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Cognitive Changes in Mild Cognitive Impairment Patients With Impaired Visual Recognition Memory

Francesca De Anna
CHU Timone, Assistance Publique Hôpitaux de Marseille, Marseille, France

Olivier Felician
CHU Timone, Assistance Publique Hôpitaux de Marseille, Marseille, France, and Institut des Neurosciences des Systèmes, Aix-Marseille Université

Emmanuel Barbeau
Université Toulouse III, Paul Sabatier

Julien Mancini
CHU Timone, Assistance Publique Hôpitaux de Marseille, Marseille, France, and Aix-Marseille Université

Mira Didic and Mathieu Ceccaldi
CHU Timone, Assistance Publique Hôpitaux de Marseille, Marseille, France, and Institut des Neurosciences des Systèmes, Aix-Marseille Université

Objective: This study aims to evaluate whether assessing memory using the visual recognition memory task DMS48 in amnestic mild cognitive impairment (aMCI) can contribute to the early diagnosis of Alzheimer's disease (AD). In an 18-month follow-up study, we assessed if longitudinal change in aMCI patients who failed on the DMS48 differs from that of patients who succeeded on this task at baseline. ***Method:*** Twenty-six controls and 33 aMCI patients underwent a complete neuropsychological assessment at baseline and at an 18-month follow-up. Patients were divided into two subgroups, according to their *z* score on the DMS48 (DMS48+ subgroup succeeding; DMS48– subgroup failing on the task). In order to detect sensitive longitudinal change over time, we calculated and compared the standardized response mean (SRM) of performance on neuropsychological tasks in the three groups. ***Results:*** We found significant differences for the mean SRM of all neuropsychological tests when comparing DMS48+ vs. controls vs. DMS48–, which was greatest for the comparison between the DMS48– and the DMS48+ subgroup. Although cognitive profiles of the two patient subgroups at baseline did not differ in cognitive domains other than memory, we found a consistent decline on all neuropsychological tasks in the DMS48– subgroup compared with the DMS48+ subgroup, except for performance on a verbal fluency test. ***Conclusions:*** As the cognitive profile of the DMS48– subgroup at follow-up resembles the typical pattern of AD described in the literature, this study confirms that visual recognition memory tasks may be useful to anticipate covert cognitive decline in aMCI patients.

Keywords: mild cognitive impairment, cognitive decline, longitudinal study, memory, DMS48

Potential diagnostic tools for the early identification of Alzheimer's disease (AD) include markers such as neuroimaging (positron emission tomography (PET), structural magnetic resonance imaging (MRI)) and cerebrospinal fluid (CSF) biomarkers (Jack et

Francesca De Anna, Service de neurologie et neuropsychologie, Pôle de Neurosciences Cliniques, CHU Timone and Assistance Publique Hôpitaux de Marseille, Marseille, France; Olivier Felician, Service de neurologie et neuropsychologie, Pôle de Neurosciences Cliniques, CHU Timone, Assistance Publique Hôpitaux de Marseille and Institut des Neurosciences des Systèmes, Aix-Marseille Université, Faculté de Médecine de Marseille, France; Emmanuel Barbeau, Université Toulouse III, Paul Sabatier, Centre de Recherche Cerveau & Cognition (Cerco), Centre National de la Recherche Scientifique/Unité Mixte de Recherche, Toulouse, France; Julien Mancini, Aix-Marseille Université, Sciences Economiques & Sociales de la Santé et Traitement de l'Information Médicale, Faculté de Médecine, Marseille, France and Service de Santé Publique et d'Information Médicale, CHU Timone, Assistance Publique Hôpitaux de Marseille; Mira Didic, Service de neurologie et neuropsychologie, Pôle de Neurosciences Cliniques, CHU Timone, Assistance Publique Hôpitaux de Marseille and Institut des Neurosciences des Systèmes, Aix-Marseille Université, Faculté de Médecine de Marseille; Mathieu Ceccaldi, Service de neurologie et neuropsychologie, Pôle de Neurosciences Cliniques, CHU Timone, Assistance Publique Hôpitaux de Marseille and Institut des Neurosciences des Systèmes, Aix-Marseille Université, Faculté de Médecine de Marseille, Marseille, France.

