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Original Research Article

Comparison of Four Verbal Memory Tests for the Diagnosis and Predictive Value of Mild Cognitive Impairment

Dina Silva[a] Manuela Guerreiro[a, b] João Maroco[c] Isabel Santana[d] Ana Rodrigues[d] José Bravo Marques[e] Alexandre de Mendonça[a, f]

[a]Dementia Clinics, Faculty of Medicine, University of Lisbon, [b]Laboratory of Language Studies, Santa Maria Hospital, and [c]Superior Institute of Applied Psychology, Lisbon, [d]Department of Neurology, Coimbra University Hospital, Coimbra, [e]Department of Neurology, Portuguese Institute for Oncology, and [f]Institute of Molecular Medicine and Faculty of Medicine, University of Lisbon, Lisbon, Portugal

Key Words
Mild cognitive impairment · Diagnostic criteria · Preclinical dementia · Alzheimer's disease · Memory impairment

Abstract
Background: Mild cognitive impairment (MCI) is considered to be an early stage of a neurodegenerative disorder, particularly Alzheimer's disease, and the clinical diagnosis requires the objective demonstration of cognitive deficits. The aim of the present study was to evaluate the predictive value of MCI for the conversion to dementia when using four different verbal memory tests (Logical Memory, LM; California Verbal Learning Test, CVLT; Verbal Paired-Associate Learning, VPAL; and Digit Span, DS) in the MCI criteria. ***Methods:*** Participants were consecutive patients with subjective cognitive complaints who performed a comprehensive neuropsychological evaluation and were not demented, observed in a memory clinic setting. ***Results:*** At baseline, 272 non-demented patients reporting subjective cognitive complaints were included. During the follow-up time (3.0 ± 1.9 years), 58 patients converted to dementia and 214 did not. Statistically significant differences between the converters and non-converters were present in LM, VPAL, and CVLT. A multivariate Cox regression analysis combining the four memory tests revealed that only the CVLT test remained significant as a predictor of conversion to dementia. Non-demented patients with cognitive complaints diagnosed as having MCI according to abnormal (<1.5 SD) learning in the CVLT test had a 3.61 higher risk of becoming demented during the follow-up. ***Conclusion:*** The verbal memory assessment using the CVLT should be preferred in the diagnostic criteria of MCI for a more accurate prediction of conversion to dementia.

Dina Silva
Instituto de Farmacologia e Neurociências, Edifício Egas Moniz
Faculdade de Medicina de Lisboa, Avenida Prof. Egas Moniz
PT–1649-028 Lisboa (Portugal)
Tel. +351 217 985 183, E-Mail dinasilva@fm.ul.pt

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Introduction

Many elderly people suffer from memory and other cognitive decline that is not severe enough to meet the criteria for dementia. These elderly people may be diagnosed as having mild cognitive impairment (MCI), implying a high risk of progression to dementia, usually Alzheimer's disease (AD), in the forthcoming years. In the initial formulation by Petersen et al. [1], MCI was based on (1) memory complaint, preferably corroborated by an informant; (2) memory impairment documented according to appropriate reference values; (3) essentially normal performance in non-memory cognitive domains; (4) generally preserved activities of daily living, and (5) absence of dementia. As repeatedly pointed out, several of these criteria would need operationalization. In particular, the test used to document the memory impairment and the cut-off score should be specified [2]. In spite of further refinements in the concept of MCI [3–10], there is still no consensus about the specific memory test that should be used for the diagnosis of MCI or prodromal phase of AD [11, 12]. Thus, there is the need to compare systematically and prospectively the inclusion of different verbal memory tests in the MCI criteria, and to examine how this modifies the predictive value of the MCI diagnosis for conversion to dementia.

Deficits in episodic memory are associated with impaired encoding of the contextual information and consolidation of new verbal material [13–15], and a lower performance on tests of episodic verbal memory is a forerunner of future cognitive decline [16–19]. A deficit in delayed recall assessment of episodic long-term memory, as opposed to the short-term or implicit memory assessment, would be particularly characteristic of initial AD [20], since it reflects involvement of the hippocampus and related medial temporal lobe structures. Significant verbal memory impairment, confirmed by neuropsychological testing, is considered the hallmark of both amnestic MCI and AD [4, 21]. So far, distinct tests of memory and learning have been used to establish the presence of memory impairment in order to fulfill the criteria for MCI, namely the Logical Memory (LM) test [19, 22–24], the Verbal Paired-Associate Learning (VPAL) test [23, 25], and the California Verbal Learning Test (CVLT) [17, 19, 26–31].

