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Original Research Article

Impaired Visual Recognition Memory Predicts Alzheimer's Disease in Amnestic Mild Cognitive Impairment

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Key Words
Alzheimer's disease · Mild cognitive impairment · Memory · Visual recognition memory · Assessment of cognitive disorders/dementia · Prognosis · DMS48

Abstract
Background: In the common form of Alzheimer's disease (AD), neurofibrillary tangles, which are associated with cognitive dysfunction, initially develop in the anterior subhippocampal (perirhinal/entorhinal) cortex before reaching the hippocampus. This area plays a key role in visual recognition memory (VRM). Impaired VRM could therefore be an early marker of AD. ***Methods:*** An extensive neuropsychological assessment including VRM tasks was performed in 26 patients with single-domain amnestic mild cognitive impairment at baseline. We evaluated the diagnostic accuracy of neuropsychological tests using ROC curve analyses in a prospective longitudinal study until conversion to probable AD or with a follow-up of at least 6 years. ***Results:*** VRM performance predicted conversion to AD with a sensitivity of 80% and a specificity of 90.9%. Combining the assessment of VRM with a verbal memory task increased diagnostic accuracy. ***Conclusions:*** Cognitive 'biomarkers' evaluating the function of brain areas that are the target of degenerative change should be considered for the early diagnosis of AD.

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Introduction

For future treatment trials, but also in order to improve clinical diagnostic accuracy, it becomes crucial to identify which patients within the spectrum of amnestic mild cognitive impairment (aMCI) have early Alzheimer's disease (AD). Despite the recent development of diagnostic tools for the early detection of AD such as CSF biomarkers and PET amyloid imaging, as well as structural and functional MRI, adding information concerning performance on memory tasks has a high predictive value in the diagnosis of AD in patients with MCI [1]. Amongst the neuropsychological tasks assessing memory that have proven useful in predicting AD at the MCI stage are the FCSR (Free and Cued Selective Reminding test), the RI-48 Cued Recall test, the RAVLT (Rey's Auditory-Verbal Learning Task), the CANTAB-PAL (paired associate learning) task and the CERAD Wordlist Learning task [1–6]. However, there is still no agreement on the type of memory which ought to be assessed and the optimal choice of memory tasks [7].

In the most common form of AD, neurofibrillary tangles, which are associated with functional deficits [8, 9], initially develop in the medial temporal lobe (MTL) in a sequential manner, appearing first in the anterior subhippocampal cortex (transentorhinal, entorhinal and perirhinal cortex) before reaching the hippocampus [10, 11]. Entorhinal cortex volume has been shown to predict decline from MCI to AD [12, 13]. Over the past years, there has been an ongoing debate on the function of the MTL and on whether the subdivisions of the MTL contribute differently to declarative memory (for a recent detailed discussion on this issue see an article by Montaldi and Mayes [14]). One view is that the MTL is a set of structures that contribute to declarative memory in a rather homogenous way [15]. An alternative view is that the subregions of the MTL, although strongly interlinked, make different contributions to anterograde declarative memory. Functionally, in line with this second proposal, there is increasing evidence that the anterior subhippocampal cortex plays a crucial role in familiarity-based 'context-free' visual recognition memory (VRM), or long-term memory of learned information which is dissociable from the context of learning when required to be recalled or recognized, while the hippocampus is essential for 'context-rich memory' (i.e. spatial memory and memory of episodic events) [14, 16–19]. We recently suggested that the dysfunction of an anterior mesiotemporal network, which includes the subhippocampal cortex [20], could lead to the earliest clinical dysfunction in AD and that the assessment of context-free memory could contribute to the diagnosis of AD in its earliest stages [21].

Using a translational approach directly derived from experiments on nonhuman primates [22], our group designed an experimental VRM paradigm assessing context-free memory adapted to human subjects, the DMS48 (delayed matching to sample – 48 items), in order to detect subhippocampal dysfunction in early AD [23]. On MRI, performance on the DMS48 correlates with the volume of the perirhinal cortex [24] and with connectivity of an anterior mesiotemporal network as assessed by resting state functional MRI [20]. aMCI patients with impaired VRM display imaging profiles of early AD on SPECT [25], structural MRI [24] and S-MRI [26]. Other studies also report impaired recognition memory in aMCI patients, with entorhinal/perirhinal volume being correlated with familiarity-based recognition [27, 28]. The aim of the present prospective longitudinal study was to determine if assessing VRM could predict AD in patients with aMCI.

