Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 11 (2019) 108-114

Cognitive & Behavioral Assessment

Quantifying memory deficits in amnestic mild cognitive impairment

Pilar Andrés[a,b,*], Helena Vico[a,c,d], Aina Yáñez[a,e], Antònia Siquier[a,b], Guillermo Amer Ferrer[f]

[a]Neuropsychology and Cognition Research Group, Research Institute on Health Sciences and Balearic Health Research Institute and IdISBa, Palma, Spain
[b]Department of Psychology, University of the Balearic Islands, Palma, Spain
[c]Valencia University Clinic Hospital, Valencia, Spain
[d]Dr Peset University Hospital, Valencia, Spain
[e]Department of Physiotherapy and Infirmary, University of the Balearic Islands, Palma, Spain
[f]Cognitive Neurology Unit, Son Espases University Hospital, Palma, Spain

Abstract

Introduction: In the present study, we use the item-specific deficit approach (ISDA), a method for characterizing memory deficits in list-learning, to portray the memory deficits in amnestic mild cognitive impairment (aMCI).
Methods: We applied the ISDA to compare memory performance of patients with aMCI and healthy controls in encoding, consolidation, and retrieval using the Free and Cued Selective Reminding Test.
Results: The results revealed clear differences in recall performance between patients with aMCI and controls. When analyzing the ISDA deficit indices, the results revealed a prominent encoding deficit, followed by a consolidating deficit. A greater sensitivity for the encoding index confirmed that a difficulty with encoding information plays a major role in explaining the episodic memory deficits experienced by patients with aMCI.
Discussion: The present study applying the ISDA reveals great sensitivity and specificity of the encoding deficit index when identifying aMCI. As aMCI constitutes a risk factor to develop Alzheimer's disease, the current findings also confirm the need to concentrate on encoding deficits as an early diagnostic sign of cognitive decline.

Keywords: aMCI; Encoding deficit; ISDA method; Episodic memory; Neuropsychology

1. Introduction

Mild cognitive impairment (MCI) is defined as a condition where changes in cognition exceed the normal, expected changes related to age, without affecting one person's daily activities [1]. When these changes involve memory, we refer to the amnestic form of MCI (aMCI), which includes several features more likely to be related to the initial symptoms of Alzheimer's disease (AD), known as prodromal AD [2–4].

Owing to the need to approach AD as early as possible, the issue of early diagnosis has become an important one for researchers. Recent evidence has revealed that the physiopathological process underlying AD starts several years before the first clinical symptoms are observed [5]. However, in the absence of an ideal biomarker for AD diagnosis [6], the diagnosis of the illness in usual clinical practice is still "probable" and based on the existence of clinical symptoms (e.g., memory). In that sense, the neuropsychological evaluation plays a major role in early diagnosis. Efficient neuropsychological tests also help to relativize the need of expensive and invasive examinations such as lumbar puncture for cerebrospinal fluid biomarker analyses. Moreover, several studies have revealed higher sensitivity for neuropsychological tests than for biomarkers when used alone [7–10]. This is specially the case for episodic memory measures of delayed free recall, which often outperform biomarkers

*Corresponding author. Tel.: 00 34 971 259812; Fax: 00 34 971 259501.
E-mail address: pilar.andres@uib.es

https://doi.org/10.1016/j.dadm.2018.12.002

such as middle temporal lobe and hippocampal volumes and tau/β-amyloid ratios in the preclinical period [11].

Different authors such as Loewenstein, Curiel, Duara, and Buschke ([12], also see [13]) have recently described the development and improvement of neuropsychological tests, making them cognitively more demanding and sensitive, minimizing possible compensating strategies, and targeting specific vulnerabilities of people with early AD.

One of the neuropsychological tests that have proven to be especially sensitive to early cognitive decline is the Free and Cued Selective Reminding Test (FCSRT, [14–16]), recommended by the International Working Group for the assessment of episodic memory failure that constitutes the core feature of typical amnesic AD [4,17]. The FCSRT has been used in the study of dementia since 1987 and has demonstrated high sensitivity and specificity in differentiating patients with AD from both healthy controls [18] and those with other forms of dementia [19–21].

