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ORIGINAL COMMUNICATION

Influence of controlled encoding and retrieval facilitation on memory performance of patients with subcortical ischemic vascular dementia and Alzheimer's disease

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Abstract
Patients with subcortical ischemic vascular dementia (SIVD) perform better than Alzheimer's disease patients (AD) on the Free and Cued Recall Selective Reminding test (FCSRT). In this test, SIVD are able to overcome their strategic retrieval deficit, whereas AD patients, whose memory impairment is due to a hippocampal storage deficit, are not. However, the FCSRT does not assess the advantage passing from free to assisted learning, which is expected to be different in frontal and hippocampal damage. We compared SIVD, AD and healthy subjects on the free recall of a 15-word list not assisted at encoding and on the free and cued recall of the FCRST. Indexes of Encoding, Cueing and Total (measuring the advantage passing from the 15-word list free recall to the free and cued recall of the FCRST) were computed. The two groups performed comparably poorly on the free recall of the 15-word list, but SIVD outperformed AD patients in the free and cued recall of the FCSRT and took greater advantage than AD patients on both learning and recall when passing from the unassisted to the assisted paradigms. All indexes significantly predicted diagnostic group membership, but the Total Index showed the larger classification accuracy with 80% of AD and 71% of SIVD correctly classified. These results confirm that the FCRST is able to differentiate AD and SIVD patients with a good level of accuracy. However, the evaluation of memory performance variation as a function of support to encoding provides additional data able to increase diagnostic reliability.

Keywords Alzheimer's disease · Vascular dementia · Memory disorders · Grober–Buschke memory procedure

Introduction

Recently, the diagnostic guidelines for the diagnosis of dementia due to Alzheimer's disease (AD) were revised based on increased clinical and biological knowledge of the disease. Nevertheless, although biomarker assessment is expected to enhance the specificity of the diagnosis, the core clinical criteria of AD continue to be the cornerstone of the diagnosis in clinical practice [1]. In particular, consistently with the precocious involvement of mesiotemporal lobe regions by degenerative changes [2, 3], a deficit of episodic memory is typically the earliest symptom of AD [4]. However, memory impairment occurs frequently in many other conditions of the elderly, such as depression, frontotemporal dementia or the subcortical–frontal dementias and, not infrequently, early in the disease course and when other symptoms specific to each type of dementia have not yet completely developed [4]. In this context, particular attention has been given to characterizing the qualitative aspects of the memory deficit. Indeed, episodic memory loss in patients with AD is due to deficient consolidation of memory traces and, therefore, it is characterized by poor learning and rapid memory decay as well as by reduced improvement when elaborative encoding at study is assisted or when subjects have to perform retrieval tasks with minimal demands, such as cued recall or recognition [5]. This memory profile (also called "hippocampal type amnesia" [6]) is considered crucial for differentiating memory loss due to AD from other clinical conditions in which the memory deficit is mainly due to attentional difficulties (such as those that occur in depression) or deficits in executive functions

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(typical of normal ageing, frontotemporal or subcortical dementias) that are responsible for inefficient encoding and/or poor retrieval strategies [4]. In the latter cases, in fact, the underlying pathology primarily affects cortical/subcortical frontal lobe circuits and causes malfunctioning of encoding/retrieval strategies rather than reduced consolidation of memory traces; in fact, the memory deficit of these individuals may improve when testing procedures are used which assist the elaborative encoding of memoranda or provide cues during the retrieval phase [7].