Methods

Subjects and Experimental Protocol

A total of 40 patients with single-domain aMCI were consecutively recruited in the memory clinic of the University Hospital La Timone in Marseilles, France, between 2002 and 2004 and enrolled in the Marseilles memory study. Only patients strictly meeting criteria for aMCI [29] were included. For this study, we selected

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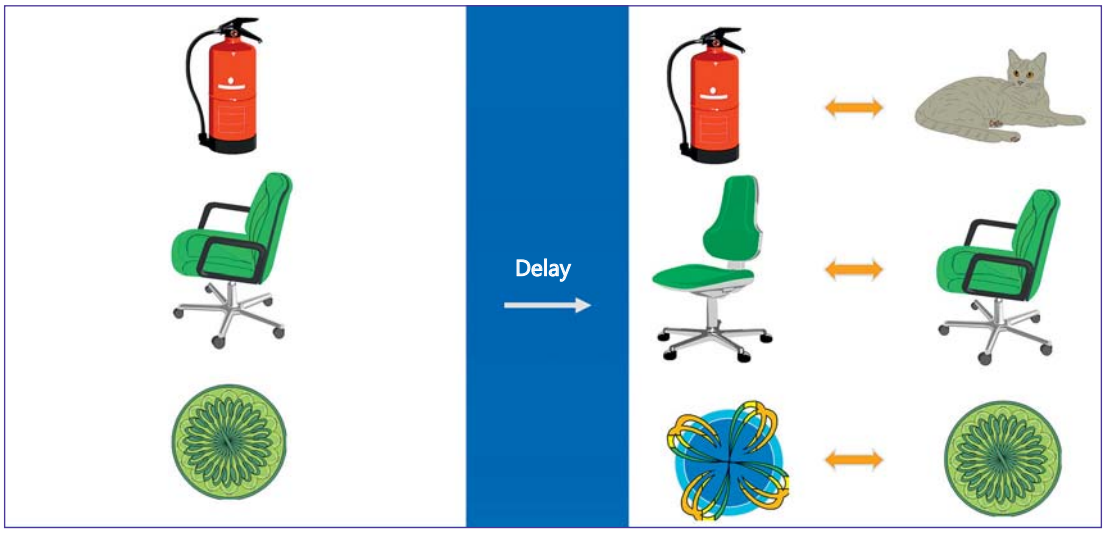

Fig. 1. Examples of stimuli used in the DMS48. Drawings are presented individually during the incidental learning phase (left side of the figure). After a delay, during the recognition task, each target is shown simultaneously with a distractor (right side of the figure) and the subject is asked to identify the target.

patients with single-domain amnestic MCI with a memory complaint, a performance of more than 1.5 SD below the mean of matched control subjects on delayed free recall of a verbal memory task, intact activities of daily living and no impairment in other cognitive domains like language, visuospatial skills or executive function, using normative data for matched controls. Brain imaging, routine biological survey, detailed neuropsychological evaluation, assessment of daily activities, psychiatric interview and physical examination had been conducted prior to the inclusion into this present study in order to exclude patients with a memory impairment due to vascular disease, tumor, subdural hematoma, treatment and concurrent diseases interfering with cognitive function. Other exclusion criteria were a history of systemic and/or neurological disease and a modified Hachinski ischemic score ≥2 [30]. This prospective study was approved by an institutional ethical standards committee. Informed consent following all the guidelines for experimental investigation with human subjects was obtained. Most patients had been referred by their general practitioner and a minority by neurologists. Over the 6-year follow-up, 2 patients died from diseases that were unrelated to their memory disorder, 2 patients withdrew early, while 10 patients dropped out of the study and had no follow-up. The present study reports on the 26 patients who were followed over a minimum period of 6 years or until conversion to AD.

All patients underwent a neuropsychological assessment before inclusion, evaluating memory, executive functions, naming, visuospatial and visuoperceptive skills. After inclusion, an extensive neuropsychological evaluation that included the DMS48 [23] was administered. This test is directly derived from experimental studies in monkeys demonstrating impaired VRM after ablation of the perirhinal cortex [22]. Stimuli consist of 48 color drawings. During the incidental learning phase, subjects were asked to look at each drawing carefully and state whether there were less or more than three colors. This was followed by an interfering 2-min phonemic fluency task. During the recognition task, each target was shown simultaneously with a distractor and the subject was asked to identify the target (fig. 1). Recognition was evaluated immediately after the interfering task and delayed recognition 1 h later. Performance is expressed in percent of correct answers/total answers (max = 100%, chance = 50%). It is possible to download the DMS48, a test designed for research purposes, at http://cerco.ups-tlse.fr/~DMS48.