To explain the rationale for the utility of the FCSRT, it is important to refer to a general model of the role played by temporal and frontal areas in declarative memory functioning. Two qualitatively different amnesic syndromes following damage to these regions have been postulated. In temporal amnesia, memory encoding and consolidation processes are affected and information cannot be recollected regardless of the facilitatory conditions (e.g., category cues) available at the time of retrieval. Conversely, although consolidation of the memory trace takes place normally in frontal lobe amnesia, the elaborative encoding of incoming information at the time of study and the ability to implement effective retrieval strategies at the time of memory testing are defective. Thus, these patients are generally poor in free recall procedures. Support for the existence of qualitatively different patterns of memory impairment following temporal versus frontal lobe damage comes from studies in patients with focal lesions in these two regions [22,23] and from neuroimaging studies [24].

The pathophysiological changes of AD and aMCI due to AD begin years before clinically evident manifestations of the disease. These neurodegenerative changes, and particularly the neurofibrillary tangles, begin primarily in the medial temporal lobe limbic structures (e.g., entorhinal/transentorhinal cortex, hippocampus) and then spread to the association cortices of the frontal, temporal, and parietal lobes over time [25]. The memory deficits typically presented by patients with AD are therefore characterized as temporal, and sometimes they are known as the amnesic syndrome of the hippocampal type [3], primarily identified by little improvement during recognition [26] and by low delayed recall [27]. Lipinska and Bäckman [28] have, however, shown that cued recall can be better than free recall in situations of deep (semantic) learning. Altogether, if free recall is poor, but it improves with cues, it is likely that both, encoding and retrieval, are affected by AD. The present study will try to evaluate this contention.

The FCSRT assesses the ability to learn a list of 16 written words that are presented with a semantic cue (fruit, clothing) to facilitate memory encoding. After three learning trials, memory is assessed by asking to recall the words first spontaneously (free recall) and then with the help of a semantic cue for the non-recalled items (cued recall). Compared with other memory tests, a major advantage of the FCSRT is controlling the encoding with semantic cuing. Semantic cuing also facilitates the retrieval of stored items, distinguishing between simple retrieval difficulties (improved by cues, and encountered, e.g., in frontal dysfunction) and genuine storage deficits (not improved by cues and characterizing typical AD). Therefore, the FCSRT enables the identification of memory storage deficits characterizing the amnesic syndrome of the hippocampal type [3].

One important question around the FCSRT in patients with aMCI putatively representing a prodomic stage of AD is the extent to which a memory deficit can be located at the encoding process. If the rationale behind the FCSRT is that it allows to identify genuine encoding memory deficits, related to the temporal and hippocampal atrophies, it would be interesting to quantify the possible encoding deficit in these patients. The amount of help provided by the cues at recall will also allow to assess the idea of a coexistent retrieval deficit.

Two studies have so far compared patients with MCI with healthy controls using the FCSRT [29]. Saka et al. [30] first compared 18 MCI patients with controls and reported values of 50% and 90.9 %, respectively, for sensitivity and specificity for total recall, and 38.9% and 87.9%, respectively, for free recall. These values represent a low capacity of the FCSRT to discriminate between patients with MCI and controls. In a more recent study, Lemos et al. [31] focused on patients with aMCI and controls, revealing significant differences between patients and controls for immediate and delayed recall. Cued recall, however, did not reach significance on immediate or delayed recall. Another important finding was that education, and gender did not show a significant effect on the FCSRT. This is important as it suggests that it might be a useful test even for patients with low educational level, irrespective of their gender. Finally, sensitivity was 72% and specificity 83% for total immediate recall, and 76% and 81%, respectively, for total delayed recall. Therefore, these studies show contradictory results and new studies are necessary to reassess the sensitivity and specificity of the FCSRT in aMCI.

The objective of the present study was to introduce for the first time the item-specific deficit approach (ISDA), to compare the performance of patients with aMCI and healthy controls on the FCSRT, following the NIA-AA's diagnostic criteria [2,4] to quantify with a new method the difference between the two groups at encoding, consolidating, and retrieval in memory.

The ISDA [32] and its construct validity were originally tested in a mixed sample of neurologically compromised individuals that included persons with HIV infection and traumatic brain injury [31,33] using the California Verbal Learning Test. Results of this investigation showed acceptable internal consistency estimates (0.64–0.84) of

the ISDA Encoding, Consolidation, and Retrieval indices and demonstrated evidence of construct separation as indicated by the lack of a significant correlation between the Consolidation and Retrieval indices [32].

