

NEUROBEHAVIORAL GRAND ROUNDS

Retrograde episodic and semantic memory impairment correlates with side of temporal lobe damage

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Abstract

Patients with damage to the mesial and anterior portions of the temporal lobes suffer from a memory impairment involving both anterograde and retrograde amnesia. In the retrograde domain, it has been suggested that the relative severity of autobiographical and nonautobiographical memory impairment may depend on the prevalent side of the temporal damage. Here we present two patients suffering from damage to the mesial and anterior portions of the temporal lobes (hippocampal formation, parahippocampal gyrus and polar cortex) as a result of herpes encephalitis. In the first case, A.S., damage predominantly affected the right temporal lobe, whereas in the second patient, R.S., the damage was bilateral but more severe on the left side. A detailed investigation of the retrograde memory deficit demonstrated a partial double dissociation between the two patients, with A.S. almost exclusively impaired in the autobiographical domain (both episodic and semantic) and R.S. with poor performances in all domains, but much more severe in the nonautobiographical (both public events and general semantic knowledge) than in the autobiographical one. These findings reinforce the view of specialization of right and left temporal lobes in the retrieval of retrograde autobiographical and nonautobiographical memories, respectively. (*JINS*, 2008, 14, 1083–1094.)

Keywords: Amnesia, Memory, Herpes encephalitis, Hemispheric specialization, Autobiographical, Double dissociation

INTRODUCTION

Organic amnesia entails a specific deficit of declarative long-term memory, involving both anterograde and retrograde amnesia. Damage to several of the components of the neural system which underlies the anterograde memory traces [medial temporal lobe (MTL), basal forebrain, anterior and medial thalamus, mammillary bodies, limbic cortex] (Squire & Zola-Morgan, 1991) has also been associated with difficulty in the retrieval of premorbid facts or events, thus emphasizing the role of these brain areas in the retrieval of memory traces stored long ago (Bayley et al., 2006; Cipelotti & Bird, 2006). Although various classifications of symptoms have been proposed in the domain of retrograde amnesia (Kopelman & Kapur, 2001),

a major distinction can be drawn between loss of memory for personally experienced events, broadly equivalent to *episodic memory*, and impaired recollection of factual knowledge, broadly equivalent to *semantic memory* (Tulving, 1987). The term “*episodic memory*” refers to the recollection of a person’s past incidents and events, which are specifically dated and located in subjective time and space. We include in this domain both recollection of the experience and retrieval of the contents of the experience. The retrieval of an episodic memory also entails a special kind of experience, called “*autonoetic*” (self-knowing) consciousness, which allows mentally representing and subjectively reliving a past experience (Tulving, 1987; Wheeler et al., 1997). The term “*semantic memory*” is instead used to indicate well-established knowledge in any domain whose memory representation typically does not include the temporal-spatial context in which it was acquired. A distinction is generally made between “*personal*” and “*public*” semantic memories. *Public semantic memories* relate

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to a kind of knowledge which is common to all people in a given historical and cultural condition, but different from a modality specific deficit associated with conditions such as acquired language disorders, visual agnosias, and so on. *Personal semantic memory*, instead, concerns basic factual knowledge about a person's own past, without specific contextual markers (names, addresses, and so on) (Kapur, 1999; Tulving et al., 1988).

Based on the report of patients with a prevalent loss of the episodic or semantic aspects of retrograde memory, some authors have postulated a relationship between hemispheric side of damage and qualitative features of the retrograde impairment (Kopelman & Kapur, 2001). De Renzi et al. (1987) first reported the case of a patient who, following herpes encephalitis, reported left inferior and anterior temporal lobe damage and showed severe impairment of semantic memory for words, objects, famous persons, and public events in the absence of episodic memory disturbances. A similar pattern of impairment was reported by Grossi et al. (1988) in a patient who suffered from a large, left parietal lesion, as a result of severe head trauma. The semantic memory loss in this patient extended to vocabulary, arithmetic, and geographical knowledge, but his recollection of personally experienced events from his entire life was excellent. A more severe deficit of semantic than episodic retrograde memory in patients with left hemisphere temporal damage has also been reported in single case investigations by Markowitsch et al. (1993) and Yasuda et al. (1997) and in groups of epileptic patients before (Lah et al., 2006) and after left temporal lobectomy for the treatment of pharmacologically resistant epilepsy (Barr et al., 1990).

