequences [24]. For both forms, A and B, time for completion was the primary index of performance. Second, the Stroop Color–Word Trial requires the participant to name the color of the ink in which a colored word is printed [25]. The task involves three test cards, one containing rows of colored rectangles, with the task being to name the colors as quickly as possible, one containing rows of color words (printed in black ink), with the task being to read the words as quickly as possible, and the third "interference" test consisting of rows of color words printed in ink colors incongruent with the word represented, with the task being to name the ink colors as quickly as possible [25]. The subject must ignore the word and name the color [25]. The score for this study was the interference effects. Third, participants were asked to name as many items as possible from a semantic category (animals) (semantic fluency) (lower scores indicate greater cognitive impairment) [26]. Fourth, the Controlled Oral Word Association Test (COWAT), a test that measures phonetic fluency, was administered [27]. Participants are provided three letters of the alphabet (F, A, and S), one letter at a time, and instructed to say as many words as possible that begin with this letter in a 60-s interval [27]. Higher scores indicate better cognitive performance [27]. Fifth, initiation and perseveration subscale of the DRS-2 was administered [22]. This subscale is composed of 11 tasks that determine the ability of the subject to initiate, exchange and finalize a specific task, in addition to verbal fluency.

Sixth, the conceptualization subscale of the DRS-2 was also administered [22]. This subscale consists of six scales that evaluate the capacity of abstraction of the subject to induce similarities and to detect differences between verbal and non-verbal stimuli. Finally, global attention subscale of the DRS-2 was administered [22]. This subscale measures attention through digit tasks directly and indirectly, complex orders and find the total of letters "A" that appear in two of the sheets presented [22].

Neuropsychiatric features were evaluated with the following tests. First, the first test was the Yesavage Depression Brief Scale (GDS) [28]. This self-administered scale was created with the purpose of being applied to elderly subjects with clinical suspicion of depression [28]. It consists of 15 items with a dichotomous response [28]. Second, the Geriatric Anxiety Inventory (GAI) which consists of a 20-item test, designed to assess anxiety in the elderly population [29] was administered. Finally, the Neuropsychiatric Inventory, a validated instrument for the clinical assessment of neuropsychiatric symptoms for dementia patients [30], was given.

Activities of daily living were evaluated with the following tests. The first was the interview for deterioration in daily living activities in dementia, which evaluates the functioning of a person in the activities of daily living from the information provided by a caregiver [31]. Second, the subscale of the CADL, which consists of 17 items that evaluate instrumental activities such as buying, paying for, and preparing food, among other areas [31], was administered. Finally, the informant's test (Informant Questionnaire On Cognitive Decline in the Elderly), one of the most widely used tests for evaluating dementia [32], was given.

Statistical analyses of clinical and neuropsychological data

To compare the baseline demographic and clinical characteristics of participants, analysis of variance, chi-square, or Fisher's exact test were used for quantitative and nominal variables, respectively. The neuropsychological variables were compared using Student's *t* or Mann-Whitney U tests for normal and non-normal variables, respectively. Normality was checked with Kolmogorov-Smirnov test and homogeneity of variances with the Levene test. Together with the p values for each test, Cohen's effect sizes were reported. Bonferroni correction for multiple comparisons was used to control for type I risk.

To assess the relationship between variables, multiple regression analyses were used. Global p-values, percentage of variance explained (R^2) and individual coefficients with their p-values were reported for each fitted model.

Statistical analyses were conducted using IBM-SPSS Version 21.0 (SPSS, IBM Corporation).

Data availability

Anonymized data will be shared by request from any qualified investigator, only for purposes of replicating procedures and results.

RESULTS

Baseline characteristics of the participants are shown in Table 1. The patients with amnestic multi-domain MCI did not differ to a significant degree from those with incipient AD or controls in terms of age, sex, educational level, and comorbidities (Table 1).

