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Impact of Executive Dysfunction on Verbal Memory Performance in Patients with Alzheimer's Disease

Ezequiel Gleichgerrcht[a,c,*], Teresa Torralva[a,b,c], Daniel Martinez[a], María Roca[a,c] and Facundo Manes[a,c,*]
[a]*Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina*
[b]*Laboratory of Neuroscience, Universidad Diego Portales, Santiago, Chile*
[c]*Institute of Neurosciences Favaloro University, Buenos Aires, Argentina*

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Abstract. It is currently accepted that there is a subset of patients diagnosed with Alzheimer's disease (AD) who show executive functioning (EF) impairments even in the earlier stages. These patients have been shown to present distinct psychiatric, behavioral, occupational, and even histopathological profiles. We assessed thirty patients with AD on two tasks of verbal memory (Logical Memory – LM, and the Rey Auditory-Verbal Learning Task – RAVLT), as well as classical tests of EF. AD patients were classified into either a spared EF (SEF) group if they showed impaired performance ($z < -1.5$ SD) in none or only one of the executive tests, or into an impaired EF (IEF) group if they showed impaired performance on two or more tasks of EF. Their performance was compared with fourteen healthy controls. SEF showed significantly more years of education than IEF, but the groups did not differ significantly on age, gender, mood symptoms, or performance on general screening tests or attentional tasks. With education as a covariate, both AD groups differed from controls on all measures of memory, but a significant difference was found between SEF and IEF patients only on the recognition phases of both logical memory ($p < 0.01$) and RAVLT ($p = 0.02$). Recognition scores significantly correlated with performance on executive tasks. Early AD patients who preserve their EF seem to have an advantage in their ability to recognize information that has been previously presented over patients with impaired EF. Such advantage seems to be strongly associated with executive performance.

Keywords: Alzheimer's disease, dementia, executive functions, neuropsychology, verbal memory

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly [1–3]. While it is now well established that memory impairments, language deficits, and decline in certain visuospatial abilities are central to the cognitive profile of these patients [4], some authors have showed that executive functioning (EF) is also impaired in AD [5–7], even during its early stages [8]. In fact, a frontal variant of AD has been proposed on the basis of clinical, histological, and molecular evidence. Briefly, AD patients presenting with marked executive dysfunction (EDF) tend to exhibit biochemical changes in the prefrontal cortex [9], prominent histopathological evidence for neuronal degeneration in the frontal lobes at postmortem [10], a higher frequency of psychiatric symptoms [7, 11, 12], as well as poorer performance on activities of daily living [7]. Indeed, Chen et al. [13] have proposed shared neurobiological mechanisms involving the frontal lobes in order to explain the executive impairment associated with neuropsychiatric symptoms and functional disability in patients with AD.

*Correspondence to: Ezequiel Gleichgerrcht or Facundo Manes, Castex 3293, Capital Federal, BA, Argentina (1425). Tel.:/Fax: +54 11 4807 4748; E-mail: egleichgerrcht@neurologiacognitiva.org (E. Gleichgerrcht), fmanes@neurologiacognitiva.org (F. Manes).

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Besides the recognition of such differential clinical profile for AD patients with EDF, little evidence is available regarding the potential cognitive differences between patients diagnosed with AD who present impaired EF and AD patients who present within-normal performance on tasks of EF, especially during the early stages of the disease. For instance, no significant differences were found on memory, language, attention, abstract thinking or visuospatial abilities between AD patients grouped according to their EF [5]. More recently, however, AD patients with EDF had significantly worse performance than patients with normal EF on screening tests for dementia [7], namely the MMSE [14] and subtests of the ADAS-cog [15]. Similarly, significant differences on various classical executive measures between AD patients grouped according to their performance on relational integration tasks were found [16], suggesting a genuine association between prefrontal cortical dysfunction and cognitive decline.

While such robust results from the aforesaid studies have been helpful in recognizing the variety of cognitive profiles associated with subgroups of patients diagnosed with the same neurodegenerative disorder, arguably there is now an imperative need to explore particular cognitive domains in detail. Because memory impairment is the hallmark of cognitive decline in this patient population, the present study sought to compare the performance on verbal memory tasks of AD patients who present impaired and normal EF. Performance was measured contemplating the three stages of memory, namely, acquisition, retrieval, and recognition. We hypothesized that AD patients with normal EF would show enhanced performance on verbal memory relative to AD patients with impaired EF.