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Correspondence concerning this article should be addressed to Francesca De Anna, Centre Hospitalier Universitaire de la Timone, Service de neurologie et neuropsychologie, 264, rue Saint Pierre, 13385, Marseille Cedex 5, France. E-mail: francesca.deanna@ap-hm.fr

al., 2010). Although these techniques contribute to the identification of AD in patients with mild cognitive impairment (MCI), one study found that performance on memory tasks has a higher predictive value in the diagnosis of AD in patients with MCI than CSF biomarkers, hippocampal volume on MRI, or hypometabolism on fluorodeoxyglucose (FDG)-PET (Landau et al., 2010). However, which aspect of memory ought to be assessed, and the optimal neuropsychological tools that could contribute to identifying AD in the predementia stage, remains to be determined (Nestor, Scheltens, & Hodges, 2004). Studies that focus on cognitive changes during the prodromal stage suggest that a subtle decline in episodic memory in older adults is a sign of development of underlying AD pathological changes (see Bäckman, Jones, Berger, Laukka, & Small, 2005, Collie & Maruff, 2000, and Smith et al., 2007, for an overview).

In order to identify cognitive decline prior to overt clinical dementia, the concept of MCI was introduced over 10 years ago (Petersen et al., 2001). Patients with MCI are at high risk of future dementia of the AD type (DAT; Morris et al., 2001; Petersen et al., 2001). This is particularly true for the clinical subtype of amnestic MCI (aMCI), defined as progressive memory impairment in subjects with normal activities of daily living (Bondi et al., 2008; Petersen et al., 2001; Stoub, Rogalski, Leurgans, Bennett, & DeToledo-Morrell, 2010). However, not all patients with aMCI will develop AD dementia, as some remain stable, whereas others improve their cognitive performances at follow-up (Palmer, Wang, Bäckman, Winblad, Fratiglioni, 2002; Ritchie, Artero, & Touchon, 2001). It is therefore crucial to develop new neuropsychological approaches of aMCI to improve the prediction of possible subsequent decline.

Neuropathological studies provide evidence that the anterior subhippocampal region (transentorhinal, entorhinal, and perirhinal cortex) is the earliest site of tangle deposition in the most common form of AD, later followed by the hippocampus, and then the frontal, temporal, and parietal neocortices, as the disease progresses (Braak & Braak, 1991; Delacourte et al., 1999). There is also evidence that subhippocampal structures are critical for successful performance on visual recognition memory tasks (Barbeau, Pariente, Felician, & Puel, 2011; Meunier, Bachevalier, Mishkin, & Murray, 1993). Our group therefore designed the DMS48 (delayed matching to sample 48 items), a neuropsychological visual recognition memory test that detects dysfunction of the subhippocampal region (Barbeau et al., 2004, 2008; Didic et al., 2010; Guedj et al., 2006). Performance on this task has also been found to positively correlate with functional connectivity within an anterior temporal network that includes the subhippocampal region and extends to the anterior temporal lobe (Gour et al., 2011). However, whether patients who fail or succeed on the DMS48 at baseline may present different neuropsychological features on longitudinal follow-up remains an unsolved issue.

In this study, we evaluated cognitive profiles in aMCI patients with an isolated memory impairment, also referred to as single-domain aMCI (Petersen et al., 2001; Winblad et al., 2004), longitudinally, depending on the performance on the DMS48 at baseline. The aim of this study was to evaluate whether assessing memory using a visual recognition memory task can contribute to the early diagnosis of AD. In particular, we tried to determine if there were differences on longitudinal follow-up between aMCI patients who failed or succeeded on the DMS48 at baseline. Our hypothesis was that the subgroup of patients who failed on the DMS48 at baseline would develop cognitive changes usually found in early AD by the 18-month follow-up. Because the focus in this study is on memory impairment, we also analyzed the type of memory profile of each aMCI subgroup.

Method

Subjects

The institutional ethic committee (Comité Consultatif de Protection des Personnes pour la Recherche Biomedicale) approved this study. Patients and control subjects signed informed consent.