The reverse pattern of memory disorder has also been reported. In particular, O'Connor et al. (1992) described a case of herpes simplex encephalitis with severe right temporal lobe damage and more limited left temporal lobe involvement. In this patient, memory loss for public events was confined to very remote ones. By contrast, autobiographical episodic memories were uniformly affected, with little sparing of more distant events. Three other patients with damage confined to the frontotemporal regions of the right hemisphere (Calabrese et al., 1996; McCarthy & Warrington, 1992), or bilateral but predominant on the right side (Markowitsch et al., 1993), also manifested a more severe retrograde deficit in the retrieval of episodic than semantic memories. Finally, a more severe deficit in the autobiographical than in the semantic remote memory domain has been reported in a group of patients with right temporal lobe epilepsy (Lah et al., 2006).

Not all of the reported neuropsychological evidence is, however, in keeping with the above-mentioned hypothesis of a dominance of the right and left cerebral hemispheres for the autobiographical and semantic aspects of the retrograde memory, respectively. For example, Kopelman and colleagues (1999) reported the expected double dissociation between two patients with unilateral left temporal lobe damage and three patients with predominantly right-sided damage on a name completion task versus an autobiograph-

ical incidents task. However, both groups performed poorly on a famous news events task, thus not confirming the expected dissociation between impaired autobiographical but spared nonautobiographical memory in right damaged patients. Partial support to the hemisphere dominance view also comes from a patient with predominantly right-sided pathology that showed a deficit of both personal episodic and personal semantic retrograde memories on the Autobiographical Memory Interview (Kopelman et al., 1989) and poor scores on a famous news events test despite preserved new word learning on a word definition test (McCarthy et al., 2005).

Contradictory data regarding the supposed hemispheric asymmetry in the representation of autobiographical and semantic retrograde memories also come from the results of functional neuroimaging investigations of healthy subjects. So, the results of a recent study by Levine et al. (2004) support the relative dominance of the right and left hemispheres in the retrieval of autobiographical and semantic memories, respectively. These authors considered episodic and personal semantic components as mediated by dissociable states of consciousness, one prompting the experience of the self at a specific moment in the past (autonoetic consciousness) and the other involving self-knowledge not requiring "mental time travel" (noetic consciousness). Using prospectively collected autobiographical stimuli and manipulating the episodic/semantic distinction, the authors found a functional neuroanatomical dissociation between episodic (right temporoparietal cortex) and personal semantic material (left temporoparietal and frontoparietal cortices) in autobiographical memory. In contrast, the results of other studies did not document any clear asymmetry in the activation pattern related to the memory retrieval of episodic and semantic memories. So, for example, Maguire et al. (2000) reported a predominantly left-lateralized network for memory retrieval which was irrespective of the episodic or semantic nature of the information to be retrieved. Moreover, the findings of a recent meta-analysis of data from 24 functional imaging studies of autobiographical memory did not support the claim of a right/left asymmetry in the retrieval of episodic and semantic memories in the autobiographical domain (Svoboda et al., 2006).

Here we report the cases of two patients suffering from lesions to the mesial and anterior portions of the temporal lobes as a result of herpes simplex encephalitis who differed as to the side of the prevalent damage. Indeed, in one patient parenchymal damage was predominant on the right hemisphere, while in the other patient it was bilateral but larger in the left temporal lobe. To evaluate possible discrepancies in the pattern of retrograde memory impairment as a function of the prevalent side of hemispheric damage, these patients were administered an extensive retrograde memory battery. The latter permitted investigating both episodic and personal semantic components of autobiographical memory and, in the nonautobiographical domain, the analysis of public semantic knowledge (meaning of words that recently entered the vocabulary) and famous events.

CASE REPORTS

A.S.