METHODS

Participants

Thirty patients with early diagnosis of AD were recruited for this study. Patients were included if they (a) fulfilled diagnostic criteria according to NINCDS-ADRDA consensus [17]; (b) were in the mild stages of the disease, as determined by a Clinical Dementia Rating Scale (CDR) score of 1 or less [18]; and (c) signed an informed consent together with their caregiver prior to inclusion in the study. Any AD patients presenting with premorbid or comorbid psychiatric or metabolic disorders were excluded from the study. Controls ($n = 14$) were recruited by word-of-mouth from similar geographical areas as the patients, and were matched for age, gender, and education. Exclusion criteria for controls included history of neurodegenerative or psychiatric disorders, including traumatic brain injury and abuse of drugs. Both AD patients and controls completed the Beck Depression Inventory II (BDI-II) [19] in order to determine the severity of mood symptoms, and were excluded from the study if they scored 14 or above (0–13 is considered no or minimal depression).

Procedure

The study was initially approved by the ethics committee at the Institute of Cognitive Neurology (INECO), in accordance with the guidelines established under the Declaration of Helsinki for research with human subjects. Following initial neurologic interview, during which the aforementioned inclusion criteria were confirmed for all participants by a senior neurologist (FM), patients and controls were referred for comprehensive neuropsychological assessment. Data for the present study were obtained from the following neuropsychological tests: (a) MMSE [14] and the Addenbrooke's Cognitive Examination (ACE) [20] for global cognitive status; (b) Forward Digit Span (FwdDS) [21] and Trail Making Test Part A (TMT-A) [22] for attention; (c) Backward Digit Span (BckDS) [21], phonological fluency (PhFlu) [23], Trail Making Test Part B (TMT-B) [22], and the modified version of the Wisconsin Card Sorting Test (WCST) [24] for executive functions; and (d) logical memory (LM) subtest of the Wechsler Memory Scale – Third Edition [25] and the Rey Auditory-Verbal Learning Test (RAVLT) [26] for verbal memory. Variables analyzed from the verbal memory tasks were as follows. For LM: (a) immediate (participants are read two stories and are asked to repeat the information back to the examiner immediately after they finish hearing each story); (b) delayed (30 minutes after the immediate phase, participants are asked to repeat the information they remember from each story); and (c) recognition (following the delayed phase, participants are presented with twenty multiple choice questions and must choose one unique correct answer from within five options each). For RAVLT: (a) immediate RAVLT (participants are read List A containing 15 unrelated nouns for a total of five times and are asked to repeat the words they remember from the list, in any order, after each trial; total immediate score is the sum of the words correctly repeated after each trial); (b) distracter list (a different list, List B, is presented once, and participants must repeat as many words as they recall from this list); (c) delayed (participants are asked to freely recall words from List A);

(d) recognition (participants are instructed to choose the words learned from the List A from within a larger list containing the 15 words from List A, the 15 words from List B, and 20 phonologically- or semantically-related new words; three scores are derived: correct – number of correctly identified words from List A, intrusions – number of words identified which corresponded to List B, and false positives – number of words identified that did not belong to neither List A nor List B).