The LM test [32] has been used for a long time to discriminate between healthy older adults and individuals with very mild dementia [33] and is still commonly used for the assessment of memory impairment in MCI patients nowadays. Recent studies associate the presence of impairment in LM with a higher rate of conversion to AD as compared with other episodic memory tests [24, 34]. Furthermore, the LM test was recently proposed as a screening tool for MCI in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study [35].

Previous studies showed that impairment in list learning tests might as well predict accurately the conversion to AD [17, 36]. Rabin et al. [19] showed that the impairment in the total learning score from the CVLT [37] had superior overall accuracy in distinguishing MCI from normal aging, even though that accuracy might be enhanced by the inclusion of the delayed recall condition of the LM test. The VPAL test was proposed to reveal the presence of memory deficits in MCI and AD patients, although the facilitation of the encoding process through the cued recall format could lead to a different memory deficit profile than in patients assessed with the CVLT [25].

Besides verbal memory impairment, some studies have evidenced that other memory domains are also altered in MCI, namely those related to working memory [13]. The Digit Span (DS) test measures auditory attention, immediate span of learning, and working memory. Impairment in the DS test was associated with future cognitive decline [38, 39]. However, it appears that working memory does not decline early in the neurodegenerative process of AD [40]. Therefore, the DS test was used in this study as a negative control to other applied

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tests that represent earlier markers of the neurodegenerative process observed in AD patients (e.g., tests assessing episodic memory and verbal learning). Another type of memory that evidenced more resistance to AD progression is semantic memory, since the lexical semantic system might be spared until the initial phase of dementia [41].

In the present study, non-demented patients with cognitive complaints who had a neuropsychological battery assessing different types of memory were followed prospectively. The aim was to determine whether the inclusion of four distinct memory tests, i.e., LM test, CVLT, VPAL test, and DS test, in the diagnostic criteria could modify the predictive value of MCI regarding conversion to dementia.

Methods

Research Participants

Participants were selected from the Cognitive Complaints Cohort [42], which is a prospective study conducted at the Institute of Molecular Medicine, Lisbon, to investigate the cognitive stability or evolution to dementia of subjects with cognitive complaints based on a comprehensive neuropsychological evaluation and other biomarkers. The study was approved by the local ethics committee.

Inclusion Criteria

The inclusion criteria were: (1) presence of cognitive complaints; (2) neuropsychological testing including all four memory tests compared in the present study, and (3) follow-up >6 months.

Exclusion Criteria

The exclusion criteria were: (1) presence of neurological or psychiatric disorders that may induce cognitive deficits; patients with major depression according to DSM-IV-TR [43] or serious depressive symptoms (indicated by a score on the Geriatric Depression Scale short version (GDS 15) of >10 points) were excluded; (2) systemic illness with cerebral impact; (3) history of alcohol abuse or recurrent substance abuse or dependence, and (4) presence of dementia according to DSM-IV-TR [43], or a Mini-Mental State Examination (MMSE) score below the cutoff for the Portuguese population, or significant impairment on activities of daily life according to the Blessed Dementia Rating Scale (BDRS) [44, 45].

Procedures

The baseline comprehensive neuropsychological assessment was carried out by the same team of trained neuropsychologists, supervised by M.G., following a standard protocol and comprising several tests and scales:

(1) MMSE [46, 47]: the MMSE is one of the most widely used brief instruments for the clinical evaluation of cognitive state in adults;
(2) Battery of Lisbon for the Assessment of Dementia (BLAD) [48]: the BLAD is a comprehensive neuropsychological battery evaluating multiple cognitive domains and validated for the Portuguese population [48]. Tests of interest for the present study were: LM (immediate and delayed recall; Wechsler Memory Scale, WMS); VPAL (immediate recall; WMS), and DS (forward and backward; WMS) [32];
(3) CVLT [27, 37]: the CVLT measures verbal learning assessing constructs as repetition learning, serial position effects, semantic organization, intrusion, and proactive interference. The word lists (list A and list B) are made up of 16 items from 4 different categories of 'shopping list' items. The trials of interest (trials with better discriminating

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ability for different stages of cognitive decline according to previous studies) [26] considered for the present study were: the total number of words from list A correctly recalled on the five learning trials (Atot) and long-delayed free recall (LDFR; number of words from list A correctly recalled after an interference period of 20 min);

(4) BDRS [44, 45]: the BDRS is a brief behavioral scale based on the interview of a close informant, assessing functional capacity for activities of daily living and changes in personality;

(5) Geriatric Depression Scale (GDS) [49–51]: the GDS is a self-report assessment used specifically to identify depression in the elderly. For this study, a short-form (15 items) of the self-report instrument was used.