At baseline, 26 control subjects, with normal cognitive functions and no history of mental and neurological disorder, and 33 patients meeting criteria for aMCI (Petersen et al., 2001; Winblad et al., 2004) were included. Patients were included if their performance was 1.5 standard deviations below the mean of control subjects on delayed free recall of these verbal memory tasks (Petersen et al., 2001). For this study, we included patients with impaired performance on either the Free and Cued Selective Reminding Test (Ergis, Van der Linden, & Deweer, 1994; Grober, Buschke, Crystal, Bang, & Dresner, 1988) or the Logical Memory subtest of the Wechsler Memory Scale (WMS-III; Wechsler, 2001). Patients with an objective deficit in one or more other cognitive domains were excluded (Winblad et al., 2004). Brain imaging, blood screening, psychiatric interview, and physical examination excluded patients with a memory disorder related to nondegenerative diseases. In order to assess daily functioning, we used the Instrumental Activities of Daily Living. The four-item version was used, evaluating the ability to use a telephone, use transportation, handle medication, and manage finances independently (Barberger-Gateau, Dartigues, & Letenneur, 1993).

All patients and control subjects underwent a complete neuropsychological assessment at baseline. The participants then completed neuropsychological tests at 18 months follow-up. Each time, the patients and control subjects underwent the same procedure: a neurological examination, a complete neuropsychological assessment, and neuroimaging investigations. Here, we analyzed the performances between the baseline and the first 18 months follow-up.

Patients with aMCI were divided into two subgroups, according to their z score on delayed recognition on the DMS48 (Barbeau et al., 2004). We chose a cutoff of -1.5 standard deviations below mean performance of controls in order to separate the subgroups, as this cutoff had been used in previous clinical and neuroimaging studies from our group (Barbeau et al., 2004, 2008; Didic et al., 2010; Guedj et al., 2006). Fifteen patients obtained a z score above -1.5 (DMS48+ subgroup) and 18 obtained a z score below -1.5 (DMS48− subgroup).

Each subject's performance was expressed as a percentage of correct answers (level of chance, 50%; correct recognition of all targets, 100%). All controls had z scores above -1.5. Demographic features of control subjects and patients are provided in Table 1.

Table 1
Demographical Data of Controls, the DMS48+ Subgroup, and the DMS48– Subgroup

	Controls	DMS48+ subgroup	DMS48–subgroup
n	26	15	18
Women/men	12 F/14 M	7 F/8 M	7 F/11 M
Age in years	65.7 (7.4)	72.06 (7)[a]	67.5 (7.1)
Years of education	11.6 (3.1)	12.4 (4.3)	12 (4.5)

Note. Age in years and years of education reported as means and standard deviations. DMS48+ subgroup = patients with normal performance on the DMS48; DMS4– subgroup = patients with impaired performance on the DMS48; F = female; M = male.
[a] $p < .05$ between control subjects and the DMS48+ subgroup.

The DMS48

The DMS48 is a test of visual recognition memory described in detail elsewhere (Barbeau et al., 2004).[1] In the DMS48, stimuli consist of colored drawings divided into three types of items: (a) abstract items, for which targets and distractors are abstract patterns that cannot be verbalized; (b) paired items, for which targets and distractors are concrete objects belonging to the same semantic category with similar shape, color, and name to prevent the use of verbal strategies; and (c) unique items, for which targets and distractors are dissimilar concrete objects. During the encoding phase, all subjects were asked to consecutively look at 48 pictures and to say whether they contained more or less than three colors. This was followed by a 2-min verbal fluency interfering task. Immediate recognition was completed using 48 distractors (Set 1). Each target was shown simultaneously with a distractor, presented in equal proportion on either the left or the right side of the sheet, and the subject was asked to identify the target, using forced-choice recognition. Without prior warning, delayed recognition was assessed 1 hr later with a different set of distractors (Set 2). Half of the targets were displaced from the left to the right side of the sheet, and vice versa, between Sets 1 and 2. In this study, most results are discussed in reference to Set 2, as we were mainly interested in studying delayed recognition.

Neuropsychological Assessment

The neuropsychological tasks used assessed six cognitive domains. For each domain, the following specific neuropsychological tests were chosen to assess evolution over the follow-up period:

Global cognitive ability: (a) the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975); and (b) the *Echelle d'Intensité de Plainte Mnesique* [Intensity Scale of Memory Complaint], a 10-item scale developed in our laboratory, with a maximum score of 30 points.