Statistical analysis

Individual raw scores on the four classical executive tasks (BckDS, PhFlu, TMT-B, and WCST) were initially transformed into *z*-scores according to available normative [23, 25] data for age- and gender-matched samples. AD patients who showed z scores ≤ -1.5 on none or one of the four executive tasks were classified into the spared executive functioning AD group (SEF). On the contrary, AD patients showing z scores ≤ -1.5 on two or more executive tasks were grouped into the impaired executive functioning AD group (IEF). During *a priori* statistical analyses, all control participants in the present study showed spared executive functioning based on these criteria, reason why they were all clustered into one unique control group (CTR). Said preliminary analyses also confirmed that patients were similarly classified into IEF and SEF groups when the *z*-scores were calculated based on the mean and SD of the control group used in this study (vs. normative scores). Demographic variables and scores on both general cognitive screening and attention tasks were compared across the groups using one-way ANOVA with Bonferroni *post hoc* comparisons when relevant, in order to determine potential variables that could have an impact on verbal memory performance besides the executive profile. Because of its categorical nature, gender was compared between the groups using a χ^2 on a 3 (groups) × 2 (male vs. female) contingency table. Variables which differed significantly between the SEF and IEF groups were used as covariates in one-way ANCOVA across the groups on variables derived from the verbal memory tasks. Correlations were conducted using Pearson's correlation coefficient. All statistical analyses were performed using SPSS 17.0 with the α-threshold set at 0.05, two-tailed.

RESULTS

Based on the criteria detailed in the Methods section, nineteen AD patients were classified into the SEF group and eleven AD patients into the IEF group (Table 1). As shown in Table 2, no significant differences were found between the groups on age ($F_{2,41} = 1.32$, $p = 0.42$), gender ($\chi^2 = 0.053$, $p = 0.97$), or the severity of mood symptoms ($F_{2,41} = 1.14$, $p = 0.65$). A significant difference was found between the groups on the CDR transformed score (CDR-TS, $F_{2,41} = 53.7$, $p < 0.001$) and the CDR sum of boxes (CDR-SOB, $F_{2,41} = 58.1$, $p < 0.001$), but the difference was not

Table 1
Mean (SD) scores on executive tasks used to classify AD patients into a spared (SEF) and an impaired (IEF) executive functioning group

	SEF ($n = 19$)	IEF ($n = 11$)
Phonological fluency	11.8 (3.2)	8.82 (3.3)
Backward digit span	3.59 (1.2)	2.5 (1.0)
Trail Making Test Part B	182 (97)	343 (55)
Wisconsin Card Sorting Test	3.00 (1.8)	2.33 (2.0)

Table 2
Mean (SD) values for demographic variables and scores on tasks of attention. Education was the only variable that differed significantly between the spared (SEF) and the impaired (IEF) executive functioning AD groups

	SEF ($n = 19$)	IEF ($n = 11$)	CTR ($n = 14$)	SEF vs. CTR	IEF vs. CTR	SEF vs. IEF
Age	76.4 (6.4)	78.2 (4.3)	75.5 (6.4)	n.s.	n.s.	n.s.
Education (years)	15.1 (3.9)	9.2 (3.3)	13.9 (4.2)	n.s.	$p < 0.01$	$p < 0.001$
Gender (M : F)	9 : 10	5 : 6	7 : 7	n.s.	n.s.	n.s.
CDR-TS	0.66 (.29)	0.86 (.43)	0	<0.001	<0.001	n.s.
CDR-SOB	6.2 (1.3)	7.8 (1.5)	0	<0.001	<0.001	n.s.
MMSE	25.2 (2.8)	23.7 (3.8)	29.2 (2.6)	<0.01	<0.01	n.s.
ACE	74.8 (8.9)	68.0 (9.8)	94.5 (5.2)	<0.001	<0.001	n.s.
BDI-II	5.9 (2.3)	6.4 (2.4)	5.9 (3.1)	n.s.	n.s.	n.s.
FwdDS	6.00 (1.2)	5.73 (1.1)	7.43 (1.3)	<0.05	<0.05	n.s.
TMT-A	89.1 (25)	110.3 (45)	39.4 (16.3)	<0.01	<0.01	n.s.

CTR = controls, CDR = Clinical Dementia Rating Scale (-TS = Transformed Score; -SOB = Sum of Boxes), MMSE = Mini Mental State Examination, ACE = Addenbrooke's Cognitive Examination, FwdDS = Forward Digit Span, TMT-A = Trail Making Test Part A, n.s. = non-significant.