A.S. was a 53-year-old, right-handed man, with an unremarkable medical history until the onset of the present disease. He had completed high school and worked as a retailer, managing his own bar. In January 2005, the patient was admitted to the hospital complaining of malaise characterized by fever and mental confusion. He was disoriented in time and space and did not recognize his relatives. A cranial CT scan, performed upon entrance, showed the presence of a focal area of hypodensity located deeply in the right temporal region, with moderate enlargement of the temporal horn of the lateral ventricle. Several cerebral magnetic resonance imaging (MRI) scans confirmed the presence of an area of signal change in the right temporal region, extending to the splenium of the corpus callosum, without any apparent additional lesion in the remaining cerebral parenchyma. Based on the results of neuroradiological exams and cerebrospinal fluid analysis (positive reaction for herpes simplex virus type 1 on polymerase chain reaction), herpes simplex encephalitis was diagnosed.

We first observed A.S. in February 2005. At that time he was still moderately agitated, disoriented in time and place (but no longer for persons), with evident memory difficulties in both anterograde and retrograde domains. Psychomotor agitation resolved in 3 to 4 weeks. In the period in which he was submitted to the below reported neuropsychological investigation (from May to July 2005), he was a fully alert, cooperative individual, with only some attentional difficulties, which made it necessary to fractionate the overall investigation into numerous, brief testing sessions. At that time his spontaneous speech was fluent, with good informative content, and without any types of errors.

R.S.

R.S. was a 37-year-old, right-handed woman. She had completed high school and up until the onset of the presently reported disease she had been working as a secretary in a primary school. In October 2004, the patient was admitted to the hospital complaining of malaise characterized by fever and mental confusion. Also in this case, the results of neuroradiological exams and virologic investigations on cerebrospinal fluid were consistent with a diagnosis of herpes simplex encephalitis.

An MRI scan, performed in December 2004, documented the presence of parenchymal damage localized in the left temporopolar cortex and hippocampal region, near a moderate enlargement ex-vacuo of the temporal horn of the homolateral lateral ventricle. An area of altered signal was also present in the right temporomedial region, but it was considerably smaller than the contralateral one. The below reported neuroradiological and neuropsychological evaluations were performed from February to July 2005. At that time R.S. was a fully alert, cooperative individual, with-

out any apparent attentional difficulty. Her main complaint was a severe memory disturbance for both retrograde and anterograde information. Her spontaneous speech was fluent, syntactically and phonologically correct, with only sparse word-finding difficulties and hesitations.

EXPERIMENTAL INVESTIGATION

A.S. and R.S. were submitted to a neuroradiological investigation aimed at clarifying the localization of brain damage and to a neuropsychological assessment of general cognitive and, in more detail, of memory abilities. The study was approved by the Local Ethics Committee.

Neuroanatomical Examination

To obtain a volumetric analysis of the anatomical structures in R.S.'s left and right temporal lobes, a high resolution MRI brain scan was performed in February 2005. Magnetization Prepared Rapid Gradient Echo (MPRAGE) T1-weighted images (TR = 11.4 ms, TE = 4.4 ms, flip angle = 15 degrees) were obtained with a Siemens Vision Magnetom R system (Siemens Medical Systems, Erlangen, Germany) operating at 1.5 T. The high spatial resolution brain sampling of $1.25 \times 0.98 \times 0.98 \text{ mm}^3$, allowing images to be rotated by small angles in the three orthogonal planes, facilitated the identification of anatomical landmarks for the selection of the region of interest. This sequence produced 128 contiguous slices of 1.25 mm thickness, which covered the whole brain. To reduce intersubject variability in the total cerebral space and to avoid error-prone, all images were registered in linear stereotaxic space into coordinates based on the Talairach atlas (Talairach & Tournoux, 1988) using a 9-parameters algorithm of registration (Collins et al., 1994).