Anterograde memory: (a) the Free and Cued Selective Reminding Test (Ergis et al., 1994; Grober et al., 1988), which consists of controlled learning of 16 words, followed by a test phase of three free and cued recall trials, and by one free and cued delayed recall; and (b) the Logical Memory subtest of the WMS-III (Wechsler, 2001), in which two stories are read to the subject, followed by immediate and delayed free recall.

Retrograde memory: (a) the Short-EVE test (Thomas-Antérion, Collomb, Borg, Nevers, & Laurent, 2006), which is a questionnaire that assesses knowledge about 10 public events; for each event, the questionnaire includes a free recall, multiple choice questions, and two closed questions, with a total maximum score of 60 (10 events × 6 points); and (b) the Didactic Acquisition Questionnaire (DAQ; Barbeau et al., 2012), which was designed in our laboratory in order to assess basic knowledge about historical French facts learned in primary and secondary school (therefore during childhood and adolescence); the questionnaire consisted of 20 questions, with a total maximum score of 20.

Executive functions: (a) the Trail Making Test Form B (Allain, Aubin, & Le Gall, 2006; Reitan, 1958); and (b) the verbal fluency with the letter "P" in 2 min (Cardebat, Doyon, Puel, Goulet, & Joanette, 1990).

Naming: the DO80 Naming Test (Deloche & Hannequin, 1997).

Visuospatial skills: the Judgment of Line Orientation Test (Benton, Hamsher, Varney, & Spreen, 1983).

Using the Free and Cued Selective Reminding Test, several scores can be derived (Ergis et al., 1994; Grober et al., 1988), including an intrusion score (number of intrusions made during the first three free recalls), a cueing efficiency score (calculated by the score of free recall – total recall)/(free recall–48) and a recognition score (using the recognition subtest of the Free and Cued Selective Reminding Test (FCSRT), which consists of recognizing, using a yes–no procedure, the 16 words that have been repeatedly learned [targets] among 32 distractors).

Statistical Analysis

An ANCOVA adjusted for age was used to compare demographic data.

In order to detect longitudinal changes over time, we calculated the standardized response mean (SRM; Norman, Wyrwich, & Patrick, 2007). By dividing the mean change by the standard deviation of the change scores, this score assesses differences between baseline and follow-up in neuropsychological tests:

$$\mathrm{SRM} = \frac{(\overline{X}_{\mathrm{post}} - \overline{X}_{\mathrm{pre}})}{SD_{\mathrm{change}}} = \frac{(\overline{X}_{\mathrm{post}} - \overline{X}_{\mathrm{pre}})}{\sqrt{\sigma^2_{p\times T} + 2\sigma^2_e}} \quad (1)$$

where $\overline{X}_{\mathrm{post}}$ is the posttest mean performance, and $\overline{X}_{\mathrm{pre}}$ is the pretest mean performance. The denominator (SD_{change}) includes the error variance multiplied by 2 ($2\sigma^2_e$), and the error variance with Patient × Treatment interaction ($\sigma^2_{p\times T}$).

One of the advantages of the SRM is that it allows a comparison of tests with different scales. Usually an SRM >0.8 is considered large, 0.5 to 0.8 is considered moderate, and 0.2 to 0.5 is considered small (Norman et al., 2007). For anterograde and retrograde memory tests,

[1] The DMS48 is downloadable for research purposes from http://www.cerco.ups-tlse.fr/~DMS48.

we chose the score that referred to the delayed recall. For other tests, we chose the score that referred to the main variable.

The first analysis was conducted in order to compare longitudinal changes of the performance averaged for all neuropsychological tests (except the DMS48) between the three groups (DMS48+, DMS48–, and control subjects) using, first, a Kruskal-Wallis one-way ANOVA; a Mann–Whitney test was then used to compare the groups. A Bonferroni correction for multiple comparisons was applied.

In order to compare the neuropsychological performance of the three groups (control subjects, the DMS48+ patient subgroup, and the DMS48– patient subgroup) at baseline and at 18 months follow-up, we used ANCOVA, systematically adjusted for age. When examining pairwise differences between groups, Bonferroni correction was used. Concerning the cognitive tasks that were not completed by controls, we used published normative data in order to establish whether the performance of patients was within normal limits.