The patients were evaluated regularly (at 18-month intervals) until conversion to AD and for a minimum of 6 years for patients who did not convert. At follow-up, the clinical assessment included neuropsychological tests, dementia rating scales and activities of daily living. After each follow-up visit, it was determined if criteria for aMCI, probable AD (or probable AD dementia according to the recently proposed nomenclature) [31], or other neurodegenerative conditions were fulfilled. The diagnosis was consensually established in the presence of neurologists (n = 4) and neuropsychologists (n = 4), all specialized in neurodegenerative diseases and blinded to the initial assessment.

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Statistical Analysis

The nonparametric Mann–Whitney U test was used to compare age and neuropsychological data for the comparison of converters and nonconverters. The χ^2 test was used to compare gender and educational level across aMCI subgroups. We performed ROC curve analyses in order to evaluate the discriminating power of the neuropsychological tests used in this study. Optimum cutoff points were determined by selecting the point with the best Youden index (sensitivity + specificity – 1) on the ROC curve.

Results

At the 6-year follow-up, 15 patients (58%) met the criteria for AD (converters) and 11 patients (42%) did not (nonconverters). For converters, the mean time to conversion was 42 ± 22.2 months.

Demographical Data

Demographical features of the aMCI patients are listed in table 1. Age, gender and educational level at baseline did not differ between converters and nonconverters.

Neuropsychological Assessment

At baseline, converters differed from nonconverters only on scores assessing memory, including both tasks assessing anterograde memory and tasks assessing retrograde, semantic memory. There was no difference between aMCI subgroups on the MMS, activities of daily living, memory complaint, a depression scale score and tests evaluating executive functions, naming, visuoperceptive and visuospatial skills (table 1).

Predictors of Conversion

Immediate recognition on the DMS48, using a cutoff score of 89%, had a high predictive value (sensitivity: 80%, specificity: 91%). However, the best predictor for conversion was delayed recall of the logical memory subtest on the Wechsler Memory Scale-III (WMS-III) using a cutoff score of 6 (scaled score; sensitivity: 73%, specificity: 100%). Other memory tasks also provided significant information concerning prediction, especially the number of intrusions and free recall on the FCSR, as well as delayed recognition on the DMS48. It is to be noted that two verbal recognition memory tasks were also highly specific in predicting conversion, but lacked sensitivity, a verbal recognition memory paradigm developed in our laboratory (sensitivity: 50%, specificity: 100%) and the recognition trial of the logical memory subtest of the WMS-III (sensitivity: 45.5%, specificity: 100%). Combining delayed recall on the logical memory subtest and immediate recognition on the DMS48 by means of binary logistic regression modeling using forward stepwise selection correctly identified all but 1 patient (false positive; sensitivity: 100%, specificity: 91%). Moreover, combining delayed recall of the logical memory subtest and immediate recognition on the DMS48 using a more specific cutoff (82; sensitivity: 66.7%, specificity: 100%) correctly identified all patients (sensitivity: 100%, specificity: 100%). Tasks evaluating attention, executive functions and verbal fluency did not predict conversion. Diagnostic accuracy scores for the neuropsychological tasks are provided in table 2.

