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Improving Amnesia Diagnostic Accuracy with RAVLT Single Scores and Composite Indices: Italian Normative Data

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Abstract

Objective: The Rey Auditory Verbal Learning Test (RAVLT) is a widely used verbal memory measure that provides scores for different aspects of memory. It involves repeated auditory presentation and recall of a 15-item word list (List A) followed by presentation and recall of a distractor list (List B) and then un-cued immediate and delayed recalls (at 15 min and 1 week) of List A as well as recognition testing. Aims of this study are to provide Italian normative data for certain RAVLT Scores and Composite Indices to improve the diagnostic accuracy of the test in clinical settings and to provide further evidence on how RAVLT can differentiate different amnesia profiles due to focal lesions.
Methods: We enrolled 440 healthy participants and RAVLT Single Scores and Composite Indices have been analyzed by means of multiple regression to verify the influence of age, education, and gender.
Results: We computed the best linear models with RAVLT Single Scores and Composite Indices, as dependent variables, and the most suitable transformation of independent variables. By reversing the signs of the regression coefficients, the adjustment factors for each level of age and, if needed, education and gender have been computed and the adjusted scores have been standardized into Equivalent Scores.
Conclusion: Using these standardized measures, we differentiate three profiles of amnesia due to selective hippocampal sclerosis with severe encoding deficit, fornix lesions with source memory problems, and temporal lobe epilepsy with consolidation failure.

Keywords: RAVLT; Normative data; Amnesia; ALF; Hippocampus; Fornix

Introduction

The need to develop reliable neuropsychological tools to enable a more precise assessment of impaired brain processes increased with the development of clinical neuroscience. One of the most used measures of verbal learning and memory is the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941; Lezak, 1995). The RAVLT is a widely used and frequently translated verbal memory measure that provides scores for different aspects of memory. It has proven to be useful in detecting dysfunctions in different memory systems with patterns of learning, retrieval, and/or recognition deficits differing according to site of lesion (Helmstaedter & Elger, 1996; Majdan, Sziklas, & Jones-Gotman, 1996; Redoblado, Grayson, & Miller, 2003).

Given the strong evidence that the RAVLT is a reliable measure to identify memory dysfunctions related to the integrity of neural systems (Thompson et al., 2008; Babiloni et al., 2009; Balthazar, Yasuda, Cendes, & Damasceno, 2010; Wolk & Dickerson, 2011; Mueller et al., 2012), updated Italian normative data for all RAVLT's measures are needed. The Italian

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normative data for the RAVLT take into account only the total of words recalled over the five trials and the delayed recall (Caltagirone, Gainotti, Carlesimo, & Parnetti, 1995). For the RAVLT used in Italy, after the five learning trials on List A, there is no distractor list and no immediate un-cued recall. Since the lack of normative data in the Italian population for testing Proactive Interference (PI), Retroactive Interference (RI), and recognition, the RAVLT might be ineffective to capture the different profiles of amnesia and at some degree the neural circuits involved.

There is a general consensus that the records of life are not formed instantaneously, but rather new memories are gradually transformed from an initially labile state to a more permanent state (Milner, Squire, & Kandel, 1998; Lechner, Squire, & Byrne, 1999). Most interesting is that there are patients who show increased rates of forgetting over longer intervals (i.e., days or weeks), so called Accelerated Long-Term Forgetting (ALF, Kapur et al., 1997; Butler & Zeman, 2008; Tramoni et al., 2011; Fitzgerald, Mohamed, Ricci, Thayer, & Miller, 2013). This is a condition whereby information is well retained when tested at short delays (i.e., up to 30 min) but lost over days or weeks. ALF has been frequently observed amongst patients with Temporal Lobe Epilepsy (TLE, Butler & Zeman, 2008; Jansari, Davis, McGibbon, Firminger, & Kapur, 2010; Tramoni et al., 2011), but also in patients with Extra Temporal Lobe Epilepsy (Ricci, Mohamed, Savage, Boserio, & Miller, 2015). It has been suggested that seizures during the retention interval might disrupt the neurophysiological processes underlying longer term memory consolidation (Binnie, 2003; Holmes & Lenck-Santini, 2006; Ricci et al., 2015). However, ALF has been described in presymptomatic autosomal dominant AD (Weston et al., 2018). Also, in another study, subjects with subjective memory complaints, who were not impaired on formal memory tests, achieved worse performances on recall and recognition of verbal information after 1-week delay (van der Werf et al., 2016; Ruggeri, Ricci, Gerace, & Blundo, 2019). More recently, Miller, Flanagan, Mothakunnel, Mohamed, and Thayer (2015) used RAVLT recall scores to detect ALF at 1-week delay amongst epilepsy patients compared with healthy subjects, suggesting how RAVLT could be used in clinical settings to detect memory problems. With respect to identifying ALF amongst patients with several conditions, it is necessary to establish a quantitative definition of ALF, such as normal memory initially (e.g., 15-min delay) with greater than expected loss over longer delays (i.e., 1-week delay), based on normative measures.

The medial temporal lobes have historically been considered as the central neural correlates of episodic memory (Scoville & Milner, 1957; Squire, Stark, & Clark, 2004). More recently, it has been proposed that successful episodic memory involves the coordination of a number of different cognitive processes that are supported by multiple large-scale cortical networks, including medial temporal lobe memory systems, but also including frontal, parietal, and lateral cortical regions comprising the Default Mode, Dorsal Attentional network, Prefrontal network, and Language network (Putcha, Brickhouse, Wolk, & Dickerson, 2019). Since these widespread networks, patients with focal damage within the medial temporal lobe remain vital for testing the theoretical claims regarding the neural basis of memory (Nadel & Moscovitch, 1997; Aggleton & Brown, 1999; Squire et al., 2004; Graham, Barense, & Lee, 2010). However, the focal damage of the hippocampus and other structures is quite rare. In this study, we present three cases with focal hippocampal and fornix lesions bilaterally and a TLE patient who showed ALF over 1-week delay. This is a unique opportunity to assess the contribution of different brain structures to the RAVLT's performances and then differentiate the corresponding profiles of amnesia.