The ISDA can be applied to any episodic memory test where there are repeated learning trials and different types of recall (free and cued), as it is the case with the FCSRT. Oltra-Cucarella et al. [34] recently used the method to test the encoding deficit hypothesis in AD. The results showed that encoding was indeed the most impaired process, followed by retrieval and then consolidation. Further analyses revealed that ISDA indices were more sensitive and specific for detecting memory impairments in AD than the raw scores.

In the present study, we expected to observe, as it was the case in patients AD [34], an important encoding deficit in patients with aMCI, without excluding the possibility that consolidation and retrieval would also be affected.

2. Method

2.1. Participants

This study was carried out in accordance with the ethical guidelines laid in the Declaration of Helsinki (1964). Informed consent was obtained from all participants, and their privacy rights were always observed.

Fifty-three participants took part in this study, from which 27 (14 women) were diagnosed with aMCI (single or multidomain).

Patients with aMCI were identified by a neurologist (who also is a neuropsychologist), according to Petersen's criteria [2,35] and operationalized as follows: (1) a complaint of memory decline (reported by the patient or an informant); (2) objective memory impairment (considered when the score on the memory subtest from the 7-minute screen test was >1.5 standard deviations below age/education adjusted norms) with or without deficits in other cognitive domains; (3) largely normal daily-life activities (global CDR ≤ 0.5); and (4) absence of vascular burden (Fazekas maximum score 2, [36]) or dementia.

The control group was composed of 26 cognitively healthy adults (15 women). There were no cognitive complaints by participants or informants, no evidence by history of functional impairment due to declining cognition, a Mini–Mental State Examination score of ≥ 27, and no cerebrovascular or other neurological or psychiatric disorder.

2.2. Procedure

Evaluation included the measure of depression symptoms by the Geriatric Depression Scale (GDS-15) [37]. General cognitive profile was measured by the Mini–Mental State Examination [38] (Spanish version by Lobo et al. [39]) and the clock drawing test [40]. Episodic memory was assessed by the 7-minute screen test [41]. Finally, crystallized intelligence was measured by the vocabulary subtest [42] and cognitive reserve by the Cognitive Reserve Scale [43].

The FCSRT was administrated in accordance with the standard instructions (Buschke's FCSRT [29] and Gramunt's [44] Spanish version) and was used to derive conventional memory process indices, as well as ISDA indices. The test consisted of three immediate free recall trials, each of which was followed by a cued recall task. A 30-minute recall task (also free at first and then cued) was also introduced. Each participant was shown a sequence of four cards (DINA4), containing each 4 words. Each item belonged to a different semantic category, and participants were asked to identify each word aloud and state the semantic category for the words according to the semantic cue provided by the examiner (fruit, clothing, etc.). After the 16 items had been correctly identified, participants were asked to perform a nonsemantic interference task lasting 20 seconds (counting backward by threes). Once they had finished, participants were given 90 seconds to freely name the words they remembered (free recall). The task was interrupted if the participant was unable to recall any of the words during a 15-second interval. Following the free word recall, participants were cued using the previously mentioned semantic cue for those words they were unable to recall spontaneously (cued recall). This procedure was repeated three times. During the first two trials, if the participant was unable to recall the word with the help of the semantic cue, the examiner would state the word.

ISDA indices were calculated according to the procedure originally described by Wright et al. [32]. The ISDA encoding deficit index is a reflection of acquisition across learning trials. It was calculated by determining the number of individual words on the learning phase, which were recalled only once or not at all over the three learning trials, divided by 16 (the total number of items) such that higher scores indicate worse performance. The ISDA consolidation deficit index was calculated as the number of items recalled more than once during list-learning, but not at all during delayed recall trials. This value was divided by the total number of words recalled at least once during learning trials to control for disparities in total word acquisition (range = 0 to 1). The ISDA retrieval deficit index was calculated by summing the individual items that were recalled at least once during list learning and at delayed cued recall divided by the total number of words recalled at least once during learning trials to control for varying levels of acquisition (range = 0 to 1). As ISDA indices are deficit indices rather than performance indices, higher deficit scores indicate poorer performance. Their sensitivity and specificity to aMCI were also calculated. Indeed, the need to report diagnostic test accuracy statistics (sensitivity and specificity) over null hypothesis testing as a way to ascertain the value of the tests has been recently emphasized by Weissberger et al. [45].