significant between SEF and IEF patients (CDR-TS: $p = 0.63$; CDR-SOB: $p = 0.59$). A significant difference was also found on the numbers of years of formal education ($F_{2,41} = 9.18$, $p < 0.001$), with the IEF group differing significantly from both SEF ($p < 0.001$) and CTR ($p < 0.01$). Performance on global cognitive screening tests (MMSE: $F_{2,41} = 57.63$, $p < 0.001$; TMT-A: $F_{2,41} = 23.0$, $p < 0.001$) and attention tasks (FwdDS: $F_{2,41} = 7.63$, $p < 0.01$; TMT-A: $F_{2,41} = 9.53$, $p < 0.01$) differed significantly across the groups. Noticeably, on all of these measures, CTR differed significantly from the AD groups (MMSE: $p < 0.01$ for both; ACE: $p < 0.001$ for both; FwdDS: $p < 0.05$ for both; TMT-A: $p < 0.01$ for both), but no significant differences were found between IEF and SEF patients neither on the MMSE ($p = 0.65$), the ACE ($p = 0.38$), FwdDS ($p = 0.96$), nor on TMT-A ($p = 0.62$).

Analysis of variance with education as a covariate showed significant differences between the groups on all variables of verbal memory except for the number of false positives ($F_{2,40} = 1.89$, $p = 0.15$) and intrusions ($F_{2,40} = 0.34$, $p = 0.80$) on the RAVLT (Table 3). In both

Table 3
Group comparisons using ANCOVA with education as a covariate. Estimated marginal mean (SE) were determined after controlling the effect of the covariate. *Post hoc* comparisons are shown on the leftmost columns

Task	Variable	$F_{2,40}$	*p*	SEF (*n* = 19)	IEF (*n* = 11)	CTR (*n* = 4)	SEF vs. CTRL	IEF vs. CTRL	SEF vs. IEF
LM	immediate	19.1	<0.001	10.0 (1.6)	8.42 (2.4)	24.9 (1.8)	<0.001	<0.001	0.41
	delayed	33.4	<0.001	2.37 (1.3)	2.35 (1.9)	19.8 (1.5)	<0.001	<0.001	0.99
	recognition	29.5	<0.001	9.48 (0.8)	4.35 (1.2)	17.0 (1.0)	<0.001	<0.001	**<0.01**
RAVLT	immediate	21.7	<0.001	21.8 (2.1)	19.4 (2.9)	42.7 (2.3)	<0.001	<0.001	0.26
	distracter list	20.2	<0.001	2.13 (0.6)	1.85 (0.9)	8.44 (0.7)	<0.001	<0.001	0.81
	delayed	50.0	<0.001	0.70 (0.5)	0.58 (0.7)	9.0 (0.6)	<0.001	<0.001	0.42
	recognition								
	correct	17.2	<0.001	7.79 (0.7)	3.81 (1.1)	12.6 (0.8)	<0.001	<0.001	**0.02**
	false positives	1.89	0.148	2.40 (0.4)	3.40 (0.5)	2.83 (0.4)	0.44	0.43	0.16
	intrusions	0.34	0.795	2.25 (0.4)	2.21 (0.6)	2.32 (0.5)	0.96	0.90	0.91

SEF = Spared Executive Functioning AD group, IEF = Impaired Executive Functioning AD group, CTR = Controls, LM = Logical Memory, RAVLT = Rey Auditory-Verbal Learning Test, Figures in bold represent significant ($p < 0.05$) values.