To sum up, aims of this study are: (1) Providing the standardization of RAVLT Single Scores and Composite Indices for the Italian population; (2) Providing normative measures to increase RAVLT's accuracy to detect ALF; (3) Providing evidence on how the RAVLT's measures can be useful to differentiate profiles of amnesia due to focal lesions and TLE.

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Part I: Normative data

Methods

Participants. Four hundred and forty healthy participants (180 males, 260 females) were recruited from different regions of Italy (both rural and urban context), they were all native Italian speaking people, and they were recruited by convenience. Brain injuries, psychiatric disorders, alcohol/drug abuse, severe medical conditions, stroke or dementia were considered exclusion criteria. The age of the participants was established on the date of birth, whereas education levels were determined on the highest school degree.

The healthy participants were distributed across age classes (age range: 20–91), gender, and education levels (see Table 1 for demographic distribution of the sample). As shown in Table 1, because of the small number of younger participants (up to 40 years old) with lower level of education (8 years or below) and older participants ($\geq$71) with higher level of education ($>$13), these data should be taken with caution.

Informed consent was obtained from all the individual participants included in the study. The human data included in this manuscript were obtained in compliance with the Helsinki Declaration. This study was approved by the Ethical Committee of the San Camillo Forlanini Hospital in Rome.

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Table 1. Demographic characteristics of the sample

Education (years)	*Age*												
	20–30		31–40		41–50		51–60		61–70		≥71		Total
	M	F	M	F	M	F	M	F	M	F	M	F	
5–8	1	–	1	1	4	3	11	10	6	12	8	16	73
9–13	17	22	10	4	11	13	20	25	11	11	5	4	153
>13	35	72	18	30	7	12	7	14	6	10	2	1	214
Total	53	94	29	35	22	28	38	49	23	33	15	21	440

Materials and procedures. The RAVLT procedure used in our Neuropsychology Unit involves five consecutive learning trials of a 15-item list (List A), followed by immediate recall of a 15-item interference list (List B); immediately after the List B recall, the List A recall is tested. After 15 min, recall and recognition of the List Ais tested again. Multiple versions of RAVLT recognition exist and in this study the recognition trial was administered orally and choices comprised (1) List A 15-items; (2) List B 15-items; (3) 15-items other words. In the version used in our center, participants were asked to respond "yes" or "no" as to whether each of the words had been a part of the List A 15-items. Participants were explicitly instructed to say "no" to List B items (for the procedure details see: Schmidt, 1996). After 1 week, recall and recognition of the List A have been tested again via in-person follow-up. The RAVLT was administered in Italian language.

The primary variables considered in this study were the RAVLT Single Scores: Total Five Trials List A, List B Immediate Recall, List A Recall after List B Recall, 15-min and 1-week Delayed Recalls, 15-min and 1-week Recognition correct Hits and False Positive (FP) responses. The second variables were the RAVLT's Composite Indices: Learning over Trials (LOTs); PI and RI; 15-min and 1-week Memory Efficiency Index (RAVLT-MEI), 15-min and 1-week Hits-FP Ratio; ALF index Recall; ALF Hits-FP ratio. Computations of these measures are summarized in Box 1.

Box 1. Computation of the RAVLT's Composite Indices.

LOT = RAVLT Total Immediate Recall - (Trial I × 5).
PI = (List B/List A Trial I) × 100.
RI = (List A After B/List A Trial V) × 100.
15-min MEI = (Delayed Recall List A: 15)/(RAVLT Total Immediate Recall/75) + (Hits/15)– (FP/30).
1-wk MEI = (Delayed Recall List A/15)/(RAVLT Total Immediate Recall/75) + (1-wk Hits/15)– (1-wk FP/30).
15-min Hits-FP Ratio = (15-min Hits/15)– (15-min FP/30).
1-wk Hits-FP Ratio = (1-wk Hits/15)– (1-wk FP/30).
ALF Index Recall = [(15-min Recall – 1-wk Recall) /15-min Recall] × 100.
ALF Index Hits-FP Ratio = (15 min Hits-FP Ratio − 1-wk Hits-FP Ratio) × 100.
LOT: learning over trials; PI: proactive interference; RI: retroactive interference; MEI: memory efficiency index; wk: week; FP: false positive; ALF: accelerated long-term forgetting.

RAVLT composite indices. *LOT* is a measure proposed by Ivnik and his coworkers (1992) and it is used to clarify how many items the subject encode across five consecutive learning trials. Nevertheless, this index should be considered with caution when retrieval deficits are present.

PI occurs when previously learned information interrupts the storage or retrieval of new information, which exerts significant control over the amount of information that can be retrieved from working memory (see Jonides & Nee, 2006 for a detailed review). In the RAVLT, PI appears when List A has a negative influence on the acquisition of List B. Many studies have considered the relationship between working memory and PI, revealing that PI is an important determinant of the success of working memory (Conway & Engle, 1994; Chiappe, Hasher, & Siegel, 2000). Other studies have pointed out that the brain regions involved to resolve the effect of PI are the inferior frontal gyrus (Postle, Brush, & Nick, 2004; Nee, Jonides, & Berman, 2007; Nelson, Reuter-Lorenz, Persson, Sylvester, & Jonides, 2009) and the left ventrolateral prefrontal cortex (for a review see: Badre & Wagner, 2007). These evidences suggest that there is a cerebral network responsible for PI resolution mostly involving the frontal lobe. We decided to compute this Composite Index as the quotient of the raw score of List B (the interference list) divided by the raw score of Trial 1 of List A, the latter being a measure of immediate memory (Geffen, Butterworth, & Geffen, 1994).

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RI occurs when the learning of subsequent material affects the recall of previously acquired information (Eakin & Smith, 2012). In the RAVLT, RI occurs when the performance on the immediate recall of List A after List B is affected negatively by the presentation of the interference List B. Recently, it has been proposed that non-specific RI (i.e., interference from any material, similar or dissimilar) affects consolidation (Dewar, Della Sala, Beschin, & Cowan, 2010). There is some evidence that the medial temporal lobes areas most closely associated with early memory processing and consolidation (Alvarez & Squire, 1994), and in particular the hippocampus, are involved in reducing associative interference during the learning process (Winocur, Becker, Luu, Rosenzweig, & Wojtowicz, 2012). Therefore, memory impairment in amnesia can be accounted for the inability to resist to the interference from irrelevant information (Andrejkovics, Balla, & Bereczki, 2014). To support these findings, profound non-specific RI was detected in a sample of amnesic patients who had temporal lobe lesions, most of them involving the hippocampus (Dewar et al., 2010). As for PI, we decided to compute this Composite Index dividing raw score of List A after List B by raw score of Trial V of List A.