3. Results

Table 1 presents recall performance on the FCSRT for aMCI and healthy participants for free and cued recall, including immediate and delayed recall. Percentages of

Table 1
Recall performance on the FCSRT for patients with aMCI and controls

Type of recall	aMCI	Controls	*P*	R^2
Immediate free recall	7.9 (5.4)	25.3 (6.0)	<.001	.75
Immediate cued recall	10.1 (5.8)	16.8 (4.4)	<.001	.24
Total recall (max = 48)	18.1 (10.6)	42.1 (5.6)	<.001	.66
Delayed free recall	1.6 (2.3)	9.5 (2.5)	<.001	.72
Delayed cued recall	3.8 (2.4)	5 (2.0)	.05	.01
Total delayed recall (max = 16)	5.4 (4.1)	14.5 (1.9)	<.001	.65

Abbreviations: aMCI, amnestic mild cognitive impairment; FCSRT, Free and Cued Selective Reminding Test.

NOTE. Means and standard deviations (in brackets). Memory performance is significantly different between patients with aMCI and controls for all measures except for delayed cued recall.

explained variance (R^2) are also included. As can be seen on Table 2, comparison of age, education, depression, cognitive reserve, and vocabulary levels between aMCI patients and controls revealed significant differences between groups for all variables except for cognitive reserve. Analyses of covariance controlling for age, education, depression, and vocabulary levels were therefore performed on the different recall measures. All recall measures, except delayed cued recall, revealed significant differences between groups. None of the covariates showed, however, a significant effect on the recall measures (all $P > .161$ for immediate free recall, $P > .715$ for immediate cued recall, all $P > .329$ for total immediate recall, $P > .223$ for delayed free recall, $P > .206$ for delayed cued recall, and $P > .531$ for delayed total recall).

We also compared free and cued recall within groups to assess the extent to which semantic cueing would help recall. The results showed that, when decomposing total recall, free recall was predominant in healthy controls, but cued recall was predominant in patients with aMCI. More specifically, whereas free recall performance was better than cued recall at immediate [t (25) = −4.86; $P < .001$, $d = .95$] and delayed [t (25) = 5.5; $P < .001$, $d = 1.1$] stages for healthy controls, the opposite pattern was observed in patients with aMCI: with cued recall higher than free recall at immediate [t (26) = −3.08; $P < .01$, $d = .56$] and delayed [t (26) = −4.86; $P < .001$, $d = .94$] recall.

Table 2
Demographics of patients with aMCI and controls

Variable	aMCI	Controls	*P*
Age	75.6 (5.6)	68.6 (6.3)	<.001
MMSE	24.1(3.9)	29.3 (0.9)	<.001
Education	7.6 (3.0)	9.7(3.4)	<.005
Depression	4.9 (3.6)	2.0 (1.6)	<.001
Cognitive Reserve	8.8 (3.9)	14.8 (4.4)	.47
WAIS Vocabulary	30.3 (15.3)	51.4 (7.2)	<.001

Abbreviations: aMCI, amnestic mild cognitive impairment; MMSE, Mini–Mental State Examination.

NOTE. Means and standard deviations (in brackets). All variables that revealed a statistically significant difference between patients with aMCI and controls were controlled as covariates.

Fig. 1 represents mean ISDA indices (encoding, consolidation, and retrieval deficits) for patients with aMCI and control participants. We carried out a 2 (group) x 3 (type of index) analysis of variance, controlling for age, education, depression, and vocabulary levels as covariates. The results showed no main effects of any of these covariates (all $P > .478$ for encoding, $P > .07$ for consolidating, all $P > .352$ for retrieval deficit indexes). The type of index did not reveal a significant main effect either, and it did not interact with education, depression, age, or cognitive reserve (all $P > .25$). A significant effect of group was, however, revealed F (1, 47) = 27.78, $P < .0001$, $\eta_p^2 = .219$, and it interacted significantly with the type of deficit index F (2, 94) = 13.21, $P < .0001$, $\eta_p^2 = .371$.

Post hoc (Newman-Keuls) analyses revealed that the difference between patients with aMCI and controls was significant for the encoding ($P < .0001$) and consolidating ($P < .01$) deficit indexes, but not for retrieval ($P > .5$).