In this context, specific neuropsychological paradigms able to differentiate memory loss due to hippocampal pathology from "frontal-like" memory deficits have been strongly recommended [4]. In fact, Grober and Buschke's [8] free and cued recall selective reminding test (FCSRT) has been widely used in the neuropsychological literature to characterize the qualitative aspects of memory loss in dementia. In this procedure, participants are guided during the study phase to actively organize items on a list according to their semantic category, to assure that possible executive deficits do not affect the elaborative encoding of memoranda. During the testing phase, following a free recall procedure (in which the subjects recall as many items as they can without any assistance), the category cues of words that are not freely recalled are provided by the examiner for the retrieval, to facilitate the recollection of those items which, despite being stored, are not retrieved for strategy problems. The critical result is the larger improvement rate passing from free to cued recall disclosed by individuals with a "frontal-like" with respect to a "hippocampal type" amnesia. Indeed, the encoding support and the cued recall condition in the FCSRT permit these subjects to overcome their executive deficits and to achieve a better memory performance than when they are not supported in the encoding and retrieval phases. This memory profile, which is peculiar to patients with involvement of the prefrontal cortex, is not observed in patients with AD because, as noted above, the poor learning and rapid memory decay of these patients is due to defective consolidation of the memory traces, thus not allowing a significant improvement when the elaborative encoding at study is supported and category cues are provided by the examiner at retrieval. Indeed, Pasquier et al. [9] and Lemos et al. [10] used the FCSRT procedure and demonstrated that although AD patients and patients with frontotemporal dementia performed similarly on free recall, patients with frontotemporal dementia outperformed AD patients significantly on cued recall. Previously, Pillon et al. [11] documented that in spite of a slight difference in free recall between AD patients and patients with various subcortical forms of dementia (such as progressive supranuclear palsy, Huntington's disease and Parkinson's disease with dementia), on the cued recall test subcortical dementia groups largely outperformed AD patients.

Vascular dementia is an umbrella term which includes patients affected by a heterogeneous group of ischemic or hemorrhagic changes affecting the central nervous system, including cortical and/or subcortical infarcts, white matter disease, silent brain infarcts, subcortical lacunar strokes, large vessel strokes and micro- as well as macroscopic brain haemorrhages [12]. Due to the large variability in the size and location of vascular-related changes, the neuropsychological profile of patients with vascular dementia varies greatly. Subcortical ischemic vascular dementia (SIVD) is a common and relatively homogeneous subtype of vascular dementia [13, 14] caused by cerebral small vessel disease and hypoperfusion which produce either arteriolar occlusion and lacunes or widespread incomplete infarction of white matter [15]. The neuroimaging-based research criteria for SIVD include predominant periventricular and deep white lesions and multiple lacunar infarcts [13]. In SIVD, cognitive decline, which predominantly affects executive functions [16–18], is usually considered to be due to the increasing number and volume of lacunar lesions, especially those located strategically within the frontal subcortical loops [19]. Indeed, there is general agreement that even though subcortical ischemic damage is diffuse and typically located in a distributed manner, it mainly interferes with the anterior network of cortical brain structures by disrupting the cortical connections mediated by specific white matter traits [17, 20, 21].

Memory deficits are not only consistently observed in SIVD patients [22], but they may be as severe as in AD [23], raising the question about whether the memory impairment is only of the subcortical frontal type or whether hippocampal damage contributes to it and, if so, to what extent. In agreement with the prevalent localization of vascular damage at the level of white matter projections to prefrontal cortex and consistent with the evidence of an executive deficit as the most prominent cognitive characteristic associated with SIVD, their memory deficits have been generally interpreted as a frontal-like memory disorder. Indeed, similar to patients with frontal lobe dysfunction, patients with SIVD typically show defective strategic learning and self-guided retrieval difficulties with relatively preserved performance on non-strategic memory tasks [24, 25]. However, at partial variance with the subcortical lacunar hypothesis, hippocampal atrophy has also been documented in this pathology [26, 27] and a correlation between cognitive decline and hippocampal atrophy in these patients has been found [28]. Moreover, concomitant AD-related pathology in mesiotemporal lobe structures has been reported in an autoptical series of SIVD patients [29]. This raises the possibility that in patients with SIVD the memory impairment may be related to the involvement of both hippocampal and frontal lobe structures. Cerciello et al. [30] reported results in partial agreement with this hypothesis. These authors used the

FCRST to compare immediate and delayed memory performance in groups of AD, FTD and SIVD patients with comparably mild dementia severity. They found that AD patients had lower free and cued recall in respect to the other two groups and were less sensitive to cueing, thus supporting the hypothesis that their memory disorder closely depended on a storage deficit. Conversely, patients with SIVD showed in the immediate recall trials a memory performance similar to that of FTD patients, characterized by a strong sensitivity to cueing, thus suggesting a difficulty in spontaneously implementing efficient retrieval strategies at the origin of their memory disorder. However, in the delayed recall trial SIVD patients showed a larger forgetting rate and a lesser advantage from the availability of category cues in respect to FTD patients. This result does not conform to the hypothesis of an exclusive frontal-like origin of the memory impairment in SIVD patients, rather, it seems to suggest a concomitant hippocampal involvement responsible of rapid decay of the memory traces.