RAVLT-MEI is a measure presented in a previous study (Ricci, Graef, Blundo, & Miller, 2012), which took into consideration all RAVLT scores to maximize sensitivity and specificity to detect memory impairments. Hence, the authors computed a composite index that combine measures of encoding and retention [(delayed recall A/15)/ (RAVLT Total Five Trials/75)]) and scores of recognition memory ([(delayed recognition hits/15) – (FP/30)]), such that very low scores would result for deficits in the former and moderately low scores would result for the latter. This index yielded good sensitivity and specificity in discriminating AD, bvFTD, and normal participants using the same cut-off points across samples (i.e., Australian and Italian; Ricci et al., 2012). It would be helpful to get normative data of this composite index that measures the memory efficiency.

Hits-FP ratio is a measure of the accuracy on RAVLT recognition trial. In our experience (Ricci et al., 2012), but also stated by others (Flanagan et al., 2016), FP on RAVLT recognition trial is a determinant score to differentiate clinical populations compared with healthy participants. Thus, since healthy participants do not produce FPs, we decided to use a widely used and easily obtained measure of discriminability, the simple discrimination index (Hits/15 – FP/30) instead of the more elaborate measures (van den Berg et al., 2020). We obtained a score that ranges from −1 (i.e., worst performance: 30/30 FP and 0/15 Hits) to +1 (i.e., best performance: 15/15 Hits and 0/30 FP). We decided to use this measure instead of the procedure proposed by other authors (McNicol, 1972; Gainotti, Marra, & Villa, 2001), based on the signal detection theory (Parks, 1966).

ALF Indices. These composite indices have been named Memory Change Score in previous studies and have been computed to detect ALF (Miller et al., 2015; Ricci et al., 2015). Some patients show ALF over days or weeks for material demonstrated to have been retained when assessed after short-term delays (Kapur et al., 1997; Tramoni et al., 2011; Fitzgerald et al., 2013). These indices measure the loss of information over 1-week delay, on both recall and recognition.

Statistical analyses. RAVLT Single Scores and Composite Indices have been analyzed by means of multiple regression to verify the influence of age, education, and gender. We tested linear, logarithmic, and square root transformations of demographic variables to find the best model based on constancy of the variation in the residual. Effect of education (expressed in years) was explored after square root transformation. Results from the best linear model were used to develop a regression equation for computing an adjusted score for each subject. By reversing the signs of the regression coefficients, the adjustment factors for each level of age, education, and sometimes gender (for statistics, gender variable was coded as 1 male and 2 female) have been derived (i.e., [raw score + or $-\beta$age (age – 44.43) + or $-\beta$edu ($\sqrt{}$edu – 3.66) + or $-\beta$gender (gender – 1.59]). When the test is upper limited, the question is whether the scores should be adjusted when the top score is attained. If a negative adjustment is made, these subjects are prevented a priori from achieving the top adjusted score, which does not seem justified. To deal with this bias, Capitani and Laiacona (1997) suggested that maximum scores and scores equal to zero should not be corrected. Parametric or non-parametric procedures, based on the normal distribution of the data, were adopted to evaluate tolerance limits that can classify a given score as normal or abnormal with 95% confidence interval.

Following the procedure suggested by Capitani and Laiacona (1997), which is largely used in the standardization of Italian normative data of neuropsychological tests, the adjusted scores have been standardized into Equivalent Scores (ESs). ES corresponds to a 5-point interval scale divided as follows: 4 indicates scores equal or higher than the median value of the whole sample; 3, 2, and 1 are obtained by dividing into three equal parts the area of the distribution between 0 and 4 with reference to the percentile of the left or right (based on the variable considered) of a normal distribution. An ES of 0 indicates a performance to the worst 5% of the population. An ES of 1 indicates a performance that falls approximately in the 6–10 percentile of the population. Then a correction grid was built for any combination of age level (10-year steps), educational level (according to the Italian educational system), and gender, for adjustments of raw scores of newly tested individuals according to demographic variables. Thus, the numbers in the correction grids correspond to the mean of residuals between predicted scores for specific demographic variables based on the regression model and raw scores. The Statistical Package for Social Sciences (SPSS, Inc., Chicago, Illinois) version 25 was used for statistical analyses.

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Table 2. Best linear model relating RAVLT Single Scores to the most suitable transformation of age, education, and gender

RAVLT scores	*Best linear model*	*R*	R^2	*Standard error of estimates*	*F*	*p*
Total 5 trials	50.16–0.19 × (age – 44.43) + 5.8 × ($\sqrt{}$edu – 3.66) – 1.97 × (gender – 1.59)	0.59	0.34	8.47	$F_{(3,437)} = 76.18$	<0.0001
List B	5.4–0.03 × (age – 44.43) + 0.78 × ($\sqrt{}$edu – 3.66)	0.46	0.21	1.83	$F_{(3,437)} = 57.93$	<0.0001
List A after B	11–0.06 × (age – 44.43) + 1.34 × ($\sqrt{}$edu – 3.66) – 0.48 × (gender – 1.59)	0.55	0.31	2.51	$F_{(3,437)} = 64.47$	<0.0001
15-min delayed recall	11.02–0.05 × (age – 44.43) + 1.59 × ($\sqrt{}$edu – 3.66) – 0.65 × (gender – 1.59)	0.55	0.31	2.59	$F_{(3,437)} = 64.68$	<0.0001
15-min recognition hits	14.11–0.02 × (age – 44.43) + 0.56 × ($\sqrt{}$edu – 3.66)	0.48	0.23	1.19	$F_{(3,437)} = 43.68$	<0.0001
15-min recognition FP	0.96 + 0.02 × (age – 44.43)– 0.77 × ($\sqrt{}$edu – 3.66)	0.37	0.14	1.87	$F_{(3,437)} = 23.04$	<0.0001
1-wk recall	8.30–0.07 × (age – 44.43) + 0.86 × ($\sqrt{}$edu – 3.66)	0.48	0.23	3.03	$F_{(3,437)} = 42.13$	<0.0001
1-wk recognition hits	13.44–0.03 × (age – 44.43) + 0.35 × ($\sqrt{}$edu – 3.66)	0.42	0.18	1.62	$F_{(3,437)} = 29.68$	<0.0001
1-wk recognition FP	2.67–0.07 × (age – 44.43)– 1.55 × ($\sqrt{}$edu – 3.66)	0.48	0.23	3.43	$F_{(3,437)} = 41.93$	<0.0001