Results

Figure 1 shows the mean SRM across all neuropsychological tests for each group. There was a significant difference between groups using the Kruskal-Wallis test ($H = 16.01$, $p < .001$). Further analyses, using Mann–Whitney tests corrected for multiple comparisons, showed significant differences between the DMS48+ and the control group ($z = 2.66$, $p < .05$), the DMS48– and the control group ($z = 3.2$, $p < .005$), and, most importantly, between the DMS48– and the DMS48+ group ($z = 2.61$, $p < .05$).

Three patients (9%) converted to AD at 18 months follow-up. It is of note that these three patients belonged to the subgroup that failed the DMS48.

Figure 2 provides the SRM for each test. We found a consistent decline over time in the DMS48– group compared with the DMS48+ group. The performance for some of the tests increased over the follow-up period for the DMS48+ group, but this was not the case for the DMS48– group. Moreover, performance in the DMS48– group, compared with the DMS48+ group, decreased on all neuropsychological tasks, except for performance on a fluency test (the letter "P").

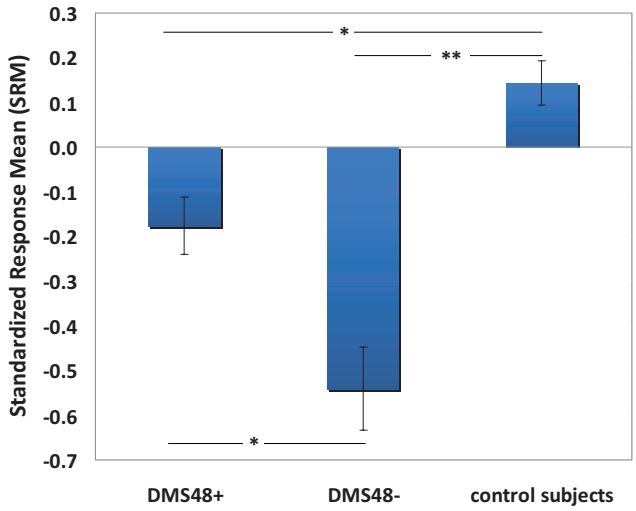

Figure 1. Mean standardized response mean (SRM) across all tests for the three groups. Negative values indicate that the mean performance decreases, for the same tests, within the 18-month period of follow-up. Positive values in the control group indicate that the mean performance increases during follow-up, probably driven by the test–retest effect. Vertical lines indicate the standard error of the mean. * $p < 0.05$; ** $p < 0.005$; all *p*s corrected for multiple comparisons.

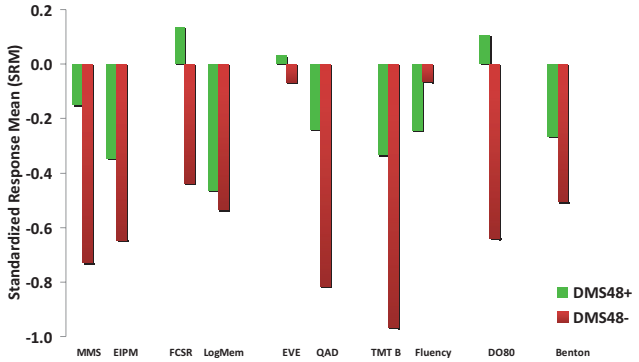

Figure 2. Standardized response mean (SRM) on each of the neuropsychological tests for DMS48+ and DMS48– groups. The performance for some of the tests increases over the follow-up period for the DMS48+ group. Performance always decreases for the DMS48– group and, furthermore, always worsens compared with the DMS48+ group, except for the fluency test (letter "P").

Table 2 shows performance on tasks assessing memory, the FCSRT and the logical memory subtest (WMS-III), which contribute to the characterization of the nature of the memory impairment found in both groups of aMCI patients compared with controls. The DMS48– group was impaired relative to the DMS48+ group on the number of intrusions performed during free recall, the efficiency of cueing, and the recognition subtest. Compared with controls, the DMS48+ group was not impaired.

Table 3 shows performance on the global cognitive assessment, tasks assessing semantic knowledge, executive function, naming, and visuospatial skills. The cognitive profile of the two patient subgroups at baseline did not differ in cognitive domains other than memory.