As can be seen in Figure 1, the patient presented severe atrophy of the left hippocampus. Slight atrophy of the right hippocampus was also evident upon visual inspection (see transverse and coronal planes). The coronal and sagittal planes of the images showed marked atrophy of the left parahippocampal gyrus, particularly in the parahippocampal cortex, while the sagittal images revealed a necrotic area in the left temporal pole. The parenchymal damage in R.S. extended beyond the anterior portions of the temporal lobe; indeed, inspection of MRI (particularly in the coronal plane) does suggest that this patient showed greater atrophy throughout the left hemisphere than on the right, including the frontoparietal region.

Volumetric analysis was performed using the interactive software DISPLAY package (J.D. McDonald, Brain Imaging Center, Montreal Neurological Institute (MNI); www.bic.mni.mcgill.ca/software/Display), that allows simultaneous viewing and segmentation of cerebral volumes in coronal, sagittal and horizontal orientations. The anatomical landmarks for manual segmentation of the hippocampal formation, perirhinal, entorhinal, and parahippocampal cortices in the parahippocampal gyrus and temporopolar cortex were in accordance with Insausti et al. (1998) and Pruessner et al.

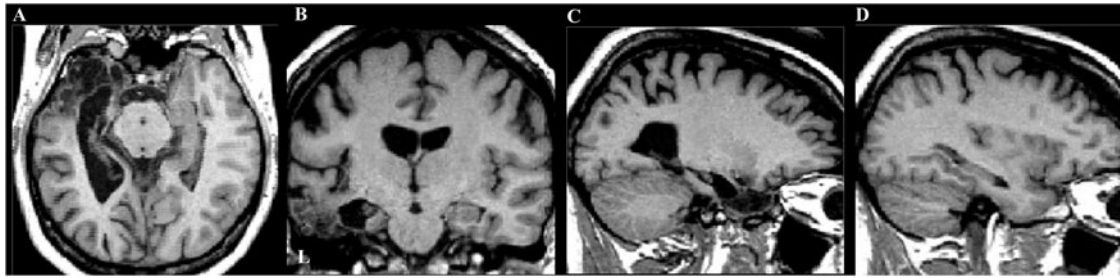


Fig. 1. T1-weighted MR images of R.S.'s brain in transverse (A), coronal (B), and sagittal plane of the left (C) and right (D) hemispheres. The sections are all at the level of the hippocampal region.

(2000, 2002). Due to the severity of damage which made difficult identification of boundaries between the various MTL cortices on the left side, anatomical landmarks were in some cases identified with reference to symmetrical boundaries on the right hemisphere. The volumetric measures collected in R.S. were compared with those of the 40 healthy subjects, ranging in age from 18 to 42, reported in the original papers by Pruessner et al. (2000, 2002). Results are shown in Table 1. R.S. presented bilateral atrophic changes of temporomesial and temporopolar structures (volumes generally falling more than 2 *SDs* below the mean of normal controls). However, at the level of the hippocampal formation and of the parahippocampal and temporopolar cortices the volumetric reduction was clearly asymmetrical, with a prevalence of atrophic changes on the left side.

Because of severe claustrophobia, it was impossible to obtain high quality MR images necessary for the manual segmentation procedure for A.S. A visual inspection of the available images obtained from a 0.5 T open MRI scanner (Figure 2) reveals the presence of a signal change in T2* weighted sequences at the level of the hippocampal and parahippocampal structures, the inferior temporal gyrus and the temporal pole in the right hemisphere. Two small areas of signal change are also present at the level of the hippocampus and polar cortex in the left temporal lobe. Outside the temporal lobes, small areas of signal change were also noted at the level of the ventral region of the right frontal lobe.

In summary, consistent with the usual localization of neuropathological changes in herpes simplex encephalitis, in both patients brain damage involved structures in the medial and polar regions of the temporal lobes. The main difference was the side of the lesion, which was almost exclusively on the right for A.S. and bilateral, but with prevalent left involvement, in the case of R.S.

GENERAL NEUROPSYCHOLOGICAL ASSESSMENT

A.S. and R.S. were given a neuropsychological battery that included tests for the assessment of general intelligence, executive functions, language and visual-constructive abilities, and, in more detail, of memory functioning. Written informed consent was obtained from the patients. Raw scores on the individual tests were adjusted for age and education according to normative data.