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Table 3. Best linear model relating RAVLT Composite Indices to the most suitable transformation of age, education, and gender

RAVLT indices	*Best linear model*	*R*	R^2	*Standard error of estimates*	*F*	*p*
LOT	17.93–0.04 × (age – 44.43) +1.44 × ($\sqrt{}$edu – 3.66)	0.19	0.04	6.89	$F_{(3,437)} = 5.71$	<0.001
PI	88.46–0.001 × (age – 44.43) + 0.012 × ($\sqrt{}$edu – 3.66)	0.00	0.00	36.50	$F_{(3,437)} = 0.001$	n.s.
RI	87.65–0.19 × (age – 44.43) +4.64 × ($\sqrt{}$edu – 3.66)	0.34	0.12	14.62	$F_{(3,437)} = 19.07$	<0.0001
15-min MEI	2.00–0.004 × (age – 44.43) +0.10 × ($\sqrt{}$edu – 3.66)	0.38	0.15	0.27	$F_{(3,437)} = 24.67$	<0.0001
1-wk MEI	1.62–0.01 × (age – 44.43) + 0.07 × ($\sqrt{}$edu – 3.66)	0.47	0.22	0.37	$F_{(3,437)} = 39.21$	<0.0001
15-min Hits-FP ratio	0.91–0.002 × (age – 44.43) + 0.06 × ($\sqrt{}$edu – 3.66)	0.55	0.31	10.29	$F_{(3,437)} = 63.98$	<0.0001
1-wk Hits-FP ratio	0.81–0.005 × (age – 44.43) + 0.07 × ($\sqrt{}$edu – 3.66)	0.59	0.34	15.64	$F_{(3,437)} = 72.42$	<0.0001
ALF index recall	24.57+ 0.35 × (age – 44.43)	0.22	0.05	24.32	$F_{(3,437)} = 6.98$	<0.0001
ALF Hits-FP ratio	10.00 + 0.22 × (age – 44.43)	0.32	0.10	13.42	$F_{(3,437)} = 16.10$	<0.0001

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Results

Table 1 shows the demographic characteristics of our sample grouped by age, sex, and educational level. The data revealed that younger adults with low level of education and older participants with high level of education are less represented in the sample. The square root transformation of education was the most effective in reducing residual variance, whereas the effect of age and gender was maximum when it was not transformed. The age was always significant; the influence of gender was detected for the RAVLT Single Scores Total 5 Trials, Lista A after B Recall, and 15-min Recall. Finally, education was always significant but for both ALF Recall and Recognition Hits-FP ratio Composite Indices. Then we computed the best linear models with RAVLT Single Scores and Composite Indices, as dependent variables, and the most suitable transformation of independent variables (Tables 2 and 3). By reversing the signs of the regression coefficients, the adjustment factors for each level of age, and if needed education and gender, have been computed (Tables 4 and 5).

Using parametric and non-parametric procedures, based on the normal distribution of the data, tolerance limits (fixed at 95% for 95% of confidence interval) have been calculated for each RAVLT Single Score and Composite Index. Values below (or above in case of FP responses and ALF indices) the tolerance limit represent the cut-off points and should be considered abnormal. Tables 4 and 5 report the corrections grids for any combination of age, educational level, and gender to allow adjustment of raw scores of newly assessed subjects. RAVLT's ES for Single Scores and Composite Indices is reported in Tables 6 and 7, respectively.

Discussion

The main focus of concern for clinicians and researchers in neuropsychology is to define the capacity of neuropsychological instruments to detect early brain process dysfunctions. The RAVLT is one of the most used and translated tool for assessing episodic memory for verbal information. It has been found to be sensitive to brain damage and relatively insensitive to mood disorders (Schmidt, 1996). It offers a variety of memory scores and indices, which we presented with the new Italian normative data to detect learning, retrieval, and rapid forgetting disorders of newly assessed subjects.

Following the most widely used psychometric approach in Italy, we used regression analyses to weigh the influence of age, education, and gender on RAVLT Single Scores and Composite Indices, and then we built correction grids for RAVLT's raw scores. The adjusted RAVLT's raw scores have been used to create an ES scale (Capitani & Laiacona, 1997). This 5-point scale offers a solution to the problem of standardizing neuropsychological scores after adjustment for age, education, and gender. The boundary between ES 0 and 1 is the cut-off line below which adjusted scores are considered not normal. This is the first study that presents RAVLT's normative data in the Italian population to detect encoding, retrieval, or consolidation deficits through its Single Scores and Composite Indices.

To the best of our knowledge, only Miller et al. (2015) presented normative data on RAVLT's recall over longer delay (i.e., 1 week). Accelerated long-term forgetting is a memory disorder, which is frequently misdiagnosed and yet people complain with memory disorders end up with a diagnosis of subjective memory disorders (Ruggeri et al., 2019). In our study, we also considered the Recognition trial and other indices at shorter and longer delays in a wider sample. Furthermore, according to our clinical experience, the number of FPs in the RAVLT's Recognition trial is an important cognitive marker to evaluate clinical populations, since amongst healthy subjects they are not detected (Ricci et al., 2012; van den Berg et al., 2020). This study provides new Italian normative data for the RAVLT Single Scores and Composite Indices to support clinicians with the complex issue of associating different memory profiles with the underlying neuroanatomical correlates, and differentiating between dementias and other clinical conditions.

Part II: The RAVLT and amnesias

In this section, we present three cases of pure amnesia, who reported different profiles of memory problems in relation to the site of lesions (i.e., hippocampus atrophy, bilateral fornix lesion, and TLE). RAVLT Single Scores and Composite Indices helped to detect these differences, and differentiate three memory profiles corresponding to specific lesion sites. Furthermore, it can be considered a good tool in clinical settings to detect ALF when memory is tested at longer delays (i.e., 1 week). As reported below, only in one patient the RAVLT's recall and recognition were tested at 1-week delay, since both the other patients achieved an ES = 0 already at 15-min delay. All patients achieved normal performances in the standard neuropsychological assessment but memory tests.