Discussion

When separated into two subgroups, aMCI patients with impaired visual recognition memory on the DMS48 at baseline (the DMS48– group) showed neuropsychological decline over the 18 months of the follow-up period. Most notably, the performance of this subgroup showed significantly more decline than the group of aMCI patients with preserved visual recognition memory (the DMS48+ group). Moreover, in the DMS48– group, longitudinal decline was found in multiple cognitive domains and was significantly more severe for each test of the assessment than in the DMS48+ group, with the exception of performance on a fluency test. Increased cognitive decline in a group of patients with aMCI failing on a visual recognition memory test over a period of 18 months may thus indicate enhanced risk of AD in this group.

Assessing Visual Recognition Memory in aMCI

The presence of cognitive decline at the 18-month follow-up, found in patients who failed on the DMS48 at baseline, confirms

Table 2
Comparison of Controls, the DMS48+, and the DMS48– Subgroups for Tests Assessing Memory at Baseline and Follow-Up

Assessment of memory	Baseline			Follow-up		
	aMCI subgroup DMS48+	aMCI subgroup DMS48–	Controls	aMCI subgroup DMS48+	aMCI subgroup DMS48–	Controls
Delayed free recall of a word list (FCSRT, max = 16)	6 (2.50)[a]	4.22 (3.33)[b]	12.96 (1.81)[ab]	6.27 (4.18)[ac]	3.56 (4.51)[bc]	12.80 (1.68)[ab]
Delayed total recall of a word list (FCSRT, max = 16)	14 (2.33)[c]	11.06 (3.93)[bc]	15.60 (1.04)[b]	14.20 (2.80)[c]	9.11 (5.86)[bc]	15.84 (0.37)[b]
Cueing efficiency (FCSRT, max = 100%)	75.74 (20.48[c]	64.04 (18.16)[bc]	87.52 (13.02)[b]	81.88 (14.70)[c]	48.41 (25.63)[bc]	89.22 (11.77)[b]
Intrusions during recall (FCSRT)	2.87 (2.85)[c]	9.35 (8.50)[bc]	0.92 (1.24)[b]	3.13 (2.58)[c]	9.17 (8.26)[bc]	1.42 (1.81)[b]
Immediate recall of Logical Memory test	8.47 (2.8)	7.28 (3.21)		8.27 (2.52)	6.67 (3.41)	
Delayed recall of Logical Memory test	8.27 (3.55)	6.33 (3.89)		7.13 (3.20)	4.27 (4.05)	

Note. Results are reported as means and standard deviations. Statistically significant results after Bonferroni's correction are denoted with lowercase letters. For the Logical Memory subtest, which was not completed by controls, we used published normative data in order to establish if the performance of patients was within normal limits. DMS48+ subgroup = patients with normal performance on the DMS48; DMS48– subgroup = patients with impaired performance on the DMS48; FCSRT = Free and Cued Selective Reminding Test.
[a] $p < .05$ between control subjects and the DMS48+ subgroup. [b] $p < .05$ between controls and the DMS48– subgroups. [c] $p < .05$ between aMCI subgroups.

and extends previous proposals that the assessment of visual recognition memory may be useful in the early detection of future AD in MCI patients (Didic et al., 2011; see Ally, 2012, for a review). Concerning neuropsychological features, a previous study using the DMS48 found that patients who failed on this task displayed clinical features of early AD, with reduced delayed free recall and cueing efficiency on the Free and Cued Selective Reminding Test (Barbeau et al., 2004). This is consistent with another study that used the Doors and People Test, reporting that recall and recognition processes were equally impaired in a group of patients with early AD (Baddeley, Emslie, & Nimmo-Smith, 1994). In addition, performance on a task assessing recognition memory was one of the four predictors of decline in MCI patients in one of the pioneering studies on MCI (Flicker, Ferris, & Reisberg, 1991). A more recent study found that impaired visual recognition memory, combined with decreased Single-photon emission computed tomography (SPECT) perfusion in the medial posterior cingulate, as well as left frontal, temporal, and parietal regions, provides a potential measure to differentiate between MCI, AD patients, and normal aging in patients with 2-year follow-up (Alegret et al., 2012). However, the assessment of recognition memory in patients with MCI, using an experimental matching-to-sample task, based

Table 3
Comparison of Controls, the DMS48+, and the DMS48– Subgroups for Neuropsychological Tests at Baseline and Follow-Up