Compared with controls, CADL impairment in both patients with amnestic multi-domain MCI and with incipient AD was associated with worse performance on tests that measured executive functions and explicit memory. Specifically, multiple regression analyses showed that in the group of patients with amnestic multi-domain MCI, 67.4% of the variability of the CADL impairment was explained by worse performance on executive functions tests ($p < 0.0001$) and 41.8% by different explicit memory components (audio-verbal episodic memory, pictorial memory, and global memory) impairment ($p < 0.0001$). Further, in patients with incipient AD, 44.0% of the variability of CADL impairment was explained by worse performance on executive functions tests ($p < 0.0001$) and 39.9% by different explicit memory components worsening ($p < 0.0001$) (Table 2).

Table 3 shows the results of multiple regression analyses examining relationships between predictive variables (components of the explicit memory and of the executive functions) and the criterion variable (CADL), in patients with amnestic multi-domain MCI and incipient AD.

For the model relating CADL to explicit memory in patients with amnestic multi-domain MCI, the significant coefficients were the associated to the variables: delayed free memory ($p = 0.015$), immediate cued-semantic ($p = 0.002$), and delayed cued-semantic ($p = 0.038$), meaning that those variables had an important role in explaining the relation to the response. The variable quantitative pictorial memory,

Table 1
Baseline demographic and clinical characteristics of participants

	Controls (N = 100)	Patients with amnestic multi-domain MCI (N = 161)	Patients with incipient AD (N = 150)	*p*
Age in years	75.66 ± 6.511	76.27 ± 8.171	77.23 ± 7.102	0.199[a]
Sex (women)	60 (60.0%)	92 (57.4%)	106 (70.7%)	0.062[b]
Educational level				
Primary school	58 (58.0%)	90 (55.9%)	79 (52.7%)	0.481[b]
Secondary studies	37 (37.0%)	62 (38.5%)	64 (42.7%)	
University studies	5 (5.0%)	9 (5.6%)	7 (4.6%)	
Current smoker	8 (8.0%)	19 (11.5%)	21 (14.0%)	0.205[b]
Alcoholism	3 (3.0%)	3 (1.8%)	7 (4.6%)	0.365[b]
Arterial hypertension	53 (53.0%)	76 (47.0%)	74 (49.0%)	0.439[b]
Diabetes mellitus	15 (15.0%)	23 (14.2%)	23 (15.3%)	0.973[b]
Stroke	1 (1.0%)	9 (5.6%)	9 (6.0%)	0.491[b]
Heart disease	17 (17.0%)	27 (16.7%)	18 (12.0%)	0.608[b]

[a]Analysis of variance; [b]Chi-square or Fisher's exact test. Mean ± standard deviation and frequency (%) are reported. MCI, mild cognitive impairment; AD, Alzheimer's disease.

Table 2
Relation and prediction of the explicit memory and executive functions on the complex activities of daily living in patients with amnestic multi-domain mild cognitive impairment (MCI) and incipient Alzheimer's disease (AD)

	EXECUTIVE FUNCTIONS		EXPLICIT MEMORY	
	Amnestic multi-domain MCI	Incipient AD	Amnestic multi-domain MCI	Incipient AD
R square	0.674	0.440	0.418	0.399
Degrees of freedom	8/161	8/157	6/220	6/224
F value	32.060	26.082	20.769	23.544
p value	<0.0001	0.0001	<0.0001	<0.0001

although it was non-significant using the standard criteria, showed some evidence of an important part of the explanation of the response ($p = 0.055$). The variables immediate free memory ($p = 0.314$) and global memory ($p = 0.655$) were non-significant. All the significant coefficients were negative, meaning that higher values of the response (CADL) corresponded to lower values of the different explicit memory variables, as expected.

For the model relating CADL to executive functions in patients with amnestic multi-domain MCI, the significant coefficients were the associated to the variables: initiation and perseveration ($p = 0.004$) and processing speed ($p = 0.024$). The coefficient for the first was also negative as before, but the second was positive, meaning that higher values of processing speed corresponded to higher values of the response.