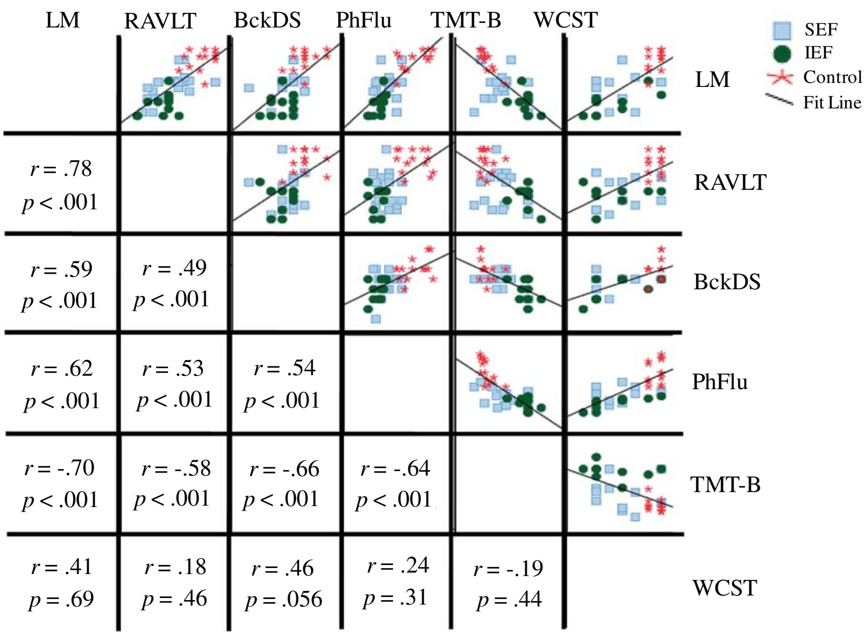

Fig. 1. Correlation matrix between the recognition phase of logical memory (LM), recognition phase of the Rey Auditory-Verbal Learning Test (RAVLT), and performance on the four classical executive tasks included in this study. Pearson's coefficients and associated *p* values are shown in the triangle blow the central diagonal line. Scatter plots showing AD patients with spared executive functions (SEF, light-blue square), AD patients with impaired executive functions (IEF, green circle), and controls (red star) are shown in the triangle above the central diagonal line.

of the latter, however, the effect of education accounted for less than 2% of the variance ($\eta^2 = 0.018$ and 0.19, respectively), implying that the lack of significant differences between the groups was not particularly associated with the covariate. Of all variables that differed significantly across the three groups, only the recognition phase of LM ($F_{2,40} = 29.5$, $p < 0.001$) and the number of correctly identified words during the recognition phase of RAVLT ($F_{2,40} = 17.2$, $p < 0.001$) showed significant differences specifically between SEF and IEF patients ($p < 0.01$ for LM, $p = 0.2$ for RAVLT). On the rest of the variables, no significant differences were found between the SEF and IEF groups, and in all cases, the CTR group significantly outperformed both AD groups.

Significant correlations were found between most executive tasks and the recognition scores on both LM and RAVLT (Fig. 1). In particular, the recognition phase of LM correlated significantly with BckDS ($r = 0.78$, $p < 0.001$), PhFlu ($r = 0.59$, $p < 0.001$), and TMT-B ($r = -0.70$, $p < 0.001$). The number of correctly identified words on the recognition phase of RAVLT correlated significantly with BckDS ($r = 0.49$, $p < 0.001$), PhFlu ($r = 0.53$, $p < 0.001$), and TMT-B ($r = -0.58$, $p < 0.001$).

DISCUSSION

The present study compared the performance of AD patients with spared (SEF) and impaired (IEF) executive functions on the acquisition, recall, and recognition phases of verbal memory tasks. Initially, demographic and other cognition variables (in this case, global cognitive status and attention) that could potentially affect memory performance were compared across the groups. IEF and SEF groups differed significantly on years of education only, which is why we used this variable in a covariant analysis of variance across the groups on measures of verbal memory. While significant differences were found between healthy controls and AD patients from both groups on the three phases of memory in both tasks, SEF and IEF differed significantly only on the recognition phase of verbal memory.

Using the criteria detailed in the Methods section in order to group AD patients based on executive performance revealed that 37% of the patients were classified into the IEF group. This percentage falls within previously reported ranges of proportions of IEF patients with AD using similar methodology (28% [5] to 64% [7]).