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Table 4. Correction's grid for RAVLT Single Scores for raw scores according to age, education, and gender

Education (years)	*Age*											
RAVLT												
Total 5 trials	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
5–8	3.24	–	4.95	2.79	6.69	3.93	7.95	6.84	12.31	9.55	15.39	13.16
9–13	−2.13	−4.40	−0.11	−2.28	1.65	0.05	4.04	1.98	5.90	3.83	8.03	6.69
>13	−4.59	−6.86	−3.58	−5.32	−0.66	−3.31	0.69	−1.19	2.54	−0.32	4.91	1.93
List B	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
5–8	0.21		0.47		0.70		1.01		1.52		2.04	
9–13	−0.55		−0.22		0.10		0.43		0.72		1.10	
>13	−0.88		−0.66		−0.29		0		0.20		0.59	
List A after B	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
5–8	0.53	–	1.07	0.53	1.60	0.89	2.02	1.72	3.19	2.52	4.17	3.55
9–13	−0.78	−1.36	−0.17	−0.68	0.40	0.03	1.14	0.63	1.72	1.21	2.38	2.07
>13	−1.33	−1.90	−0.97	−1.39	−0.09	−0.76	0.37	−0.09	0.94	0.21	1.63	0.90
15-min delayed recall	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
5–8	0.93		1.41	0.71	1.90	1.03	2.27	1.70	3.48	2.61	4.36	3.40
9–13	−0.46	−1.08	0.30	−0.69	0.52	0	1.14	0.44	1.46	1.04	2.33	1.85
>13	−1.07	−1.41	−0.77	−1.10	−0.06	−0.77	0.27	−0.32	0.80	−0.10	0.59	0.54
15-min recognition hits	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
5–8	0		0.16		0.15		0.54		0.96		1.30	
9–13	−0.07		−0.06		0.03		0.20		0.40		0.66	
>13	−0.19		−0.13		−0.04		0		0.10		0	
15-min recognition FP	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
5–8	0		0		−0.30		−0.66		−1.01		−1.12	
9–13	0.04		0.02		0		−0.14		−0.31		−0.52	
>13	0.18		0.12		0.05		0		0		−0.10	
1-wk delayed recall	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
5–8	−0.36		0.27		0.71		1.54		2.52		3.52	
9–13	−1.39		−0.65		0.14		0.94		1.69		2.58	
>13	−1.75		−1.12		−0.22		0.50		1.03		1.16	
1-wk recognition hits	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
5–8	−0.20		0.09		0.29		0.63		1.03		1.48	
9–13	−0.34		−0.17		0.04		0.31		0.61		1.16	
>13	−0.37		−0.22		−0.04		0.17		0.37		0.27	
1-wk recognition FP	**20–30**		**31–40**		**41–50**		**51–60**		**61–70**		**≥71**	
5–8	−0.31		−0.46		−0.63		−1.89		−2.89		−3.35	
9–13	0.55		0.34		−0.13		−0.71		−1.27		−2.47	
>13	0.86		0.72		0.27		−0.06		−0.52		−0.41	

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Table 5. Correction's grid for RAVLT Composite Indices for raw scores according to age, education, and gender

Education (years)	*Age*					
RAVLT						
LOT	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
5–8	0.65	0.98	1.28	1.70	2.46	3.19
9–13	−0.68	−0.24	0.16	0.59	0.97	1.48
>13	−1.31	−1.06	−0.58	−0.21	0.02	0.57
RI	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
5–8	1.17	2.75	4.19	6.10	9.18	12.40
9–13	−3.45	−1.39	0.58	2.65	4.47	6.82
>13	−5.39	−3.40	−1.75	0.08	1.32	3.74
15-min MEI	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
5–8	0.03	0.06	0.09	0.13	0.20	0.27
9–13	−0.07	−0.03	0.01	0.06	0.10	0.15
>13	−0.12	−0.09	−0.04	0	0.03	0.08
1-wk MEI	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
5–8	−0.07	0.01	0.07	0.15	0.27	0.40
9–13	−0.17	−0.08	0.01	0.11	0.20	0.30
>13	−0.20	−0.12	−0.01	0.07	0.14	0.24
15-min recognition hits-FP ratio	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
5–8	0	0	0.01	0.03	0.06	0.09
9–13	−0.01	−0.01	0.01	0.01	0.04	0.08
>13	−0.02	−0.10	0	0.01	0.03	0.07
1-wk recognition hits-FP ratio	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
5–8	−0.06	−0.02	0.01	0.06	0.11	0.17
9–13	−0.07	−0.04	0	0.07	0.09	0.15
>13	−0.05	−0.03	0	0.05	0.09	0.04
ALFindexRecall	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
	5	2.57	0	−2.97	−5.95	−8.26
ALFindexHits-FP ratio	**20–30**	**31–40**	**41–50**	**51–60**	**61–70**	**≥71**
	3	2	0	−3	−5	−8

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Table 6. ESs for adjusted values on RAVLT Single Scores

ES	RAVLT I-V Trials	List B	List A after B	15-min delayed recall	15-min recognition hits	15-min recognition FP	1-wk delayed recall	1-wk recognition hits	1-wk recognition FP
0	< 35.18	< 2.16	< 5.45	< 6.44	< 12.11	> 2.77	< 3.05	< 10.56	> 7.11
1	< 40.17	< 3.24	< 7.27	< 7.97	< 12.82	> 2.03	< 4.82	< 11.58	> 5.56
2	< 45.15	< 4.32	< 9.10	< 9.49	< 13.53	>1.31	< 6.57	< 12.57	> 4.01
3	< 50.13	< 5.40	< 10.90	< 11.01	< 14.24	> 0.60	< 8.32	< 13.56	> 2.46
4	≥ 50.13	≥ 5.40	≥ 10.90	≥ 11.01	≥ 14.24	≤ 0.60	≥8.32	≥13.56	≤ 2.46