Diagnosis of MCI

Diagnosis of MCI was based on criteria given by the MCI Working Group of the European Consortium on Alzheimer's disease [4]:

(1) Cognitive complaints coming from the patients or their families;

(2) The reporting of a decline in cognitive functioning relative to previous abilities during the past year by the patient or informant;

(3) Presence of cognitive impairment: in this study, four distinct memory tests to fulfill this diagnostic criterion were compared: LM, CVLT, VPAL, and DS; 3 cutoffs to define impairment were also analyzed (1, 1.5, and 2 SD below the mean);

(4) Absence of major repercussions on daily life (the patient may report difficulties concerning complex day-to-day activities).

Patients were assessed at follow-up for the presence of dementia and diagnosis of AD, according to the DSM-IV-TR [43] criteria.

Data Analysis

Demographic, clinical, and neuropsychological data were analyzed using the Mann-Whitney U test for numerical data and Pearson χ^2 test for nominal data. All tests were two-tailed and a p value of <0.05 was assumed as statistically significant.

The neuropsychological assessment was standardized according to the age and education norms for the Portuguese population and z scores were calculated. The 1, 1.5, and 2.0 SD cutoffs below the mean were compared for establishing impairment on the memory tests.

Survival methods were chosen for analysis, since MCI conversion to dementia occurred at different times and the observations were censored. To explore the effect of impairment in different memory tests on the conversion to dementia during follow-up, univariate and multivariate Cox proportional hazards regression models were performed. For multivariate models, the Enter selection method was used to build the regression models. The memory tests were introduced as a binary variable (presence or not of impairment, coded as 0 and 1, respectively, and according to the cutoffs established, 1, 1.5, and 2.0 SD). Since converters to dementia were older at the baseline than non-converters, the multivariate model was adjusted for age. Survival time was calculated as the interval from the initial baseline evaluation to the diagnosis of dementia. For patients who remained non-demented, survival time was censored at the date of the last clinical assessment. A forest plot with the estimated hazard or risk of conversion to dementia for the different memory tests and cutoffs was displayed. Statistical analyses were performed using IBM SPSS Statistics 19 for Windows (2010 SPSS Inc., an IBM Company) and GraphPad Prism 5 for Windows (GraphPad Software, Inc., San Diego, Calif., USA) for graphical displays.

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Table 1. Baseline demographic and clinic characterization data

	Converters (n = 58)	Non-converters (n = 214)	p value
Age, years	69.9 ± 8.7	66.2 ± 9.3	0.004#, *
Gender (female/male)	38/20	122/92	0.293‡
Formal education, years	9.3 ± 5.1	10.1 ± 4.8	0.221#
Follow-up time, years	2.8 ± 1.7	3.1 ± 1.9	0.427#
GDS	4.8 ± 3.7	4.8 ± 4.1	0.831#
BDRS	3.4 ± 2.5	2.9 ± 1.9	0.450#
MMSE	25.4 ± 2.5	28.3 ± 1.9	0.001#, *

Data are number of patients or mean ± SD. # Mann-Whitney test. ‡ Pearson χ^2 test. * Statistically significant ($p < 0.05$).

Table 2. Verbal memory tests at baseline

		Converters (n = 58)	Non-converters (n = 214)	p value#
LM	Immediate recall	−1.46 ± 1.09	−0.89 ± 1.00	<0.001*
	Delayed recall	−1.61 ± 1.11	−0.84 ± 1.08	<0.001*
	Forgetting index	−0.38 ± 0.47	−0.11 ± 0.45	0.001*
VPAL		−1.48 ± 1.14	−0.74 ± 1.15	<0.001*
CVLT	Five learning trials total	−3.22 ± 1.45	−1.81 ± 1.44	<0.001*
	Long delayed recall	−3.30 ± 1.77	−1.64 ± 1.61	<0.001*
	Forgetting index	−0.11 ± 0.65	0.06 ± 0.44	0.142
DS	Forward	0.40 ± 1.63	0.41 ± 1.27	0.837
	Backwards	0.05 ± 1.30	0.30 ± 1.15	0.084

Data are mean ± SD. Means of Z scores, calculated according to the equation [z = (x – mean)/SD]. # Mann-Whitney test. * Statistically significant ($p < 0.05$).