	Baseline			Follow-up		
	aMCI subgroup DMS48+	aMCI subgroup DMS48–	Controls	aMCI subgroup DMS48 +	aMCI subgroup DMS48–	Controls
Global cognitive assessment						
MMSE	27.7 (1.64)[a]	27.33 (1.22)[b]	28.80 (1.11)[ab]	26.80 (2.67)[a]	25.62 (2.54)[b]	29 (1.04)[ab]
EIPM	15.4 (4.8)[a]	17 (3.13)[b]	4.17 (2.86)[ab]	13.73 (4.25)[a]	14.46 (4.57)[b]	4.29 (4.32)[ab]
IADL	0 (0)	0 (0)	0 (0)	0.05 (0.23)	0.43 (0.75)	0 (0)
Semantic knowledge						
Total recall Short-EVE Test	29.79 (11.11)[a]	25.67 (8.47)[b]	44.80 (10.22)[ab]	29.93 (9.87)[ac]	25.25 (8.74)[bc]	46 (9.91)[ab]
DAQ	12 (4.5)	12.8 (4.8)[b]	16.96 (4.68)[b]	11.42 (4.59)[a]	11.11 (4.61)[b]	16.64 (4.24)[ab]
Verbal skills						
Verbal fluency "P" in 2 min	19.40 (4.5)[a]	17.28 (6.99)[b]	26.88 (7.34)[ab]	18 (5.64)[a]	16.94 (6.87)[b]	27.96 (7.23)[ab]
Executive functions						
Trail Making Test (form B)	123.71 (53.7)	129.72 (70)				
Naming skills						
Naming Test (DO80)	79.07 (1.62)	79.50 (1.15)				
Visuospatial skills						
Judgment of Line Orientation	28.53 (1.64)	27.50 (2.14)				

Note. Results are reported as means and standard deviations. Statistically significant results after Bonferroni's correction are denoted with lowercase letters. For the three cognitive tasks (Trail Making Test B, Naming Test, Judgment of Line Orientation) not completed by controls, we used published normative data in order to establish whether the performance of patients was within normal limits. aMCI = amnestic mild cognitive impairment; DMS48+ subgroup = patients with normal performance on the DMS48; DMS48– subgroup = patients with impaired performance on the DMS48; MMSE = Mini-Mental State Examination; EIPM = Echelle d'Intensité de Plainte Mnesique [Intensity Scale of Memory Complaint]; IADL = Instrumental Activities of Daily Living (4-item version); DAQ = Didactic Acquisition Questionnaire.
[a] $p < .05$ between controls and the DMS48+ subgroup. [b] $p < .05$ between control subjects and the DMS48– subgroup. [c] $p < .05$ between aMCI subgroups.

on a translational approach and replicating a task that is used in experiments with nonhuman primates, remains relatively novel in the field. More recent studies that relate impaired visual recognition memory to neurofibrillary tangle (NFT) in the mesial temporal lobe (MTL) also report impaired recognition memory in aMCI patients (Wolk, Signoff, & Dekosky, 2008), with entorhinal/perirhinal volume being highly correlated with familiarity-based recognition (Wolk & Dickerson, 2011).

Features of AD in the DMS48– Subgroup

The fact that the DMS48– group was impaired when compared with the DMS48+ group on the number of intrusions performed during free recall may be suggestive of AD, as this feature has been reported to be a hallmark of this disease (Manning, Greenhut-Wertz, & Mackell, 1996; Fuld, Katzman, Davies, & Terry, 1982). Efficiency of cueing was also found to be lower, as already found in a previous study, and suggestive of a *genuine* memory impairment related to medial temporal dysfunction rather than an *apparent* memory dysfunction related to frontal dysfunction (Barbeau et al., 2004). Lastly, decreased performance of these patients on the recognition subtest of the FCSRT also strongly supports the postulate of genuine memory impairment rather than a difficulty simply related to recall, and the possibility of medial temporal dysfunction related to AD pathological changes. It is worth noting that the DMS48– group performed more poorly on memory tasks (but not on other neuropsychological tasks) at baseline than the DMS48+ group, which could have suggested that future decline is predicted by quantitative rather than qualitative measures. However, the fact that there was no significant difference on free delayed recall between the two subgroups supports the notion that qualitative differences in memory performance suggests mesiotemporal dysfunction. It is also of note that the three patients of the present study who converted at the 18-month follow-up belong to the subgroup that failed the DMS48.