Table 7. ESs for adjusted values on RAVLT Composite Indices

ES	RAVLT LOT	PI	RI	15-min MEI	1-wk MEI	15-min Hits-FP ratio	1-wk Hits-FP ratio	ALF index recall	ALF index hits-FP ratio
0	< 5.76	< 24.00	< 61.82	< 1.38	< 0.98	<0.72	<0.52	>57.40	>40
1	< 9.82	< 45.51	< 70.44	< 1.59	< 1.48	<0.79	<0.63	>46.32	>30
2	< 13.88	< 66.99	< 79.04	< 1.79	< 1.53	<0.85	<0.72	>35.04	>20
3	< 17.93	< 88.47	< 87.64	< 2.00	< 1.58	<0.92	<0.82	>24.00	>11
4	≥ 17.93	≥ 88.47	≥ 87.64	≥ 2.00	≥ 1.58	≥0.92	≥0.82	≤24.00	≤11

Case 1

In this study we present a patient (DGL), who developed convulsive generalized seizures after bupivacaine lumbar infiltration, later evolving into a convulsive generalized epileptic status. This right-handed 38-year-old male, with 13 years of education, developed a severe anterograde and retrograde amnesia (temporal gradient of 6 months, with older memories retained better than the recent ones) after a prolonged status epilepticus (i.e., 12 h). As shown in Fig. 1, a severe bilateral hippocampal atrophy was already evident after 3 weeks (Fig. 1B) from the first seizure (Fig. 1A).

On RAVLT (Table 8), he did not show learning capacity exceeding his short-term memory span (i.e., Digitspan forward: 6, backward: 5; RAVLT learning curve: 7–6–7–7–6), and he was unable to encode new information.

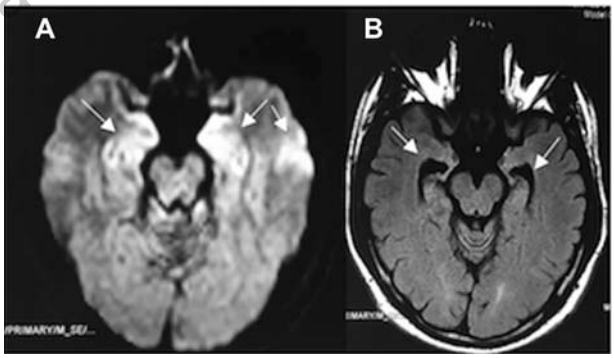

Fig. 1. (A) Brain MRIDWI axial image. Altered signal localized in the medial temporal lobes and in the left lateral temporal lobe (white arrows). (B) Brain MRI-FLAIR axial image. Hippocampal atrophy (white arrows).

Case 2

SC is a right-handed 35-year-old woman with a bachelor's degree in architecture. In 2016, she went to the hospital's emergency for headache. Magnetic resonance imaging (MRI) of the brain revealed a third ventricle colloid cyst and she underwent neurosurgery for its removal. After the surgery, SC became excessively talkative, developed a binging disorder, hyperemotionalism, repeated things she already said, and was unaware about her disorders. After 2 months of the surgery, her

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Table 8. Raw scores achieved by the three cases on RAVLT scores and composite indices

RAVLT	DGL	SC	MG
Total 5 trials	33[a]	43	33
List B	4	5	3
List A after B	4[a]	4[a]	8
15-min delayed recall	0[a]	5[a]	10
15-min recognition hits	1[a]	11[a]	13
15-min recognition FP	0[a]	6[a]	4[a]
1-wk delayed recall	–	–	5
1-wk recognition hits	–	–	5
1-wk recognition FP	–	–	11
LOT	−2[a]	13	18
PI	57	83	100
RI	67	44[a]	77
15-min MEI	0.07[a]	1.11[a]	2.26
15-min Hits-FP ratio	0.07[a]	0.53[a]	0.74
1-wk MEI	–	–	0.71
1-wk Hits-FP ratio	–	–	−0.04[a]
ALF index Recall	–	–	50
ALF index Hits-FP ratio	–	–	78[a]

[a]Values below the cut-off level (ES = 0)

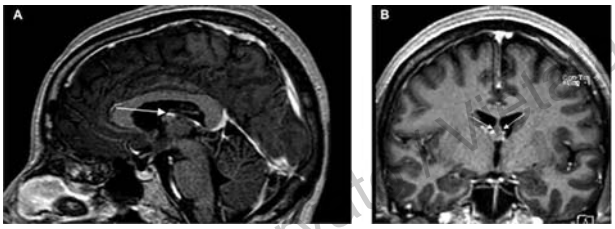

Fig. 2. (A) Brain MRI T2 sagittal image, showing the fornix lesion (white arrow); (B) MRI-FLAIR coronal image, showing fornix lesions bilaterally (white arrows).

cognitive, behavioral, and emotional status improved. However, she started complaining with memory problems. She was unable to recollect if an event really happened or if she just dreamt it, and she referred that her memories faded over very short delays. Brain MRI (Fig. 2A and B) 2 months after the surgery showed lesions circumscribed to the fornices. This is a common sequela of surgical removal of colloid cysts, either for the direct inferior compression of the tumor to the fornices or for the surgical procedure.

On RAVLT, she performed within the normal range on learning trials; she did not show PI, whereas RI was detected. At 15-min Recall, her performance was below the cut-off level, and on Recognition trial she recognized items of list B as belonging to List A, revealing a source memory problem (Table 8).

Case 3

MG is a right-handed 72-year-old man (with 13 years of education), who complained topographical disorientation episodes lasting few minutes. In the last year, he also referred memory problems for everyday events (e.g., "I can't remember if I saw a movie just few days before or if I did a trip. It is like my memory fades over few days"). The brain MRI was unremarkable; however, the 24-h EEG recording revealed frequent frontal-central and temporal discharges bilaterally during NREM sleep (Fig. 3), for which a diagnosis of TLE was assigned.

On RAVLT, MG's performance did not reveal any learning, retrieval, or storage disorders when tested at 15-min delay, as shown by the 15-min RAVLT-MEI score. Thus, his memory was tested also after 1 week, and at longer delay his memory started fading with the 1-wk RAVLT-MEI showing a rapid drop till the edge of the cut-off level. On the 1-week Recall, his performance achieved an ES = 1 (lower limit of normal range) with only five words recollected. On the Recognition trial, he did the same number of correct hits but with many FPs regardless of the source list (Table 8).