Table 1. Demographical and neuropsychological data of aMCI patients at baseline

	Nonconverters (n = 11)	Converters (n = 15)	p
Age at inclusion, years	68.9 (10.8)	71.8 (6.0)	NS
Education, years	11	11	NS
M/F	5/6	9/6	NS
MMSE	27.3 (1.7)	26.9 (1.2)	NS
IADL	0	0	NS
CDR	0.5 (0)	0.5 (0)	NS
FAB	16 (2)	16 (2)	NS
Hamilton Depression Scale	3 (6)	2 (2)	NS
EPM (memory complaint scale)	17 (4)	17 (5)	NS
Tasks assessing attention and executive functions			
Digit span scaled score (WAIS)	9 (3)	9 (3)	NS
Digit symbol test (WAIS)	9 (2)	9 (2)	NS
Trail making test A, s	57 (15)	53 (19)	NS
Trail making test B, s	136 (66)	154 (64)	NS
Verbal fluency (animals)	26 (7)	25 (7)	NS
Verbal fluency (letter p)	17 (5)	17 (6)	NS
Matrices scaled score (WAIS)	10 (2)	10 (2)	NS
Information scaled score (WAIS)	8 (3)	8 (3)	NS
Modified card sorting test (categories)	5 (1)	5 (1)	NS
Tasks assessing verbal memory			
Immediate recall logical memory WMS III	9 (3)	7 (2)	0.049
Delayed recall logical memory WMS III	9 (2)	6 (2)	0.001
Recognition logical memory WMS III	22 (3)	18 (4)	0.04
FCSR Immediate recall	14 (1)	13 (3)	NS
FCSR free recall	21 (5)	12 (6)	0.003
FCSR total recall	42 (4)	34 (10)	0.02
FCSR recognition	16 (1)	14 (3)	0.04
FCSR delayed free recall	6 (3)	4 (3)	0.07
FCSR delayed total recall	14 (1)	11 (4)	0.03
FCSR index of cueing	0.79 (16)	0.63 (23)	0.08
FCSR number of intrusions	2 (2)	11 (8)	0.001
Verbal recognition task 'yes-no' (lab test), %	80 (0.10)	67 (0.13)	0.02
Tasks assessing visual memory			
Rey's figure – immediate recall	14 (9)	9 (5)	NS
Rey's figure – delayed recall	14 (9)	7 (5)	0.03
DMS48 immediate recognition, %	95 (0.05)	82 (0.09)	0.001
DMS48 delayed recognition, %	94 (0.04)	83 (12)	0.004
Face recognition WMS-III (immediate)	12 (3)	10 (3)*	0.03
Face recognition WMS-III (delayed)	13 (4)	11 (3)	NS
Visual recognition task 'yes-no' (lab test), %	93 (0.07)	81 (13)	0.01
Semantic memory tasks			
Naming task (DO80)	79 (2)	80 (1)	NS
Knowledge for public events (free recall)	10 (4)	6 (4)	0.047
Knowledge of public events (total recall)	32 (9)	22 (10)	0.02
Geographical knowledge (lab test)	17 (3)	13 (5)	0.04
Pyramid palm tree test	51 (1)	48 (8)	NS
Famous face naming (lab test)	28 (7)	21 (9)	NS
Tasks assessing visuoperceptive and visuospatial skills			
Rey's figure – copy	32.9 (3.4)	29.6 (8.1)	NS
Benton facial recognition	46 (4)	47 (3)	NS
Benton judgment of line orientation	29 (2)	27 (3)	NS

IADL = Instrumental Activities of Daily Living (The 4-item version was used, evaluating the ability to use the telephone, use transport, handle medication and manage finances independently); CDR = Clinical Dementia Rating Scale; FAB = Frontal Assessment Battery; WAIS = Wechsler Adult Intelligence Scale. Values are mean with SD in parentheses. Significant values ($p < 0.05$) and trends ($0.05 < p < 0.10$) are shown for tests of differences between converter and nonconverter groups. The neuropsychological assessment was completed by 4 trained neuropsychologists. NS (nonsignificant) = $p > 0.05$.

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Table 2. ROC analysis

Test	AUC	95% CI		p value	n	Cutoff	Se, %	Sp, %	PPV, %	NPV, %
Delayed recall logical memory WMS-III	0.903	0.779	1.000	0.001	26	6	73.3	100.0	100.0	73.3
DMS48 immediate recognition	0.888	0.754	1.000	0.001	26	0.89	80.0	90.9	92.3	76.9
FCSR number of intrusions	0.885	0.710	1.000	0.001	26	3	80.0	90.9	92.3	76.9
FCSR free recall	0.852	0.702	1.000	0.003	26	17	80.0	81.8	85.7	75.0
DMS48 delayed recognition	0.836	0.680	0.993	0.004	26	0.91	80.0	81.8	85.7	75.0
Verbal recognition yes/no	0.798	0.616	0.979	0.018	23	0.64	50.0	100.0	100.0	56.3
Knowledge of public events (total recall)	0.783	0.592	0.975	0.019	24	26	76.9	81.8	83.3	75.0
Visual recognition yes/no (lab test)	0.773	0.592	0.953	0.020	26	0.97	93.3	45.5	70.0	83.3
FCSR total recall	0.773	0.590	0.956	0.020	26	37	66.7	90.9	90.9	66.7
Recognition logical memory WMS-III	0.768	0.560	0.975	0.044	20	18	45.5	100.0	100.0	60.0
Rey's figure – delayed recall	0.766	0.568	0.964	0.025	25	10	85.7	63.6	75.0	77.8
Geographical knowledge (lab test)	0.759	0.543	0.975	0.037	24	17	86.7	66.7	81.3	75.0
Face recognition WMS-III (immediate scaled score)	0.752	0.560	0.944	0.031	26	12	93.3	45.5	70.0	83.3
FCSR total delayed recall	0.748	0.557	0.940	0.033	26	12	60.0	90.9	90.0	62.5
Knowledge of public events (free recall)	0.738	0.527	0.948	0.049	24	8	76.9	72.7	76.9	72.7

Diagnostic accuracy of demographic factors and neuropsychological tests. Only tests in which significant differences between converters and nonconverters were found are presented. No imputation for missing tests was done. Se = Sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value.