The aim of this study was to further evaluate the effectiveness of FCRST in differentiating patients affected by SIVD from patients with AD of comparable dementia severity. In consideration of the ambiguous results of the only previous study which investigated SIVD patients with FCRST [30], we included here a further condition, namely the free recall of a word list whose encoding during the study phase was not assisted. In this way, in the present study we had two main contrasts: (1) the free recall of a list which had not been assisted at encoding vs the free recall of an encoding assisted list, and (2) the free vs the cued recall of the same list previously assisted at encoding. We predicted that the proposed different mechanisms underlying the memory deficit in AD and SIVD dementias (namely a hippocampal-like consolidation deficit in the former group and, conversely, a prevalent frontal-like impairment in elaborative encoding and strategic retrieval in the latter group) would be revealed by the distinct memory profiles on this memory paradigm. In particular, we expected that SIVD patients benefit of both assisted category encoding during the study phase and category cues at retrieval more than AD patients; this would be revealed by a larger performance improvement passing from the free recall of the encoding unassisted list to the free recall of the encoding assisted list and from the free to the cued recall of the encoding assisted list.

Methods

Subjects

Twenty subjects suffering from AD (14 F and 6 M), 17 with a diagnosis of SIVD (6 F and 11 M) and 20 healthy subjects (10 F and 10 M) were recruited from the Memory Unit of Foundation IRCCS Santa Lucia of Rome. All AD patients met the clinical criteria established by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for the diagnosis of probable AD [1]. They showed the typical AD symptoms (insidious onset, predominant and progressive memory deficit coupled with disorientation, language and visuospatial disorders) and MR (19 cases) or CT (2 cases) evidencing cortical atrophy with an exclusive or prevalent involvement of the medial temporal lobes. The SIVD patients were diagnosed on the base of the NINDS-AIREN criteria for vascular dementia [31] and the criteria specifically devised for SIVD [13, 15]. All of them had MR exam evidencing relevant subcortical ischemic damage and a Hachinski ischemic score ≥ 5. Patients with concomitant subcortical ischemic damage and diffuse cortical atrophy (possible mixed vascular/degenerative dementia cases) as well as patients with large ischemic infarcts were not included in the study.

Common inclusion criteria for participants in both the AD and SIVD groups were: (1) school attendance ≥ 5 years; (2) first admission to the Memory Unit, (3) not affected by previous or current neurological diseases or current severe medical conditions, (4) affected by a mild level of dementia, as confirmed by a Mini-Mental State Examination (MMSE) [32] score > 18 and a Clinical Dementia Rating [33] score ranging from 0.5 to 1, (5) absence of moderate to severe depression and/or anxiety as revealed by Beck Depression Inventory [34] and Hamilton Anxiety Scale [35]) scores ≤ 14). Inclusion criteria for NC participants were the following: (1) absence of current or previous neurological or psychiatric disorders; (2) no history of alcohol or drug abuse; (3) absence of subjective memory disturbance; (4) MMSE score > 27.

Research and manuscript have been performed in agreement with the ethical standards of the Committee on Human Experimentation of the IRCCS Santa Lucia Foundation, Rome, Italy, in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All authors report no conflict of interests.

General neuropsychological assessment

The general neuropsychological assessment battery included tests that evaluate the following cognitive domains: episodic memory (Immediate and Delayed Recall of a 15-Word List [36]; Rey's Immediate and Delayed Figure Recall [37]), short-term memory (Digit Span and Corsi Block Tapping test [38]), executive functions (Phonological Word Fluency [36]; Modified Card Sorting test [39]), language (Naming of objects and action subtests of the Battery for the Analysis of Aphasic Deficits [40]), abstract reasoning (Raven's

Coloured Progressive Matrices [36]), constructional praxis (Rey's Figure Copy [37]), praxis (Copy of Drawings and Copy of Drawings with Landmarks [36]). Published normative data for score adjustment according to age, education and gender as well as normality cutoff scores (corresponding to a performance ≥ 95% of the lower tolerance limit of the normal population distribution) are available for all tests.