To evaluate the diagnostic accuracy of the standard FCSRT and ISDA measures in discriminating aMCI from cognitively healthy controls, the receiver operating characteristic [46,47] curve and the corresponding predictive values were performed. The receiver operating characteristic curves (see Table 3) revealed that the ISDA indices had good areas under the curve, with the Encoding deficit index revealing the best values (.97).

The optimal cutoff scores for maximum accuracy (Youden index, [48]) for the ISDA indices and recall measures, and their respective values of sensitivity, specificity, and confidence intervals are also presented in Table 4.

4. Discussion

The aim of this study was to investigate episodic memory in patients with aMCI by applying a method (ISDA) that

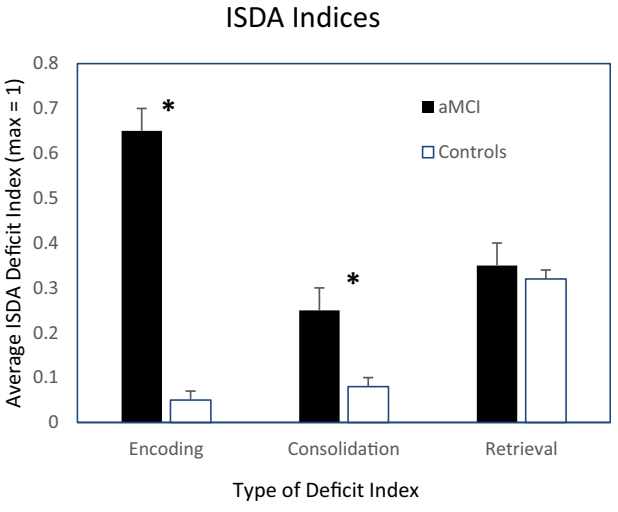

Fig. 1. ISDA indices (encoding, consolidation and retrieval) for patients with aMCI and controls. Higher deficit scores indicate poorer performance. Error bars represent standard errors. Abbreviations: aMCI, amnestic mild cognitive impairment; ISDA, item-specific deficit approach. * indicates significant difference at $P < .05$ level.

Table 3
AUCs for the three FCSRT ISDA indexes (encoding, consolidation, and retrieval) and 95% confidence intervals

ISDA indexes and types of recall	AUC	95% confidence intervals	
		Inferior	Superior
Encoding Index	.97	.93	1.01
Consolidation Index	.79	.67	.91
Retrieval Index	.56	.40	.72
Immediate free recall	.98	.95	1
Immediate cued recall	.81	.70	.92
Total immediate recall	.97	.93	1
Delayed free recall	.98	.95	1
Delayed cued recall	.66	.51	.81
Total delayed recall	.96	.92	1

Abbreviations: aMCI, amnestic mild cognitive impairment; AUC, area under the curve; FCSRT, Free and Cued Selective Reminding Test; ISDA, item-specific deficit approach.

NOTE. The results show great AUC for most measures except for the Retrieval Index and delayed cued recall that seem to discriminate less well between patients with aMCI and controls.

allows to dissociate the different mnemonic processes and quantify the possible deficits at encoding, consolidating, and retrieval. Our key prediction was that the main deficit would be located at the encoding stage, that is, the greater deficit index would be the encoding deficit index. That would confirm that early signs of memory difficulties in patients with aMCI are characterized as temporal or hippocampal deficits.

The results showed significant differences between patients with aMCI and controls in all FCSRT recall raw scores except in delayed cued recall. When analyzing the benefit of cues at recall, by comparing free and cued recall in both groups, the results revealed that cued recall was superior to free recall for both immediate and delayed recall in patients with aMCI (also see [15]), but the opposite (better free than cued recall) was observed in healthy controls. Also the percentage of explained variance (R^2) by the group effect on recall performance was greater for free than for cued recall in both immediate and delayed recall. This may be an important finding as the increase in cued recall observed in patients with aMCI in a situation of deep (semantic) learning suggests that part of the memory deficit observed in these patients relates to a difficulty in freely retrieving the material. It is however noteworthy that the very low delayed free (1.6 of 16) and cued (3.8 of 16) recall scores observed in these patients indicate that encoding of the items was poor. This is more so when considering that the low free delayed recall in patients with aMCI leaves more room for an increase in cued recall compared with healthy controls. The absence of significant differences in delayed cued recall between groups suggests therefore a signature for a clear encoding deficit in these patients.