The model used to study the relationship between CADL to explicit memory in patients with incipient AD, showed only one significant coefficient corresponding to the variable delayed cued-semantic ($p < 0.0001$), also with a negative coefficient.

Finally, the model relating CADL to executive functions in patients with incipient AD had four significant variables: inhibitory control ($p = 0.040$), phonetic verbal fluency (0.039), initiation and perseveration ($p < 0.0001$), and processing speed ($p = 0.022$). The three first coefficients were negative and the last positive, as before.

Table 4 shows the Cohen's d effect size of most important domains in amnestic multi-domain MCI and incipient AD patients compared to the control group. Notice that Cohen's d effect size in the initiation and perseveration became from small to large in patients with amnestic multi-domain MCI and incipient AD. In the remainder of significant components, the effect size was large in both conditions. The only significant subtest that allowed us to differentiate both conditions was the initiation and perseveration of the DRS-2.

DISCUSSION

In the current study, CADL impairment in both patients with amnestic multi-domain MCI and patients with incipient AD were associated firstly by involvement of different components of executive function and secondly by involvement of explicit memory. The most common components in executive

Table 3
Multiple regression analyses examining relationships between predictive variables (components of the explicit memory and of the executive functions) and the criterion variable (complex activities of daily living), in patients with amnestic multi-domain mild cognitive impairment (MCI) and incipient Alzheimer's disease (AD)

	EXPLICIT MEMORY							
	Amnestic multi-domain MCI ($N = 161$) Coefficients				Incipient AD ($N = 150$) Coefficients			
	B	Standard error	T	*p*	B	Standard error	T	*p*
Audioverbal episodic memory								
Hopkins Verbal Learning Test-Revised								
Immediate free memory	0.018	0.128	–0.138	0.314	–0.003	0.006	–0.500	0.617
Delayed free memory	0.040	0.312	–0.127	**0.015**	0.007	0.012	0.589	0.557
Immediate cued-semantic	**–0.807**	**0.403**	**–2.00**	**0.002**	0.015	0.016	0.935	0.351
Delayed cued-semantic	**–0.794**	**0.379**	**–2.094**	**0.038**	**–0.084**	**0.015**	**–5.724**	**<0.0001**
Global Memory								
Dementia Rating Scale-2	–0.036	0.054	–6.54	0.655	–0.006	0.005	–1.087	0.278
Quantitative pictorial memory								
Rey-Osterrieth Complex Figure Test	–0.281	0.145	–1.934	0.055	–0.005	0.003	–1.494	0.136
	EXECUTIVE FUNCTIONS							
Global attention								
Dementia Rating Scale-attention	0.067	0.096	0.697	0.487	0.376	0.137	2.741	0.228
Inhibitory control								
Stroop Color–Word Trial	–0.094	0.050	–1.874	0.063	**–0.100**	**0.048**	**–2.069**	**0.040**
Mental flexibility								
Trail Making Test-B	0.002	0.004	0.594	0.553	0.003	0.003	0.821	0.473
Phonetic verbal fluency								
Controlled Oral Word Association Test Test	–0.113	0.070	–1.617	0.108	**–0.137**	**0.066**	**–2.085**	**0.039**
Semantic verbal fluence								
Animals	–0.199	0.135	–1.478	0.141	–0.008	0.005	–1.477	0.169
Initiation and perseveration								
Dementia Rating Scale-2	**–0.533**	**0.181**	**–2.939**	**0.004**	**–0.389**	**0.093**	**–4.208**	**<0.0001**
Conceptualization								
Dementia Rating Scale-2	–0.091	0.174	–0.522	0.602	–0.041	0.161	–0.258	0.963
Processing speed								
Trail Making Test-A	**0.023**	**0.010**	**2.281**	**0.024**	**0.026**	**0.005**	**5.330**	**0.022**

Significant values are in bold font. *Adjusted for age, sex, and years of education.