General Neuropsychological Examination

As reported in Table 2, A.S.'s full-scale WAIS IQ was in the upper middle range, with a prevalence of Verbal over Performance IQ, due to poor scores on the Object Assembly and Digit Symbol subtests. On the contrary, R.S.'s total IQ was in a low range due to her particularly poor scores on some verbal subtests (Vocabulary, Comprehension, and Sim-

Table 1. Volumes (mm^3) of R.S.'s left and right hippocampal, parahippocampal, and temporopolar structures compared to mean values (and standard deviations) of the original normative sample (Pruessner et al., 2000, 2002)

	Left hemisphere			Right hemisphere		
	R.S.	Mean value (<i>SD</i>) in healthy controls	<i>SDs</i> below mean of healthy controls	R.S.	Mean value (<i>SD</i>) in healthy controls	<i>SDs</i> below mean of healthy controls
Hippocampus	478	4243 (438)	-8.59	2464	4395 (468)	-4.13
Perirhinal	331	2415 (696)	-2.99	963	2456 (631)	-2.36
Entorhinal	591	1684 (306)	-3.57	1118	1818 (204)	-3.43
Parahippocampal	293	2810 (445)	-5.65	1054	2454 (358)	-3.91
Temporopolar	401	6570 (1437)	-4.29	3250	6868 (2006)	-1.80

Note. For each anatomical structure considered, the entity of the atrophic change in R.S.'s brain, expressed as the number of *SDs* below the mean of normal controls, is also reported.

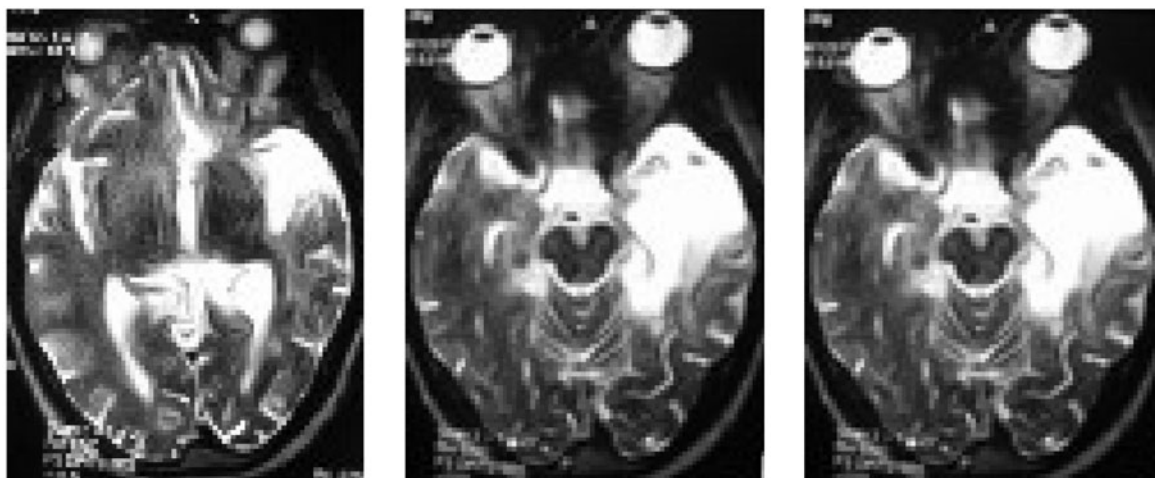


Fig. 2. T2-weighted MR images of A.S.'s brain in transverse plane at the level of MTL structures. Damage to right hippocampal, parahippocampal, and temporopolar structures is evident. Two small areas of signal change are also present at the level of the hippocampus and temporopolar cortex on the left side.

ilarities) and scores in the lower portion of the normal range on the Information and Block Design subtests which suggest a pervasive loss of basic semantic knowledge and some difficulties on the visual abstract processing and problem solving. A.S.'s scores on most of the tests of the neuropsychological battery were in the normal range, with the exception of less than normal score (<5%ile of the score distribution of healthy controls) on a phonological verbal fluency test (FAS) and a score in the lower portion of the normal range (<10%ile of the normal score distribution) on a test of copy of drawings. R.S., instead, obtained scores in the lower portion of the normal range on some tests sensitive to frontal lobe damage (Modified Card Sorting Test and FAS) and on tests of constructional praxis.