This hypothesis is further supported by previous neuroimaging findings that suggest that patients who fail on the DMS48 have imaging and neuropsychological features of AD. Imaging data from studies in a group of patients that failed the DMS48 showed hypoperfusion in the MTL using brain SPECT, also encompassing the posterior cingulate and temporoparietal cortices (Guedj et al., 2006), a functional profile classically reported in early AD (Borroni, Di Luca, & Padovani, 2006; Nobili et al., 2009). Moreover, a profile of gray matter loss in the MTL and the temporoparietal cortices, usually reported in early AD, was also evidenced in aMCI patients failing the DMS48 (Barbeau et al., 2008). More recently, a study using proton magnetic resonance spectroscopy found reduced MTL NAA/mIno ratios, associated with AD type changes, only in the MTL of aMCI patients with impaired performance on the DMS48 (Didic et al., 2010). Overall, this converging evidence strongly supports the view that patients failing on the DMS48 are at increased risk for AD.

Cognitive Decline in the DMS48– Subgroup

In the subgroup that failed the DMS48, longitudinal decline over the follow-up period was widespread and, in addition to verbal anterograde memory, was also found in executive functions, semantic knowledge, naming, and visuospatial abilities. Studies that focused on the cognitive features of the prodromal stage of dementia (Bäckman, Small, & Fratiglioni, 2001; Bondi, Salmon, Galasko, Thomas, & Thal, 1999; Chen et al., 2001; Collie & Maruff, 2000; Fox, Warrington, Seiffer, Agnew, & Rossor, 1998) show that anterograde memory decline often occurs several years before the emergence of objective cognitive changes required for a clinical diagnosis of AD. Our findings are also in line with other studies that found that the cognitive performance of pre-AD patients falls between that of normal controls and patients with probable AD (Collie & Maruff, 2000, for a review). Episodic, but also semantic, memory is impaired early in the course of the disease (Barbeau et al., 2012; Joubert et al., 2008, 2010; Leyhe, Muller, Eschweiler, & Saur, 2010). Moreover, our results are in keeping with previous studies that indicate that impaired memory is not the only marker of the predementia stage of AD (Albert, Blacker, Moss, Tanzi, & McArdle, 2007; Amieva et al., 2005, 2008; Twamley, Ropacki, & Bondi, 2006).

Cognitive Stability in the DMS48+ Subgroup

The subgroup that succeeded on the DMS48 showed smaller decline than the DMS48– group. However, their decline was significantly lower than the group of control subjects, which, in contrast, showed better performance at the 18-month follow-up. This better performance is probably driven by a test–retest effect but shows that neither the DMS48+ nor the DMS48– group was helped by test repetition. Although DMS48+ patients were all included at baseline using strict criteria of aMCI (Petersen et al., 2001; Winblad et al., 2004), their evolution was not the same than DMS48– patients. Interestingly, the only test on which the DMS48+ group evolution was worse than the DMS48– group was on the phonological fluency test, an executive test unrelated to semantic performance that is known to be impaired in AD. This confirms the known heterogeneity in MCI that led several authors to question this concept (Dubois & Albert, 2004). The present data confirms the necessity for longitudinal follow-up, as recommended by recently updated criteria by the workgroup of National Institute on Aging and Alzheimer's Association for symptomatic predementia phase of AD (Albert et al., 2011), in which it was suggested that it is important to obtain longitudinal assessment of cognition for these patients, because it evidences the progressive decline in cognition over time and provides more accuracy in establishing the diagnosis.

Conclusions

The cognitive profile that becomes apparent for the subgroup that failed the DMS48 at baseline shows impairment across several cognitive domains, as in the typical pattern of AD described in the literature. This suggests that evaluating subhippocampal functions using visual recognition memory tasks, like the DMS48 test, may be useful in discriminating aMCI patients who are likely to decline in the future, and to anticipate an overt cognitive decline very similar to cognitive pattern of probable AD. However, as demonstrated in another study from our group, combining the assessment of visual recognition memory with tasks that evaluate other types of memory, like story recall, is likely to increase the diagnostic accuracy of AD in aMCI patients (Didic et al., 2013).

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