SEF and IEF patients did not differ significantly on their age, gender, or dementia severity (neither by transformed score nor by the sum of boxes on the CDR). However, a significantly lower educational level was observed for the IEF group relative to the SEG patients, yet the latter had similar education levels as that of controls. This result may support a point that has been extensively researched in the literature: the fact that education is associated with higher cognitive performance and that it may indeed have a protective effect against the development of dementia [27–30]. This finding, however, has been challenged by some authors [31, 32], and perhaps somewhat contradictory results may have emerged due to radical differences on the methods used in studying the protective effects of education against development and progression of dementia. Furthermore, some authors have linked the incongruent results to the overlooked potential interactions between education and lifestyle choices (e.g., diet, physical activity), and the impact of the latter on dementia [33]. In the present study, it could be the case that education may have protected against executive dysfunction in patients who have developed AD. An alternative perspective is that relatively more individuals who showed more dysexecutive characteristics achieve lower levels of education because of such deficits. Because patients diagnosed with AD who presented premorbid psychiatric disorders were excluded from this study, it is unlikely that this is the case, but the specific relationship between education and preserved executive functions is worthy of further research. Noticeably, the AD groups did not differ significantly on their severity of dementia, nor on their performance on general cognitive tests or tasks of attention, in accordance with the reports from previous studies using similar methods to classify patients according to their performance on tasks of EF [5]. This is an important finding, as variables such as severity of dementia, global cognitive performance, and attention can have a strong impact on other cognitive domains in AD patients [34].

Because this potential controversy regarding the effect of education on cognitive decline, and due to the significant difference found between SEF and IEF on this particular variable, group comparisons on verbal memory were carried out controlling for years of education as a covariate. The acquisition phase revealed no significant differences between the AD groups, although, as expected, both patient groups differed significantly from controls. Similar results were observed for the delayed recall phase on both logical memory and list learning. However, the recognition phase of both verbal memory tasks significantly differed between the groups, with SEF outperforming IEF patients with early AD. The former, however, still performed significantly worse than controls. According to Vakil and Blachstein [35], who have studied the structure of verbal tests in detail, the recognition score more closely reflects memory storage than recall scores, because by bypassing retrieval, recognition indicates the amount of information efficiently stored in memory. Overall, our results suggest that AD patients with SEF are more capable of identifying words they have previously learned both in the form of a cohesive and logical story (LM) and as an arbitrary list of words (RAVLT). This advantage of SEF over IEF patients during the recognition phase of verbal memory does not seem to be related to (a) age, gender, severity of dementia, attention, or mood symptoms as these variables did not differ significantly between the groups; (b) education, as it was controlled by the statistical method; (c) the number of mistakes (intrusions and false positives) during recognition, as these variables did not differ significantly between the groups. Not surprisingly, the recognition scores on LM and RAVLT correlated significantly with performance on classical tests of EF, suggesting a close relationship between executive functioning and the ability to recognize information that has been previously presented.

The results of this study must be interpreted within the context of certain limitations. First, our sample size requires further replication of the procedure in this study to examine the validity of the generalization of our findings. Small sample sizes can potentially affect the power to detect differences between the groups, and replications of this study using larger patient populations are encouraged in order to decrease the possible effect of Type II errors. However we do find significant effects, and the study groups are of comparable size to those employed in the other relevant reports [5, 13, 16]. Second, there may be other factors that could potentially affect memory performance, which have not been included as part of the analysis. For instance, Nakaaki et al. [36] demonstrated that AD patients who showed both apathy and depression had worse executive functioning that AD patients who presented either apathy or depression. While the two AD groups in the present study did not differ significantly in their objective depression rating, future studies should look at the effect of other behavioral and psychiatric factors on EF and verbal memory. In addition, statistically controlling for level of education can only partially compensate for the difference between the groups. In the present study, patients were recruited from the same geographic areas and were all considered part of the same socioeconomic group based on their and their families' ability to access private health services. Yet, it will be important for future studies to prospectively match AD patients with spared and impaired executive functions based on their education levels in order to determine the potential for replication of the results.

In summary, the present study shows that there may be a strong association between performance on EF and the ability to recognize previously presented information in patients with early AD, despite no apparent benefit of spared executive functioning on acquiring or recalling such information. Furthermore, these results suggest a potential role of EF on protecting stored information, even when its amount stored is deficient relative to individuals with unaffected memory. These findings also have potential relevance from a clinical perspective. Understanding the impact of executive dysfunction on memory performance in patients with AD could potentially facilitate the design of appropriate rehabilitation strategies with the objective of improving the influence of these cognitive deficits in patients' daily living. For example, if AD patients with normal executive functioning have relatively superior recognition of verbal information, it is perhaps more ideal for new rehabilitation strategies to target this specific cognitive domain in order to access previously learned or encountered information in future scenarios faced by the patient.

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