Short-Term and Anterograde Episodic Memory

As reported in Table 3, both patients were compromised on free recall measures of episodic long-term memory involving both verbal data (less than normal scores on the immediate and delayed recall of a word list and scores in the lower portion of the normal range on the immediate and delayed recall of a short prose passage) and visual-spatial data (less than normal scores on the immediate and delayed reproduction of the Rey's Figure). However, with the exception of R.S.'s poor score on the Corsi span, their performances on short-term memory tasks were in the normal range.

RETROGRADE MEMORY

Retrograde memory tests were selected with the aim of evaluating in the autobiographical domain both personal episodic and personal semantic components, and in the non-autobiographical domain, public memory for famous events

and word meaning. Due to the lack of published norms, for all of these tests the patients' performance scores were compared directly with those of a group of 10 healthy controls, composed of 5 men and 5 women matched for age, education and gender to A.S. and R.S., respectively. Written informed consent was obtained from the subjects. Because the performance scores of the two subgroups of healthy controls did not significantly differ in any case, the scores of the two patients were compared directly with those of the overall group of normal controls using the procedure developed by Crawford and Garthwaite (2002) to estimate the abnormality of an individual patient's test score when the normative or control sample against which the patient is compared is modest in size.

Autobiographical Memory Interview

A modified version of the Autobiographical Memory Interview (Kopelman et al., 1989) was used to test retrograde memory for personal events and facts. This semistructured interview is divided into three main blocks, each investigating autobiographical memories pertaining to a specific life period: childhood-adolescence (0-18 years), early adult life (20-30 years) and late adult life (30-disease onset). For each period, the subject is required to produce personal memories in response to three questions concerned with specific incidents from his own past (e.g., an event involving a teacher or a friend that occurred while the subject was attending the primary school, an episode occurring during his own wedding or some wedding he attended), and three questions about specific information about his own past, which could be retrieved without it being linked to any particular spatiotemporal context (e.g., the address where he was living in the childhood and the names of his secondary school teachers and friends).

Table 2. Performance scores of A.S. and R.S. on tests of general intelligence, executive functions, constructional praxis, and language

Test	A.S.	Percentile score	R.S.	Percentile score	Maximum score
General Intelligence					
WAIS-R (Wechsler, 1997)					
Information	13	>50%	6	<10%	18
Digit span	7	>10%	7	>10%	19
Vocabulary	16	>50%	4	<5%	19
Arithmetic	11	>50%	7	>10%	17
Comprehension	13	>50%	4	<5%	19
Similarities	14	>50%	3	<5%	18
Picture Completion	7	>10%	7	>10%	17
Picture Arrangement	7	>10%	9	>25%	17
Block Design	7	>10%	6	<10%	19
Object Assembly	4	<5%	12	>50%	18
Digit Symbol	5	<10%	4	<5%	19
Verbal IQ	121		72		150
Performance IQ	95		91		150
Full-scale IQ	111		78		150
Raven's Coloured Matrices (Carlesimo et al., 1996)	29.3	>50%	27.5	>25%	36
Executive Function					
Modified Card Sorting Test (Nocentini et al., 2002)					
Criteria achieved	6	100%	4.9	<10%	6
Perseverative Errors	2	>25%	5.6	<10%	47
FAS (Carlesimo et al., 1996)	7.6	<5%	17.3	<10%	
Constructional praxis					
Copy of Drawings (Carlesimo et al., 1996)	9.5	>25%	7.1	<10%	12
Copy of Drawings with Landmarks (Carlesimo et al., 1996)	69.2	>25%	63.7	<10%	70
Rey's Figure Copy (Carlesimo et al., 2002)	24.2	<10%	23.8	<10%	36
Language					
Naming Test (Miceli et al., 1991)	30	100%	26	>25%	30

Note. Scaled scores are reported for WAIS subtests. For the other tests the scores have been adjusted for age, gender and years of formal education according to published normative data (references in brackets). Percentile scores, calculated with respect to the score distribution in the normative population, are also reported.