Free recall of 15-Word list

To assess the free learning and recall of a list of items whose encoding at the time of study was not assisted by the examiner, patients were also administered the Immediate and Delayed recall of a 15-Word list test [36]. The material for this test consists of a list of 15 unrelated names of concrete objects. The examiner reads the word list aloud five times. Immediately following each presentation and 15 min after the last one, the patient is requested to recall as many words as possible without a time limit and in any order. The Immediate recall score consists of the total number of words recalled in the five immediate trials (range 0–75) and the Delayed score consists of the number of words recalled after the 15 min delay (range 0–15). This task was part of the general neuropsychological assessment and therefore was administered to all subjects a week before the Grober and Buschke procedure (see below).

Grober and Buschke procedure

For the assessment of memory performance in a condition in which both the encoding during the study phase and the retrieval during the recall phase were assisted, we used a modified version of the original FCSRT paradigm, as in our previous research studies [41, 42]. The material consists of 24 figures that belong to 12 different semantic categories (flowers, musical instruments, animals, desserts, clothing, vegetables, vehicles, jobs, furnishings, drinks, tools and fruits), 2 objects for each individual category (e.g., musical instruments: a harp and a drum; flowers: a tulip and a poppy; jobs: a teacher and a mason; animals: a hen and sheep, etc.).

In the study phase, six tables, each representing four figures from different semantic categories, are individually presented to the subject. During the presentation of each table, the examiner names a category and the subject has to point to and name the picture that belongs to that category. For instance, when the examiner says "clothes", the subject has to point to and name the item on the table that can be classified in this category (e.g., "tie"). Immediately after all four items are correctly identified, the table is covered and the subject's memory of the items on the just presented table is examined by means of a category cued recall test (i.e., the examiner names a category and the subject has to name the item belonging to that category which was present on the table). If the subject fails to recall one or more items, the table with the four pictures is shown again and the above procedure is repeated until he/she accurately retrieves all four items.

After the study phase, two test phases are administered. In the immediate test, after a 20-s delay in which the subject is engaged in an attentional task (i.e., counting backwards from 20 to 1), an immediate free recall test is administered. When the subject shows that he is unable to recall any other studied items, a category cued recall task for the items that were not freely recalled is given. For the items that are not recalled even after the category cue, the examiner provides the correct response. This phase (free recall followed by cued recall) is repeated three times in a row. Following a 15-min delay, during which subjects are administered intercurrent cognitive tasks that do not involve learning or verbal data processing (e.g., constructional praxis test), a single delayed test of free recall followed by a category cued recall test is administered with the same modalities as above.

The two test phases provide Free recall scores (number of items freely recalled) and Cued recall scores (number of items recalled in both the Free and Cued tests) (range 0–72 for the immediate test and 0–24 for the delayed test).

Sensitivity indexes

The performance scores on the FCRST Cued recall are a spurious measure of the effectiveness of semantic cues in improving item retrieval. In fact, since Cued recall is performed only on the items that are not recollected in the Free recall test, it is highly dependent on Free recall performance. To control for this effect, in line with Sarazin et al. [43] we computed an Index of Cueing using the following formula: (% Total recall score − % Free recall score)/(100 − % Free recall score). In the statistical analyses, we used this index to quantify the facilitation effect of Cued recall compared to Free recall. Analogously, we computed also an Index of Encoding which quantified the percentage improvement passing from recall of the 15-word list to the FCRST Free recall using the formula (%FCRST Free recall score − %15 Word-list recall score)/(100 − % 15-Word-list recall score). Finally, we computed a Total Index quantifying the overall improvement provided by the assistance in encoding and retrieval, i.e., passing from the 15-Word list recall to the FCRST Cued recall, using the formula (% Total recall score − % 15 Word-list recall score)/(100 − % 15 Word-list recall score). Since we were interested in evaluating the effect exerted by the presence or absence of an external support to encoding and/or retrieval on the long-term memory performance of AD and SIVD participants, and since the immediate recall trials of both the FCRST and the 15-Word list test are contaminated by short-term memory processes (e.g., the recency effect in immediate recall), we compared

groups only on the delayed recall tests and on the delayed Indexes of Cuing, Encoding and Total.