Results

At baseline, 272 patients reporting subjective cognitive complaints and not demented were included. During the follow-up time (3.0 ± 1.9 years), 58 patients (21%) converted to dementia, and 214 (79%) did not. Most cases that progressed to dementia were diagnosed as AD (85%). The presence of depressive symptoms and functional capacity did not differ between converters and non-converters (table 1). Likewise, the follow-up time was not significantly different between the two groups (table 1). The converters were older than the non-converters at the baseline assessment (table 1). Statistically significant differences between the converters and non-converters were present in all measures of verbal memory administrated with the exception of the DS test and a measure of forgetting from the CVLT (table 2). The analysis of other neuropsychological tests from the BLAD also showed significantly lower performances in converters as compared to non-converters, namely in measures of attention, initiative, and conceptual thinking; however, all scores were within 1 SD of the mean, showing that the converters had no major impairments in non-memory cognitive domains that would qualify them for a diagnosis of dementia (results not shown).

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Table 3. Number of subjects diagnosed as MCI according to distinct measures and cutoffs of memory tests

		1 SD	1.5 SD	2 SD
LM, n (%)	Immediate recall	152 (55.9)	106 (39)	47(17.3)
	Delayed recall	137 (50.4)	98 (36)	55 (20.2)
CVLT, n (%)	Five learning trials total	195 (71.7)	166 (61)	123 (45.2)
	Long delayed recall	147 (54)	117 (43)	91 (33.5)
VPAL, n (%)		132 (48.5)	86 (31.6)	47 (17.3)
DS, n (%)	Forward	31 (11.4)	24 (8.8)	3 (1.1)
	Backward	36 (13.2)	14 (5.1)	9 (3.3)

Of the 272 patients reporting subjective cognitive complaints and not demented, 33 (12%) had no alterations at the baseline in the memory tests selected for the present study (considering the cutoff <1.5 SD), 72 (26%) had deficits at only 1 of the memory tests, 167 (62%) showed deficits in ≥2 memory tests (from those, 4 (2%) had deficits in at least 1 measure of all memory tests). The number of patients diagnosed as having MCI based on each specific memory test and 3 different cutoff values is shown in table 3. The CVLT test was the verbal memory test that categorized more individuals as MCI across the 3 cutoffs (table 3).

Since the conversion to dementia occurred during the follow-up time at different moments, a survival analysis was performed. The diagnosis of MCI on the basis of an abnormal value for each of the memory tests, LM, CVLT, and VPAL, according to the cutoffs determined for impairment, carried a significant risk of conversion to dementia during the follow-up (univariate Cox regression model fitted to the results of each memory test; fig. 1). The diagnosis of MCI on the basis of an abnormal value for the DS backward condition (all cutoffs) and forward condition (1 and 2 SD cutoffs) was not significantly associated with the risk of conversion to dementia during the follow-up (fig. 1). The three significant memory tests showed overlapping hazard risks for conversion to dementia (fig. 1).

To test whether the verbal memory tests used in the diagnostic criteria of MCI (LM, CVLT, and VPAL) that individually had shown to accurately predict future conversion to dementia, could be combined to improve their predictive value, a multivariate Cox regression analysis was performed. In an attempt to increase the power of multivariate analysis, we reduced the number of measures in the study and selected two at maximum for each memory test. The measures not selected for the present study also showed overlapping hazard risks and did not add any further accuracy for predicting future conversion to dementia. In the multivariate Cox regression analysis only the CVLT (learning measure for the cutoff <1.5 SD and long delayed recall for the other cutoffs) remained significant as a predictor of conversion to dementia (table 4). Non-demented patients with cognitive complaints diagnosed with MCI according to abnormal (cutoff commonly used of <1.5 SD) learning in the CVLT had a 3.61 higher risk of becoming demented in the follow-up as compared to those who had normal learning in the CVLT (table 4).

Discussion

The present study shows that different verbal memory tests, LM, CVLT, and VPAL, when used in non-demented patients with cognitive complaints to establish memory impairment in the diagnosis of MCI, are not significantly different to predict the progression to