Discussion

In this study, performance on an experimental VRM task, designed to assess the function of the brain region where neurofibrillary tangles first develop in AD, predicted probable AD dementia in patients with aMCI with a sensitivity of 80% and a specificity of 91%. This adds to previous findings that suggest that aMCI patients with impaired VRM may be at particularly high risk for AD [23–26, 32].

Only delayed recall of the logical memory subtest of the WMS-III had higher specificity than immediate recognition on the VRM task (DMS48), but lower sensitivity. A very high predictive value was obtained combining both memory tasks. This is probably related to the fact that recall of context-rich material like the logical memory subtest of the WMS-III, reflecting the function of the hippocampus, is likely to be impaired at the aMCI stage of AD in addition to dysfunction of the anterior subhippocampal cortex [21]. It is to be noted that two verbal recognition memory paradigms were also highly specific in predicting conversion, while lacking sensitivity. Although the experimental visual recognition task did not clearly perform beyond neuropsychological tasks that have previously been shown to be useful in predicting AD (like logical memory) and performed only slightly beyond the FCSR, it is complimentary to standard measures as it improves their diagnostic accuracy. It is significant that one study reported discordances in older aMCI patients with some patients failing on the DMS48 while succeeding on the FCSRT and vice versa, which confirms that the tasks are complimentary in that they assess memory based on different sensory modalities and, possibly, distinct aspects of declarative memory [33]. This joins previous proposals that combining tasks that assess different types of memory increases the diagnostic accuracy of AD in aMCI patients [34, 35].

It has to be emphasized that dysfunction along the ventral visual pathway due to other pathological conditions is also likely to lead to impaired performance on VRM tasks, as previously reported in dementia with Lewy bodies, thus differentiating dementia with Lewy bodies from Parkinson's disease dementia [36]. Hence, while impaired VRM in aMCI patients may be

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predictive of AD, within the context of associated cognitive fluctuations and extrapyramidal signs it is likely to indicate dementia with Lewy bodies.

The findings of the present study only apply to the most common form of AD with an initial amnestic deficit related to MTL dysfunction [37, 38], but not to other 'nonmemory' subtypes of AD where lesions first appear in neocortical regions. Moreover, the relatively low proportion of aMCI patients who converted during the follow-up period could be related to the selection of single-domain aMCI patients only. This may have led to an overrepresentation of aMCI patients with slowly progressive amnestic decline [37–39]. We can therefore not exclude that some of the patients who did not develop AD at the 6-year follow-up will convert later. It is of interest that, at baseline, converters also differed from nonconverters on tasks that assess retrograde semantic memory, a finding that has previously been reported in patients with MCI [40–42], including patients who later developed AD [43–45].

Using cognitive tasks which assess neural networks that are the target of pathological change, as in the present study, could lead to consider these tasks as 'cognitive biomarkers' reflecting neural dysfunction on a clinical level. Also, assessing memory in the visual modality is suitable for use in multicultural settings or for international collaborative studies. Most importantly, the choice of a recognition procedure causes minimal distress for the patient, who is always able to provide an answer. Since immediate recognition had a higher predictive value than delayed recognition, the former could be sufficient, limiting the time of completion to only 10 min. Amongst the limitations of the present study are the small number of patients enrolled and the absence of neuropathological data. Therefore, studies on a larger patient sample using CSF and imaging biomarkers ought to be conducted in order to confirm the present findings. Finally, while many studies focus on hippocampal dysfunction in the early diagnosis of AD [46], the present findings confirm that taking into account the dysfunction of the subhippocampal region using VRM tasks could also critically contribute to early diagnosis of AD. It remains to be established if the assessment of the dysfunction of the anterior subhippocampal cortex using more sensitive tasks could contribute to the diagnosis of the earliest stage of AD referred to as the preclinical stage [47].

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Disclosure Statement

The authors disclose no conflicts of interest in relation to the work presented in this study.

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