Table 4
Cohen's d effect size. T and *p* value of the most decisive domains in amnestic multi-domain mild cognitive impairment (MCI) and incipient Alzheimer's disease (AD) patients compared with respect to the control group

	Amnestic multi-domain MCI			Incipient AD		
	T	*p*	Effect size	T	*p*	Effect size
AUDIOVERBAL EPISODIC MEMORY						
Immediate cued-semantic	1.04	<0.001*	10.46	11.163	<0.001*	1.36
Delayed cued-semantic	–1.615	<0.001*	12.02	19.115	<0.001*	1.61
EXECUTIVE FUNCTIONS						
Initiation and perseveration						
Dementia Rating Scale-2	–0.35	<0.001*	2.576	13.783	<0.001*	1.69
Processing speed						
Trail Making Test-A	–1.13	<0.001*	9.520	–8.672	<0.001*	–1.13

*Significant using Bonferroni correction.

functions in both groups were initiation and perseveration of the DRS-2 and the processing speed of TMT-A. In explicit memory, common components in both groups were delayed cued-semantic in audioverbal explicit memory.

In patients with incipient AD, cognitive impairments, especially those related with memory and executive functions, can cause an inability to carry out some activities of daily living. In incipient AD, the most affected activities of daily living are the

CADL, while basic activities of daily living tend to remain preserved until more severe stages of AD [8, 11, 13, 33–37]. Hence, there is a clear relationship between cognition and function in patients with incipient AD [38]. However, few studies have examined this relationship in MCI. One study found in multi-domain MCI only one executive function component, working memory, which contributed significantly to functional status after controlling for demographic, health-related, and other cognitive factors [39]. A second study found executive impairment correlated with basic, instrumental, and advanced activities of daily living [40].

In our study, 44.0% of impairment in CADL in patients with incipient AD would be explained by the alteration in executive functions and 39.9% by the alteration in explicit memory. Similarly, in patients with amnestic multi-domain MCI, 67.4% of impairment in CADL would be explained by alteration in executive functions and in a 41.8% by alteration in explicit memory.

Better performance in executive functions and memory tests in patients with amnestic multi-domain MCI was associated with less impairment in CADL. Conversely, those who showed a greater alteration of those cognitive domains, had a greater impairment of CADL. Although our research is descriptive, we feel that our findings may help clarify who is at high risk to develop AD among patients with amnestic multi-domain MCI as previously observed by other independent groups [10, 41, 42]. Executive dysfunction, together with memory impairment, in multi-domain MCI and incipient AD, are indicators of decline in early stages of cognitive impairment [43–45].

Regarding the relationship between explicit memory and CADL impairment, the significant component in the multiple regression model was the difference on means in audio-verbal episodic memory, both in patients with amnestic multi-domain MCI and incipient AD. Hence, the assessment of explicit audio-verbal episodic memory, with semantic delayed facilitation, would be a recommended clinical tool to clarify the relationship between memory impairment and impairment of CADL [46].

With respect to executive functions, the cognitive tests, which were significant in the multiple regression analyses of both groups of patients, were the initiation and perseveration subscale of the DRS-2 and the TMT-A test (processing speed). These findings are in agreement with those previously reported by Brown et al. [47] who found that the common deficits in MCI and AD were associated with a worse score in the TMT-A test.

The study was not without limitations. First, the design was cross-sectional, not longitudinal. Second, the diagnosis of AD was based on clinical criteria. It would have been useful to have confirmed the diagnosis by analyzing the cerebrospinal fluid with established biomarkers like amyloid-beta protein, tau protein, and phospho-tau expression levels. We also acknowledge that TMT-A is not always considered a measure of executive functions, as it measures aspects of attention, visuospatial tracking scanning, motor coordination, and speed, but, nevertheless, we included it as it has been associated with activities of daily living in MCI in a previous study [40].

In summary, we found a clear relationship between cognitive function, especially memory and executive function, and CADL impairment in incipient AD. This relationship has also been observed in patients with amnestic multi-domain MCI. Given the continuum between MCI and AD, we conclude that CADL impairment may be a clinical indicator of impending progression of amnestic multi-domain MCI to AD.

DISCLOSURE STATEMENT

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-1263r1).

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