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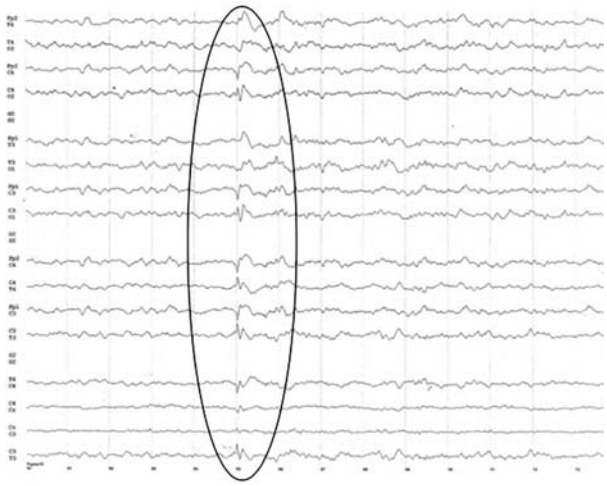

Fig. 3. Example of MG's frontal-central and temporal discharges (black circle) on the 24-h EEG recording during NREM sleep.

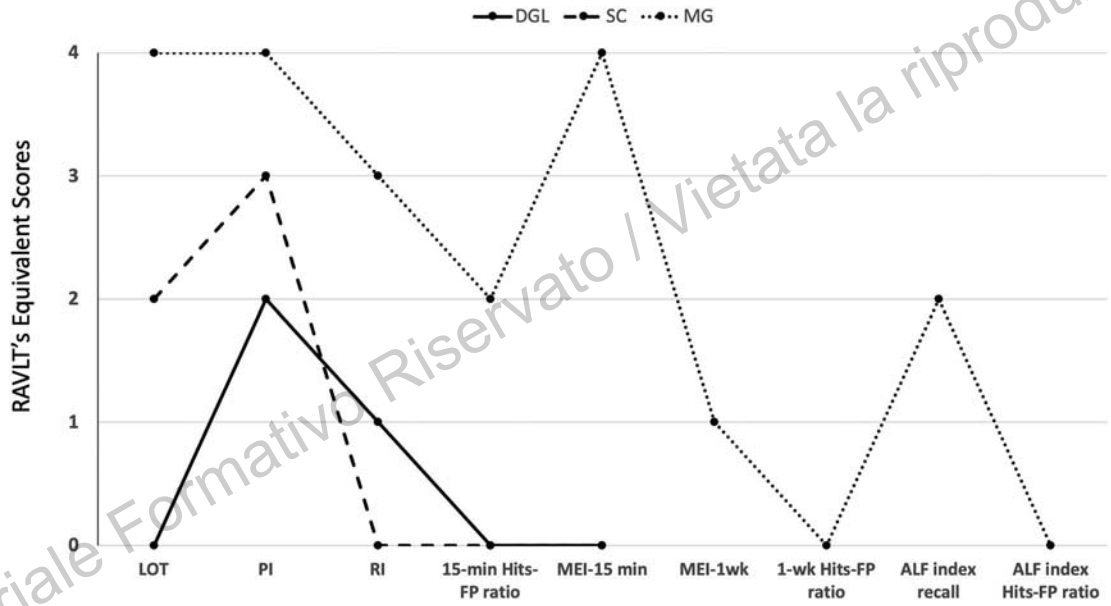

Fig. 4. ESs reported by the three patients on RAVLT's Composite Indices. Performances below the limit of tolerance are represented by 0 (i.e., pathologic performance), whereas the Equivalent Score of 1 corresponds to the lower limit of the normal range, and 4 to performances equal or above the median value of the control sample (i.e., normal performance).

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Discussion

We reported three cases with different profiles of amnesia as a consequence of the involvement of different neural circuitry within the medial temporal lobe. As shown in Fig. 4, the patient with hippocampal atrophy showed a flat learning curve, with a retroactive interference but no PI was detected. Instead, the patient with the bilateral fornix lesions could learn new items over trials; however, the information was not well retained at 15-min delay (RAVLT-MEI ES = 0), with many FP errors from List B committed on the recognition trial, revealing a source memory problem. The source memory refers to recalling the source of learned information, such as knowledge of when or where something was learned. On the RAVLT, she was unable to discriminate the contextual learning of either List A or B. Most interestingly, the patient with TLE yielded a good performance when tested at 15-min delay. However, as reported in the graph (Fig. 4), he showed ALF already at 1-week delay.

Supra-span list learning tests are sensitive measures used to assess temporal lobe dysfunctions. According to the structure of the RAVLT, during the first of the five consecutive learning trials, the short-term memory component is the highest and steadily

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decreases over the following learning trials, whereas the long-term memory component concurrently increases and reaches its maximum at the delayed recall after a retention interval (Müller, Hasse-Sander, Horn, Helmstaedter, & Elger, 1997). As reported by Witt and his coworkers (2019), amongst epilepsy patients who underwent left hippocampus removal, the hippocampal integrity became already relevant when the information load, which should be immediately recalled, exceeded the working memory capacity during the RAVLT learning trials. Also, they found that the relevance of hippocampus integrity increased along with the increasing degree of long-term memory involvement (i.e., RAVLT delayed free recall). In a detailed review (Saury & Emanuelson, 2017), it was assessed the RAVLT capability to predict the integrity of the neural structures underlying episodic memory (i.e., the hippocampus). The results showed that learning capacity (assessed by the RAVLT Immediate Recall Score) was dependent on the hippocampal formation integrity and in particular the Dentate Gyrus and CA3. The retrieval process was also dependent on the hippocampal formation integrity and these processes primarily activate the CA1 and the subiculum. However, in Saury and Emanuelson' study (2017), the retrieval process was assessed by three tasks in the RAVLT: List A after list B, Delayed Recall, and Recognition Hits. It is evident that the hippocampus damage predicts worse performances on RAVLT's delayed free recall and recognition trial (Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Balthazar et al., 2010; Bartsch et al., 2010; Pedro et al., 2012). Nevertheless, it is our opinion that comparing scores on the Composite Index Recognition Hits-FP proposed in this study with scores on Delayed Recall is more appropriate to evaluate retrieval efficiency on RAVLT, with higher scores on Recognition Accuracy (i.e., Hits-FP) and lower scores on Delayed Recall revealing deficit on retrieval processes. As reported earlier, patients with hippocampal damage struggle with supra-span learning, thus it obscures retrieval deficit detection. In line with these findings, our patient DGL, with a severe atrophy restricted to the hippocampus bilaterally, demonstrated an inability to learn new information exceeding his short-term memory span. The relatively good performance on PI reveals that hippocampus might be not crucial to resolve interference with newly acquired information, which is probably more dependent on working memory system. Also, our patient did not clearly resolve the issue of the contribution of hippocampus to retroactive interference, with a performance at the edge of the cut-off level. However, his performance on RAVLT retroactive interference showed a trend towards forgetting similar to another case described in the literature reporting hippocampal lesions (Andrejkovics et al., 2014). Our findings are in line with what has been recently proposed, that the hippocampus has a role in the mechanism that controls the retroactive interference, and help to differentiate between conflicting content-dependent memories (Winocur et al., 2012).