Table 4
Sensitivity and specificity with 95% confidence intervals in brackets for FCSRT ISDA indexes and standard measures

ISDA indexes and types of recall	Sensitivity	Specificity	Cutoff score
Encoding Index	96.2 (81.1–99.3)	96.3 (81.7–99.3)	<.16
Consolidation Index	73.1 (53.9–86.3)	81.5 (63.3–91.8)	<.08
Retrieval Index	44.4 (27.6–62.7)	80.8 (62.1–91.5)	<.40
Immediate free recall	89 (72–96)	96 (81–99)	<16
Immediate cued recall	52 (34–69.3)	96 (81–99)	<12
Total immediate recall	89 (72–96)	96 (81–99)	<34
Delayed free recall	88 (72–96)	100 (87–100)	<5
Delayed cued recall	74 (55–87)	58 (39–75)	<5
Total delayed recall	85 (67–94)	100 (87.1–100)	<9

Abbreviations: aMCI, amnestic mild cognitive impairment; FCSRT, Free and Cued Selective Reminding Test; ISDA, item-specific deficit approach.

The data reveal that the most sensitive and specific deficit index is the Encoding index. Cutoff scores (Youden index) are also included.

When analyzing specifically encoding, consolidation, and retrieval processes using the ISDA method, we observed that the difference between patients with aMCI and controls was significant for the encoding and consolidating deficit indexes, but not for retrieval. Because the retrieval deficit index calculated for the FCSRT takes into account the number of items cued-recalled after a 30-minute delay, the present results, together with Oltra-Cucarella et al.'s [34], suggest that recall of items semantically encoded is a more resistant process, preserved in aMCI although affected in AD. Finally, it is worth noting that the results also revealed better sensitivity and specificity for free (delayed and immediate) than cued recall, confirming the idea that patients with aMCI also experience some difficulty with freely retrieving the items.

The encoding index came across as presenting the highest sensitivity (96.2%), with also high specificity (96.3%). Sensitivity and specificity were also high for standard recall measures. They were clearly higher than the ones observed in Saka et al.'s [30], where patients with MCI were not of amnestic profile.

Therefore, altogether, our results (recall performance, ISDA indices, areas under the curve, and sensitivity and specificity) confirm the hypothesis that there is a prominent encoding deficit in patients with aMCI. Consolidating is also affected, although in a smaller proportion.

In our analyses, none of the demographic variables (age, education, depression, crystallized intelligence, and vocabulary), considered as covariates in our analyses, showed a significant effect on the ISDA indices. Because most of the screening and cognitive tests are sensitive to education (i.e., [49]), this is an important result as it offers the advantage to be a specifically sensitive test to study memory differences between aMCI and healthy older adults.

These patients with MCI presented with an amnesic profile (aMCI, single or multidomain). Some diagnostic guidelines (i.e., [50]) recommend to include clinical information concerning biomarkers, as it may increase the likelihood of patients being in the AD continuum. In this study, we have not presented the results of core AD biomarkers, available in a small percentage of our patients. This might be considered a limitation. However, it is worth noting that Jack et al. [50] emphasize that this biomarker research

framework is "premature and inappropriate to use in general medical practice" because biomarkers are not always available (as was the case in our study due to different reasons). They conclude that the biomarker research framework "should not be used to restrict alternative approaches to hypothesis testing that do not use biomarkers" (p. 536). Future work might, however, consider to evaluate the relationship between the different FCSRT ISDA indices and core AD biomarkers.

To conclude, the present findings suggest that the ISDA analysis of FCSRT is a useful tool to confirm that a distinctive feature of memory deficits in patients with aMCI is located at the encoding memory stage. This is compatible with the pathophysiological changes of aMCI (a risk factor for AD), beginning primarily in the medial temporal limbic structures (e.g., entorhinal/transentorhinal cortex, hippocampus).

Acknowledgments

The authors thank the Ministry of Science, Innovation and Universities (REF PSI2016-75484-R) and IdISBa for providing funding grants to this project. They also thank Verónica Lobera for her contribution in data collection and Antonio del Olmo Rodríguez and Jose Miguel Santonja for their help in patient recruitment.