In summary, with the computation of these indexes, we had three measures of the patients' advantage in delayed recall passing from (1) free encoding/free recall to assisted encoding/free recall (Index of Encoding), (2) assisted encoding/free recall to assisted encoding/cued recall (Index of Cuing), (3) free encoding/free recall to assisted encoding/cued recall (Total Index), with the aim of differentiating the qualitative pattern of memory disorder in hippocampal-like from frontal-like patients.

Statistical analysis

One-way ANOVAs were performed with group (AD, SIVD and NC) as between factor and general data as dependent variables. However, only AD and SIVD groups were compared by one-way ANOVAs on the tests of the neuropsychological battery. A mixed two-way ANOVA with group as between factor (AD, SIVD and NC) and test (15 Word-list recall vs FCSRT free recall vs FCSRT cued recall) as within factor was performed to analyse performance accuracy on the delayed recall of the experimental tests. Instead, one-way ANOVAs were used to compare the three groups on Encoding, Cuing and Total Indexes. Finally, to assess the ability of the three indexes to discriminate AD and SIVD group membership, a series of logistic regression analyses were conducted with the three indexes, i.e., Cueing, Encoding and Total as dependent variables and AD and SIVD group membership as the independent variable.

Results

Subjects

As can be seen in Table 1, subjects in the AD, SIVD and NC groups were comparable for age and years of formal education. As expected, the three groups differed on the MMSE because NCs obtained higher scores than the AD and SIVD groups ($p < 0.001$ in both comparisons); the two dementia groups did not differ from each other ($p = 0.17$). Finally, as expected, the SIVD patients obtained significantly higher Hachinski ischemic scores than the AD patients. Patients in the SIVD group had overall a higher prevalence of vascular risk factors that AD patients: hypertension in 8 AD and 14 SIVD patients; hyperlipidemia in 3 AD and 14 SIVD patients; diabetes mellitus in 4 AD and 6 SIVD patients; atrial fibrillation in 4 SIVD patients; current smoking in 1 AD and 3 SIVD patients.

Table 1 Means (and standard errors) of age, years of formal education and MMSE score for AD, SIVD and NC groups

	AD	SIVD	NC	*F*	*p*
M/F	4/16	11/6	10/10		
Age	76.4 (1.1)	77.9 (1.3)	76.5 (1.2)	0.46	n.s.
Education	8.9 (1.0)	10.0 (1.1)	10.0 (1.0)	0.42	n.s.
MMSE	22.8 (0.5)	23.8 (0.5)	29.9 (0.5)	50.59	< 0.001
Hachinski ischemic score	.30 (0.3)	7.0 (0.3)	–	232.11	< 0.001

General neuropsychological assessment

Table 2 reports means and SEs of the raw test scores obtained by AD and SIVD patients on the tasks of the neuropsychological assessment battery. No significant difference between groups was detected for any test.

Word-list recall procedures

Percentage scores obtained by AD, SIVD and NC groups on the delayed recall of the 15-Word List and delayed Free and Cued recall of the FCSRT are reported in Fig. 1. As can be seen, all groups disclosed a recall accuracy increase passing from the 15-Word list to the FCRST Free and Cued recall. Passing from free recall of the unassisted (15-Word list) to the assisted (FCRST) list, the rate of improvement was larger in NCs than in the two groups of demented patients and in the SIVD than in the AD group. Instead, passing from the FCRST Free to Cued recall, the rate of improvement was very limited in the NC group (because of a ceiling effect of performance) and considerably larger in the SIVD than in the AD group.

The ANOVA showed a significant group effect [$F_{(2,53)} = 75.92$, $p < 0.001$], because NCs (M = 72.6, SE = 2.9) performed better than both AD (M = 22.9, SE = 2.9, $p < 0.001$) and SIVD (M = 40.6, SE = 3.2, $p < 0.001$) patients and participants with SIVD were more accurate than those with AD ($p < 0.001$). The test effect was also significant [$F_{(2,106)} = 251.40$, $p < 0.001$]. Post hoc comparisons showed that across groups the percentage accuracy on the FCSRT Cued recall (M = 72.5, SE = 2.5) was better than on the FCSRT Free recall (M = 44.2, SE = 2.3), which in turn was better than on the 15-Word list recall (M = 19.4, SE = 1.7) ($p < 0.001$ in all comparisons). Finally, the group × test interaction was also significant [$F_{(4,106)} = 11.40$, $p < 0.001$]. Planned comparisons made to qualify this interaction revealed that although the NC group obtained higher percentage scores on the 15-Word list recall than either the AD or the SIVD groups ($p < 0.001$, in both comparisons) which, in turn, did not differ each other ($p = 0.12$), on both the FCRST Free and Cued recall NCs obtained higher scores than both SIVD