More interestingly, the patient SC (with a focal lesion restricted to the fornix bilaterally) showed a good ability to learn new information and she did not show PI, given her good working memory functions. However, her ability to retrieve information previously learned after an interference list was deeply impaired (Retroactive Interference). To the best of our knowledge, this is the first case which demonstrated an implication of the fornix to resolve retroactive interference. SC's performance on RAVLT recognition trial revealed source memory problems (she was unable to discriminate the contextual learning of either List A or B's words). Mammillary bodies (MBs) have been described as implicated in source memory impairments, with a defect to encode the contextual frame of new information (Tanaka, Miyazawa, Akaoka, & Yamada, 1997; Kapur et al., 1998). MBs, directly connected to the fornix, have reciprocal connections with the hippocampal formation through the Gudden's tegmental nuclei and it has been proposed that the MBs play a vital contribution to mnemonic processing through their direct and indirect projections to the medial temporal lobe (Vann & Aggleton, 2004). The hippocampal output is largely via the fornix fibers, ending in the MBs of the hypothalamus (Raslau et al., 2015). Fibers from the MBs pass backward into the anterior thalamic nuclei via the mammillo-thalamic tract, and then on to the anterior cingulate gyrus via specific thalamo-cortical projections (Yamada et al., 1998). The cingulum is connected with the association cortices and also the hippocampus via the retrosplenial cortex, thus closing the loop through the parahippocampalgyrus (Aggleton & Brown, 1999; Catani, Dell'acqua, & Thiebaut de Schotten, 2013).

In our study we also considered consolidation deficit at longer delays (i.e., 1 week). Our patient MG was diagnosed with TLE, and many discharges were detected on EEG recordings. MG demonstrated ALF already at 1-week delay, but no impairments on learning, retrieval, or interference sensibility when tested at 15-min delay. More interestingly, our patient worsened most of all on the Recognition trial at 1-week delay, producing many FPs regardless the list source. Similar results have been presented by Miller et al. (2015), even though the Recognition trial was not considered in that study.

It has been reported that, similarly to patients with Alzheimer's Disease (AD), those with temporal lobe lesions (Majdan et al., 1996; Jones-Gotman et al., 1997; Redoblado et al., 2003) showed more pervasive memory deficit that included a high rate of FP errors in the RAVLT's Recognition trial. In another study (Ricci et al., 2012), AD patients committed significantly more FP errors on RAVLT Recognition trial, regardless the list source, compared with frontotemporal dementia group and controls. In an exhaustive review (Eichenbaum, Yonelinas, & Ranganath, 2007), it has been suggested that recollection and familiarity are functionally dissociable processes and that different circuits within the medial temporal lobe make different contributions to recognition memory. Although the hippocampus has a specific role in recollection and not familiarity, a specific memory subsystem comprising the perirhinal cortex and medio-dorsal thalamus is crucial for familiarity-based recognition

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(Aggleton & Brown, 1999). The hypothesis proposed by the authors claims that during encoding, information about stimuli to be remembered, processed by perirhinal and lateral entorhinal regions, and the information about their context (especially spatial), processed by the parahippocampal cortex, converge in the hippocampus. When a previously encountered stimulus is processed, perirhinal and lateral entorhinal cortices can signal its match to a preexisting item representation. This matching signal can be propagated back to neocortical areas, and it might be sufficient to generate the sense of familiarity without the involvement of the hippocampus.

Going back to our patient MG, his performance on RAVLT Recognition trial with many FP errors might be the result of a dysfunctional process involving perirhinal and entorhinal cortices. Our patient DGL did not produce FP errors on recognition, which accounts for a lack of contribution of the hippocampus in producing false responses on item-based recognition memory. Although other evidences are needed to clarify the contribution of hippocampus, fornix, and MBs on recognition memory circuitry.

Conclusion

The RAVLT is a powerful clinical instrument in spite of its simplicity. It is easy to administer and it has been widely used as reliable test of episodic memory. Also, the RAVLT demonstrated to obtain similar results across cultural, demographic, and language differences (Ricci et al., 2012). To the best of our knowledge, this is the first study that provides RAVLT exhaustive normative data in Italian population on Single Scores and Composite Indices at shorter delay (i.e., 15 min), and most importantly at longer delay (i.e., 1 week). This tool can be used now in clinical settings to detect ALF and improve diagnostic accuracy amongst amnesic patients.

Limitations

We did not measure specifically neither the number of intrusions during recalls nor the List B false responses in the Recognition trial. Both scores should account for prefrontal dysfunctions, with the former depending on inaccurate retrieval strategies, and the latter on source memory impairments. However, clinicians should consider that healthy subjects did not show any intrusions during recall, and a very limited number of List B false responses.

Also, given the paucity of subjects with lower level of education, we could not differentiate the 5- and 8-year groups of education. For the reason reported earlier, the data regarding younger subjects (up to 40 years old) with lower level of education (8 years or below) and older subjects ($\geq$71) with higher level of education ($>$13) should be taken with caution.

The 1-week administration of recall and recognition was administered in person. This might be a limitation for anyone who may consider to administer these RAVLT's trials via telehealth.

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Conflict of interest

None declared.

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