RESEARCH IN CONTEXT

1. Systematic review: We used MEDLINE, Scopus, and Web of Science to search, identify, and evaluate the accumulated knowledge related to our scientific question.
2. Interpretation: By using a method (ISDA) that allows quantifying memory deficits, this study confirms the existence of a genuine memory problem in people with the amnestic form of mild cognitive impairment. It demonstrates that the most prominent difficulty observed in patients with amnestic mild cognitive impairment relates to encoding and then consolidating new information in episodic memory. These results reveal that an encoding deficit (as measured by the Free and Cue Selective Reminding test) is highly sensitive to early decline of memory and suggest to focus on this memory process as an early diagnostic sign of cognitive decline.
3. Future directions: Future work could consider replicating these results in patients with biomarker evidence of Alzheimer's disease.

References

[1] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.
[2] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Demen 2011:270–9.
[3] Dubois B, Albert M. Amnestic MCI or prodromal Alzheimer's disease? Lancet 2004;3:246–8.
[4] Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. Lancet Neurol 2007;6:734–46.
[5] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011:280–92.
[6] Brookmeyer R, Abdalla D. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimers Dement 2018;14:981–8.
[7] Callahan B, Ramirez J, Berezuk C, Duchesne S, Black S. Predicting Alzheimer's disease development: a comparison of cognitive criteria and associated neuroimaging biomarkers. Alzheimers Res Ther 2015;7:68.
[8] Dukart J, Sambataro F, Bertolino A. Accurate Prediction of Conversion to Alzheimer's Disease using Imaging, Genetic, and Neuropsychological Biomarkers. Journall Alzheimer's Dis 2016:1143–59.
[9] Luis C, Abdullah L, Ait-Ghezala G, Mouzon B, Keegan A, Crawford F, et al. Feasibility of predicting MCI/AD using neuropsychological tests and serum β-amiloid. Int J Alzheimer's Dis 2011:786264.
[10] Palmqvist S, Hertze J, Minthon L, Wattmo C, Zetterberg H, Blennow K, et al. Comparison of brief cognitive tests and CSF biomarkers in predicting AD in mild cognitive impairment: six-year follow-up study. PLOS One 2012:e38639.
[11] Smith G, Bondi M. Mild cognitive impairment and dementia. Oxford: Oxford University Press; 2013.
[12] Loewenstein DA, Curiel RE, Duara R, Buschke H. Novel Cognitive Paradigms for the Detection of Memory Impairment in Preclinical Alzheimer's Disease. Assessment 2017;25:348–59.
[13] Rentz D, Parra M, Amariglio R, Stern Y, Sperling R, Ferri S. Promising developments in neuropsychological approaches for the detection of preclinical Alzheimer's disease: a selective review. Alzheimer's Res Ther 2013;5:58–68.
[14] Grober E, Buschke H. Genuine memory deficits in dementia. Developmental Neuropsychol 1987;3:13–36.
[15] Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988;38:900.
[16] Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. J Int Neuropsychological Soc 2008;14:266–78.
[17] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13:614–29.
[18] Grober E, Sanders AE, Hall C, Lipton RB. Free and cued selective reminding identifies very mild dementia in primary care. Alzheimer Dis associated Disord 2010;24:284–90.
[19] Grober E, Hall C, McGinn M, Nicholls T, Standford S, Ehrlich A, et al. Neuropsychological strategies for detecting early dementia. J Int Neuropsychol Soc 2008;14:130–42.