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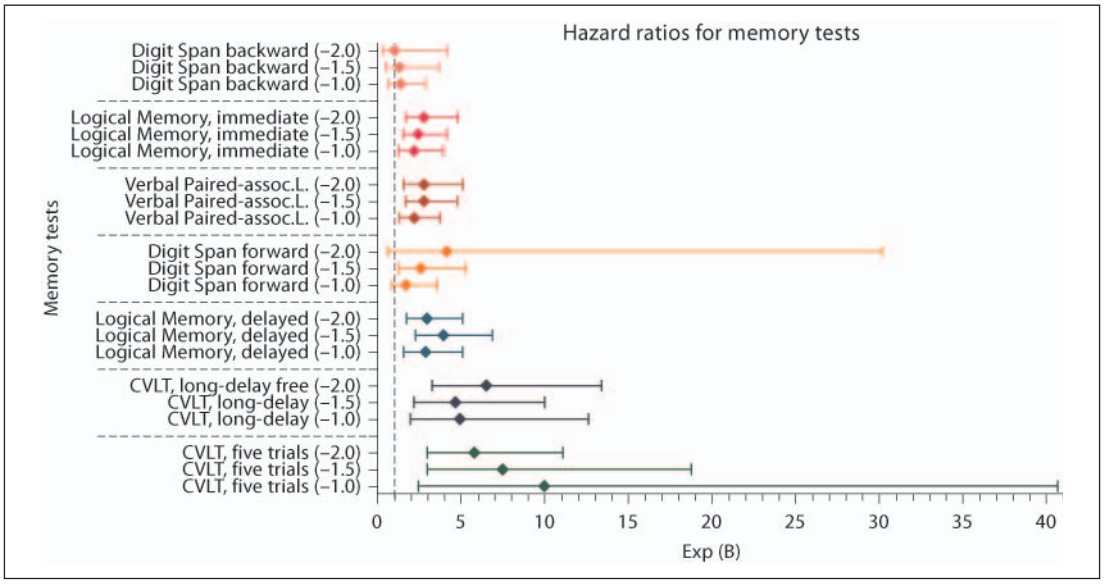

Fig. 1. Verbal memory tests and risk of progression to dementia (hazard ratios and confidence intervals from univariate Cox regression analysis).

dementia. However, the MCI criteria using the CVLT had the highest predictive value, which was not improved by adding other memory tests.

Although it has been argued that the use of a memory test battery offers a better sensitivity to the earlier diagnosis of MCI [52], we showed that only the CVLT remains significant on the multivariate Cox regression model as a predictor of progression to dementia, and other memory tests did not significantly add to the predictive value. The assessment of verbal memory based on list learning was found to be predictive of future conversion to dementia in earlier phases, possibly due to the reduced use of learning strategies [53]. Previous studies have also suggested that list learning represents a more demanding encoding test than story recall, is more sensitive to executive dysfunction, and offers a better prediction of conversion to dementia [19, 54, 55]. The higher frequency of impaired performance for CVLT at baseline highlights the demanding character of the task, indicating that it might be an early marker for cognitive decline [17].

Different measures of verbal memory tests used for the diagnosis of MCI may assess different stages of the neurodegenerative process by relying on distinct cognitive resources, so the contribution to diagnostic accuracy and predictive value is unique [14]. Both measures of immediate and delayed free recall were analyzed, because there is some evidence that long-term memory is more extensively impaired in MCI patients than short-term memory and, more importantly, has evidenced a greater sensitivity for the identification of amnestic MCI which will progress to dementia [20]. Verbal memory impairment can possibly correspond to either a defective consolidation of information relying on an alteration of mesiotemporal areas, or to a difficulty in elaborative encoding and afterwards correct retrieval of information, which in this case is associated with an alteration of frontal areas. MCI patients at risk of conversion to AD are expected to present deficits in learning (encoding and storage) rather than in the retrieval process [56, 57]. Some verbal memory tests assess primarily the capacity of storage, and for that aim semantic cues are systematically provided during the encoding phase in order to facilitate the retrieval process. For instance, the Free and Cued Selective Reminding Test [58] assesses specifically the storage capacity of MCI patients with

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Table 4. Verbal memory tests and risk of progression to dementia (multivariate Cox regression analysis)