Table 2 Means (and standard errors) of raw scores obtained by AD and SIVD patients on the tests of the neuropsychological battery

Tests	AD	SIVD	*F*	*p*
Episodic long-term memory				
Immediate Recall of a 15-Word List	18.6 (1.4)	21.1 (1.7)	0.57	n.s.
Delayed Recall of a 15-Word List	1.4 (0.4)	1.8 (0.4)	0.46	n.s.
Rey's Figure Immediate Recall	2.8 (0.9)	3.9 (1.2)	1.40	n.s.
Rey's Figure Delayed Recall	2.1 (1.1)	3.2 (1.3)	0.75	n.s.
Short-term memory				
Digit Span	4.6 (0.3)	4.5 (0.4)	0.23	n.s.
Corsi Block Tapping	3.6 (0.2)	3.5 (0.3)	0.01	n.s.
Executive functions				
Phonological Word Fluency	25.7 (2.6)	21.7 (3.2)	3.89	n.s.
Modified Card Sorting test	1.1 (0.3)	2.25 (0.4)	3.67	n.s.
Abstract reasoning				
Raven's Coloured Progressive Matrices	20.1 (1.5)	22.7 (1.9)	0.47	n.s.
Praxis				
Rey's Figure Copy	16.6 (3.3)	17.5 (4.1)	0.25	n.s.
Copy of Drawings	6.5 (0.6)	8.2 (0.7)	0.29	n.s.
Copy of Drawings with Landmarks	59.8 (1.8)	63.2 (2.2)	0.25	n.s
Language				
Naming of Objects	26.0 (1.0)	287.1 (1.2)	0.19	n.s.

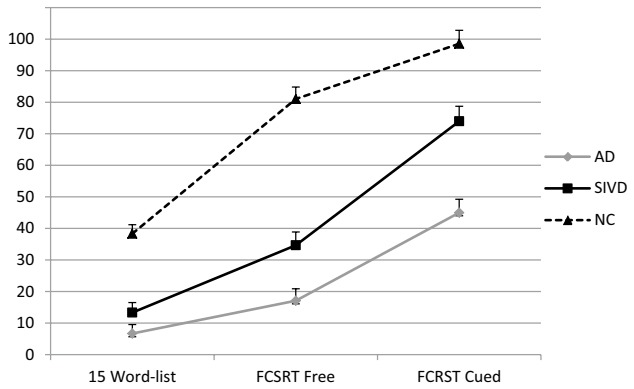

Fig. 1 Percentage performance scores (and standard errors) obtained by participants of the NC, AD and SIVD groups on the 15-word list delayed recall and delayed Free and Cued Recall of the FCSRT

and AD groups ($p < 0.001$ in all comparisons) and patients in the SIVD group performed better than AD participants ($p = 0.003$ and $p < 0.001$ in Free and Cued recall, respectively). Moreover, planned comparisons documented that the rate of improvement passing from the 15-Word list to the FCRST Free recall was significantly larger in NCs than in both the SIVD [$F_{(1,53)} = 11.80$, $p = 0.001$] and AD [$F_{(1,53)} = 30.26$, $p < 0.001$] groups, whereas the larger improvement in the SIVD than the AD group approached significance [$F_{(1,53)} = 3.06$, $p = 0.08$]. Instead, passing from the FCRST Free to Cued recall, the SIVD group obtained a significantly higher advantage than the AD group [$F_{(1,53)} = 6.40$, $p = 0.01$].