[20] Lemos R, Duro D, Simões MR, Santana I. The free and cued selective reminding test distinguishes frontotemporal dementia from Alzheimer's disease. Arch Clin Neuropsychol 2014;29:670–9.
[21] Teichmann M, Epelbaum S, Samri D, Levy M, Michon A, Hampel H, et al. Free and Cued Selective Reminding Test - accuracy for the differential diagnosis of Alzheimer's and neurodegenerative diseases: A large-scale biomarker-characterized monocenter cohort study (ClinAD). Alzheimer's Demen 2017;13:913–23.
[22] Janowsky J, Shimamura AKM, Squire L. Cognitive Impairment Following Frontal Lobe Damage and Its Relevance to Human Amnesia. Behav Neurosci 1989;103:548–60.
[23] Shimamura AP, Janowsky JS, Squire LR. Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. Neuropsychologia 1990;28:803–13.
[24] Fletcher PC, Henson RNA. Frontal lobes and human memory: Insights from functional neuroimaging. Brain 2001:849–81.
[25] Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica 1991:239–59.
[26] Rémy F, Mirrashed F, Campbell B, Richter V. Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. Neuroimage 2005;25:253–66.
[27] Graham NL, Emery T, Hodges JR. Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia. J Neurol Neurosurg Psychiatry 2004;75:61–71.
[28] Lipinska B, Bäckman L. Encoding-retrieval interactions in mild Alzheimer's disease: the role of access to categorical information. Brain Cogn 1997;34:274–86.
[29] Buschke H, Sliwinski MJ, Kuslansky G, Lipton RB. Diagnosis of early dementia by the Double Memory Test: Encoding specificity improves diagnostic sensitivity and specificity. Neurology 1997; 48:989–97.
[30] Saka E, Mihci E, Topcuoglu MA, Balkan S. Enhanced cued recall has a high utility as a screening test in the diagnosis of Alzheimer's disease and mild cognitive impairment in Turkish people. Arch Clin Neuropsychol 2006;21:745–51.
[31] Lemos R, Simões MR, Santiago B, Santana I. The free and cued selective reminding test: Validation for mild cognitive impairment and Alzheimer's disease. J Neuropsychol 2015;9:242–57.
[32] Wright MJ, Woo E, Schmitter-Edgecombe M, Hinkin CH, Miller EN, Gooding AL. The Item-Specific Deficit Approach to evaluating verbal memory dysfunction: Rationale, psychometrics, and application. J Clin Exp Neuropsychol 2009;31:790–802.
[33] Wright M, Schmitter-Edgecombe M, Woo E. Verbal memory impairment in severe closed head injury: The role of encoding and consolidation. J Clin Exp Neuropsychol 2010;32:728–36.
[34] Oltra-Cucarella J, Pérez-Elvira R, Duque P. Beneficios de la codificación profunda en la enfermedad de Alzheimer. Análisis del rendimiento en una tarea de memoria mediante el Item Specific Deficit Approach. Neurología 2014;29:286–93.
[35] Petersen R. Mild cognitive impairment: current research and clinical implications. Semin Neurol 2007;27:22–31.
[36] Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Neuroradiol 1987;8:421–6.
[37] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37–49.
[38] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatry Res 1975;12:189–98.
[39] Lobo A, Esquerra J, Gomez Burgada F, Sala JM, Seva A. El Mini-Examen Cognoscitivo: un test sencillo y práctico para detectar alteraciones intelectuales en pacientes médicos. *Actas Luso Esp* Neurol Psiquiatr 1979;3:189–202.
[40] Freedman M, Leach L, Kaplan E, Winocur G, Shulman K, Delis D. Clock-drawing: a neuropsychological analysis. New York, NY: Oxford University Press; 1994.
[41] Solomon P, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux R, et al. A 7minute neurocognitive screening battery highly sensitive to Alzheimer's disease. Arch Neurol 1998;55:349–55.
[42] Wechsler D. Wechsler Adult Intelligence Scale. 3rd ed. San Antonio, TX: Psychological Corporation; 1997.
[43] Rami L, Valls-Pedret C, Bartres-Faz D, Caprile C, Sole-Padulles C, Castellvi M, et al. Cuestionario de reserva cognitiva. Valores obtenidos en población anciana sana y con enfermedad de Alzheimer. Revista de Neurología 2011;52:195–201.
[44] Gramunt Fombuena N. Normalización y validación de un test de memoria en envejecimiento normal, deterioro cognitivo leve y enfermedad de Alzheimer. Blanquerna, España: Doctoral dissertation, Universitat Ramon Llull; 2008.
[45] Weissberger G, Strong J, Stefanidis K, Summers M, Bondi M, Stricker N. Diagnostic accuracy of memory measures in Alzheimer's dementia and MCI: a systematic review and meta-analysis. Neuropsychological Rev 2017;27:354–88.
[46] Altman DG, Bland JM. Diagnostic tests 3: receiver operating characteristic plots. BMJ 1994;188.
[47] Schisterman EF, Perkins NJ, Liu A, Bondell H. Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples. Epidemiology 2005:73–81.
[48] Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5.
[49] Jefferson A, Gibbons L, Rentz D, Carvalho J, Manly J, Bennet D, et al. A Life Course Model of Cognitive Activities, Socioeconomic Status, Education, Reading Ability, and Cognition. J Am Geriatr Soc 2011; 59:1403–11.
[50] Jack CR Jr, Bennett DA, Blennow K, Carrillo M, Dunn B, Haeberlein S, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Demen 2018; 14:535–62.