		B	SE	Exp (B)	95% CI for Exp (B)	Wald statistic	p
–1 SD							
Logical Memory test	Immediate recall	0.03	0.54	1.04	0.36–2.97	0.004	0.95
	Delayed recall	0.71	0.50	2.04	0.77–5.44	2.04	0.15
California Verbal Learning test	Five learning trials	1.24	0.78	3.45	0.75–15.91	2.52	0.11
	Long delayed recall	1.30	0.57	3.65	1.20–11.09	5.22	0.02*
Verbal Paired Associate Learning test		0.25	0.35	1.29	0.65–2.55	0.53	0.47
Digit Span test	Forward	0.29	0.53	1.34	0.47–3.78	0.30	0.58
	Backwards	0.31	0.47	1.37	0.55–3.43	0.45	0.50
–1.5 SD							
Logical Memory test	Immediate recall	0.03	0.43	1.03	0.44–2.41	0.004	0.95
	Delayed recall	0.52	0.45	1.68	0.69–4.06	1.31	0.25
California Verbal Learning test	Five learning trials	1.28	0.57	3.61	1.19–10.99	5.12	0.02*
	Long delayed recall	0.76	0.49	2.13	0.81–5.60	2.37	0.12
Verbal Paired Associate Learning test		0.55	0.38	1.73	0.83–3.61	2.12	0.15
Digit Span test	Forward	0.92	0.53	2.51	0.89–7.06	3.04	0.08
	Backwards	0.60	0.75	1.82	0.42–7.97	0.64	0.43
–2 SD							
Logical Memory test	Immediate recall	0.64	0.43	1.89	0.82–4.37	2.21	0.14
	Delayed recall	0.43	0.43	1.53	0.66–3.58	0.96	0.33
California Verbal Learning test	Five learning trials	0.79	0.55	2.21	0.75–6.54	2.07	0.15
	Long delayed recall	1.45	0.59	4.26	1.35–13.43	6.11	0.01*
Verbal Paired Associate Learning test		0.28	0.43	1.32	0.57–3.05	0.41	0.52
Digit Span test	Forward	–8.63	408.64	<0.001	0.00–n.d.	<0.001	0.98
	Backwards	–0.07	1.03	0.94	0.12–7.11	0.004	0.95

* Statistically significant ($p < 0.05$).

focus on the amnestic syndrome of the medial temporal type associated with a future progression to dementia [52, 53]. According to a recent review, the studies that determined the predictive value of this test for future conversion to dementia also evidenced that delayed recall measures were less sensitive and specific than immediate recall measures, supporting the hypothesis of a failure at the initial learning process (although providing semantic cues), instead of forgetting due to inadequate storage of the information [57]. Other studies have shown that MCI patients at risk of conversion to dementia (namely AD) could benefit from semantic cues on the encoding phase in a similar way as normal controls, suggesting that the deficits in encoding correctly the information during the learning process, and not a difficulty in the storage process itself, would lead to retrieval impairment [27, 57, 61].

Bearing in mind the above mentioned, we decided to examine the CVLT performance for the total learning and delayed recall, which are also the measures associated with a better discrimination between normal aging, MCI, and AD [26]. Verbal learning tests were analyzed on associative (VPAL) and non-associative (CVLT) conditions in order to assess different stages of impairment progression. Deficits in associative learning tests are present in a more advanced stage of progression in MCI [62] and, therefore, may not be the best predic-

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tors for conversion at earlier phases. Interestingly, the use of different cutoffs for CVLT impairment did not considerably modify the risk of progression to dementia.

The present results suggest that a measure of working memory, like the DS backward, should not be used to qualify for memory impairment in the MCI diagnostic criteria, and the prediction of future conversion to dementia would be unreliable. Working memory and visuospatial ability have been proposed as functions that decline slowly in MCI patients [63]. A recent study showed that subjects presenting subjective cognitive complaints and impairment in DS might have a higher risk of future conversion to MCI but did not compare the DS predictive value to other memory tests [38].

One limitation of the present study is the focus on a restricted number of verbal memory tests commonly used in clinical practice to evaluate memory in non-demented patients with suspected cognitive decline. Clearly, it would be interesting to evaluate other memory modalities, with visual or semantic memory tests. Nevertheless, several studies showed that their diagnostic value in the identification of MCI patients at risk of conversion to dementia do not clearly overtake that of verbal episodic memory tests [18, 64–66]. Another limitation of the present study was that it focused on neuropsychological data, and other biomarkers were not considered. Recently, many studies have been published combining different biomarkers in non-demented subjects with cognitive complaints for predicting future conversion to dementia. Consequently, the choice of specific verbal memory tests in the neuropsychological assessment, in conjunction with other biomarkers, may be crucial to accurately predict future conversion to dementia.

In conclusion, different memory tests, namely LM, CVLT, and VPAL, can be used to establish the diagnosis of MCI and predict the progression to dementia. Considering our results, the MCI criteria using the CVLT had the highest predictive value, which was not improved by adding other memory tests, and taking into account that there are frequent limitations in clinical practice to apply an extensive neuropsychological battery to all individuals with suspected cognitive decline [67], we propose that a list learning task could be the preferred test to establish memory impairment in MCI diagnosis.

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