Table 3 Mean values (and standard errors) of the indexes quantifying the rate of improvement on experimental tests as a function of encoding or retrieval assistance in the three experimental groups

Groups	Index of encoding	Index of cueing	Total index
AD	0.12 (0.05)	0.38 (0.04)	0.42 (0.05)
SIVD	0.26 (0.05)	0.63 (0.05)	0.71 (0.05)
NC	0.67 (0.05)	0.93 (0.04)	0.97 (0.05)

Values of indexes quantifying the improvement rate as a function of encoding or retrieval assistance are reported in Table 3. One-way ANOVAs revealed a highly significant difference between groups for all indexes, Encoding: $F_{(2,53)} = 33.33$, $p < 0.001$; Cueing: $F_{(2,53)} = 38.42$, $p < 0.001$; Total: $F_{(2,53)} = 37.25$, $p < 0.001$). Post hoc comparisons revealed that for all indexes NCs had significantly higher values than the two dementia groups (p consistently < 0.001). The SIVD group, in turn, had significantly higher values than the AD group (Index of Encoding: $p = 0.05$; Index of Cueing: $p < 0.001$; Total Index: $p < 0.001$).

Logistic regression analysis

Results of the logistic regression showed that, taken singularly, the Cueing and Total Indexes significantly predicted diagnostic group membership ($t = 4.33$; $p < 0.007$ and $t = 4.23$; $p < 0.004$, respectively), whereas the predictive power of the Encoding Index approached significance ($t = 0.163$; $p = 0.05$). However, when the three predictors

were inserted together, only the Total Index survived ($t = 4.23$; $p < 0.004$), with 80% of AD and 71% of SIVD correctly classified.

Discussion

Although AD and SIVD are typically characterized by different profiles of cognitive decline, frequent similarities have been documented that may impede differential diagnosis based on the results of the neuropsychological assessment [14, 43]. In particular, although the cognitive hallmark of AD is an episodic memory deficit, whereas the cognitive decline in SIVD patients typically involves executive functions [17, 18], lower performance on memory tests has also been frequently reported in SIVD patients, sometimes with a severity level not dissimilar to that of AD patients [22, 23]. It has been suggested, however, that the genesis of the memory impairment is dissimilar in the two conditions: i.e., in AD it is mainly due to defective consolidation of episodic memory traces resulting from hippocampal pathology and in SIVD to deficient elaborative encoding and/or inefficient strategic retrieval resulting from frontal-like executive dysfunction. Nevertheless, mixed results have been reported by studies aimed at investigating the qualitative characteristics of the memory impairment in these two populations of demented patients. Some studies have supported the above hypothesis of discrepant memory profiles [24] and others have reported a more homogeneous deficit in the two groups [22, 23]. In particular, a recent study investigated the performances of SIVD and AD patients on the FCSRT and, consistently with the assumption of a deficit in vascular patients in implementing autonomous retrieval strategies, it reported a larger improvement rate in SIVD than in AD patients passing from Free to Cued recall [30]. However, SIVD patients performed better than AD patients also on Free recall, suggesting that the lack of a support to retrieval (as occurs in FCRST free recall) does not completely account for impaired memory performance in vascular patients. Indeed, this finding was probably an expression of the fact that assisted encoding in the FCSRT facilitated their memory performance even in a condition in which no help was given at retrieval. Indeed, the FCRST permits appreciating the effect of cueing with respect to free memoranda retrieval, but does not permit evaluating the effect of the support to encoding during the study phase with respect to non-assisted learning. Thus, in the attempt to replicate previous FCRST data (which demonstrate greater improvement in SIVD that in AD patients passing from free to cued recall) and to extend this observation by assessing performance improvement passing from the retrieval of an encoding unassisted list of items to the retrieval of an encoding assisted list, we compared a group of AD and one of SIVD patients and a group of matched NC on the delayed recall of 15-Word list task (in which the examiner provides no assistance at either encoding or retrieval) and on the delayed free and cued recall of the FCRST. The performance improvement passing from free recall of the encoding unassisted list to recall of the encoding assisted list and from the free to cued recall of the encoding assisted list was quantified as Encoding, Cue and Total Indexes by means of computational procedures which took into account the number of unrecalled items in the least supported list. The two groups of patients were comparable for overall severity of dementia and level of memory impairment based on their performance results on a broad neuropsychological screening battery that also included the immediate and delayed recall of a 15-Word List and Rey's Figure.

Results were quite straightforward in supporting the view of the differential sensitivity of the two groups of demented patients to the external support provided in both the encoding and retrieval phases. Indeed, the lack of any support (which occurred in the Free recall of the 15-Word list) rendered fully comparable the performances of the SIVD and AD groups. Such comparably poor performance was, however, likely due to different kinds of impairments in the two groups of demented patients. Indeed, providing assistance at encoding (as in the FCRST free recall) and, even more, a support for retrieval (as in the FCRST cued recall) rendered the performance levels of the two groups strikingly dissimilar; that is, it improved the performance of SIVD patients much more than that of AD patients. This differential sensitivity of the two groups of patients to the encoding and retrieval assistance was reflected in better diagnostic accuracy when performance on the 15-Word list was considered together with that on the FCRST. Indeed, a logistic regression analysis documented that the Total Index, which took into account improvement rates resulting from both assistance at encoding and support at retrieval, correctly classified the membership of the two groups of demented patients more accurately than the Encoding and Cue Indexes, which considered the two kinds of improvement separately.

These results are by and large consistent with the view that the memory impairment in AD and SIVD patients is mainly based on distinct deficits: a hippocampal failure in storing new information resistant to facilitating strategies such as controlled learning and retrieval cues in AD and, conversely, impairment of executive strategies that prevents efficient elaborative encoding and strategic retrieval recall in SIVD [24]. These results, on the other side, do not support the view that a consolidation deficit or an executive impairment are the only factors responsible for the disrupted episodic memory in AD and SIVD, respectively. Indeed, suggesting that some deficit in the consolidation of new memory traces is also present in SIVD patients, even with full external support (as in the FCRST cued recall), the performance of vascular patients remained considerably

worse than that of NCs. On the other side, the experimental procedures used here are not appropriate for excluding that a concomitant executive deficit could have contributed to the episodic memory deficit in patients with AD. In fact, although not expressly selected for this purpose, the results of the neuropsychological screening battery documented a comparably severe executive dysfunction in AD and SIVD groups (thus leading us to surmise that some of the memory deficit in these patients actually resulted from poor encoding or retrieval strategies. In conclusion, the dichotomy between "hippocampal" vs "frontal" memory impairment in the two groups of patients is not absolute but relative. It is, however, sufficiently remarkable to characterize the performances of the two groups of patients and to make them distinguishable when opportune testing instruments are used that are able to highlight the contribution of consolidation and executive deficits to the appearance of the memory deficit.

Several limitations of the present study should be considered: the relatively small size of the experimental samples that could have minimized significant differences among groups in the clinical memory tests, the lack of CSF biomarkers and/or amyloid PET imaging which would have permitted a more accurate classification of patients, the lack of homogenous neuroimaging data which would have allowed relating the qualitative patterns of memory impairment to the crucial neuroanatomical regions (either frontal or mesiotemporal) and, finally, the heterogeneity of the testing materials used to evaluate performance in different experimental conditions. In particular, the 15-Word list test differed from the FCRST in many respects (e.g., the number of items to be learned, verbal vs pictorial memoranda, 3 vs 5 immediate recall trials) besides that of the interests of the present study (i.e., providing a measure of free recall of items following the unassisted encoding condition to be compared with free and cued recall after assisted encoding condition). Future studies should compare AD and SIVD patients (and probably other groups of demented patients and patients with amnestic mild cognitive impairment or prodromal AD) with a new instrument developed specifically to contrast the various experimental conditions of the present study on homogeneous testing material.

In sum, results of the present study confirm that the FCRST, which provides a measure of memory performance variation as a function of external support to retrieval, is able to differentiate between AD and SIVD patients with a good level of accuracy. The provision of another experimental condition, which permits evaluating memory performance variation as a function of support to encoding, provides additional data able to increase diagnostic reliability. This suggests that a new testing instrument based on homogenous material and testing modalities could improve diagnostic accuracy based on memory data in patients with different forms of dementia.

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Compliance with ethical standards

Conflicts of interest All authors report no conflicts of interest.

Ethical standards Research and manuscript have been performed in agreement with the ethical standards of the Committee on Human Experimentation of the IRCCS Santa Lucia Foundation, Rome, Italy, in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experimentsinvolving humans. This study was supported by the Italian Ministry of Health (grant number 217/RF-2013-02359074).

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