In the Personal Episodic section of the interview, the score is determined by the descriptive richness of the responses. In particular, for each question a score of 3 is given for the report of a clearly defined episode in a specific temporal and spatial context, 2 for a personal event with few details or for which time and place are not accurately recalled, 1 for a vague personal memory and, finally, 0 for no event or for a response based purely on general knowledge. In the Personal Semantic section of the interview, the score is assigned in terms of correctness, with 2 for perfect recall, 1 for partial recall, 0.5 for only one detail (e.g., only the city or the street instead of the entire address) and 0 for no recall. For both the Personal Episodic and Personal Semantic sections of the interview, the two patients' responses were checked for accuracy with the help of close relatives.

Two independent raters scored performance of the two patients and of the healthy controls on this test. Agreement between the two raters was moderate/good (weighted Cohen's Kappa for the various scores ranged between .41 and .80). For this reason, the reported scores are the mean between the two raters.

In the Personal Episodic section (Figure 3), A.S. recalled a total of three events, two consisting of incidents without specific time and place and the other of a vague personal memory. Differently, R.S. scored a total of 10 episodes: on one she obtained the maximum score, six were inaccurate for time and place, and three were vague memories. Both patients performed significantly worse than controls in all periods examined (A.S.: $t = 13.03, 10.33, \text{ and } 18.69$ for childhood–adolescence, early, and late adult life, respec-

Table 3. Performance scores of A.S. and R.S. on tests of short-term and anterograde episodic memory

Test	A.S.	Percentile score	R.S.	Percentile score	Maximum score
Short-term memory					
Digit Span forward (Orsini et al., 1987)	6.6	>50%	5.8	>50%	9
Corsi Span forward (Orsini et al., 1987)	4.7	>25%	3.7	<10%	9
Verbal episodic memory					
15-word list (Carlesimo et al., 1996)					
Immediate recall	22.4	<5%	23.0	<5%	75
Delayed recall	3.3	<5%	0	<5%	15
Short Story (Carlesimo et al., 2002)					
Immediate recall	4.5	>10%	3.3	<10%	8
Delayed recall	3.1	<10%	2.4	<10%	8
Visual-spatial episodic memory					
Rey's Figure (Carlesimo et al., 2002)					
Immediate recall	2.2	<5%	1.7	<5%	36
Delayed recall	1.7	0%	0	0%	36

Note. The reported scores have been adjusted for age, gender, and education according to published normative data (references in brackets). Percentile scores, calculated with respect to the score distribution in the normative population, are also reported.

tively; $p < .001$ in all cases; R.S.: $t = 4.13, 4.92,$ and 10.12 ; $p < .001$ in all cases). However, A.S.'s accuracy was consistently below R.S.'s. Indeed, A.S.'s scores fell on average more than 15 *SDs* below the mean of normal controls; instead, R.S.'s scores, while substantially abnormal, fell on average less than 7 *SDs* below the mean of normal controls.

In the Personal Semantic section of the interview (Figure 3), both patients performed significantly worse than healthy controls for childhood–adolescence (A.S.: $t = 7.22$; $p < .001$; R.S.: $t = 1.56$; $p < .05$) and early adult life (A.S.: $t = 4.17$; $p < .01$; R.S.: $t = 2.25$; $p < .05$). As for late adult life, R.S. still performed significantly worse than NCs ($t = 1.57$; $p < .05$), while A.S. obtained the maxi-

imum score possible. The overall performance did not differ among patients. Indeed, both A.S. and R.S. scored on the average approximately 3 *SDs* below the mean of controls.

Crovitz Test

This test, first devised by Crovitz (Crovitz, 1970, Crovitz & Shiffman, 1974), was administered in the Italian version, edited by Ghidoni et al. (1995). In this procedure, subjects are provided with a list of 60 words, 30 concrete (e.g., river) and 30 abstract (e.g., happy), and are required to describe an incident from their own life that is related

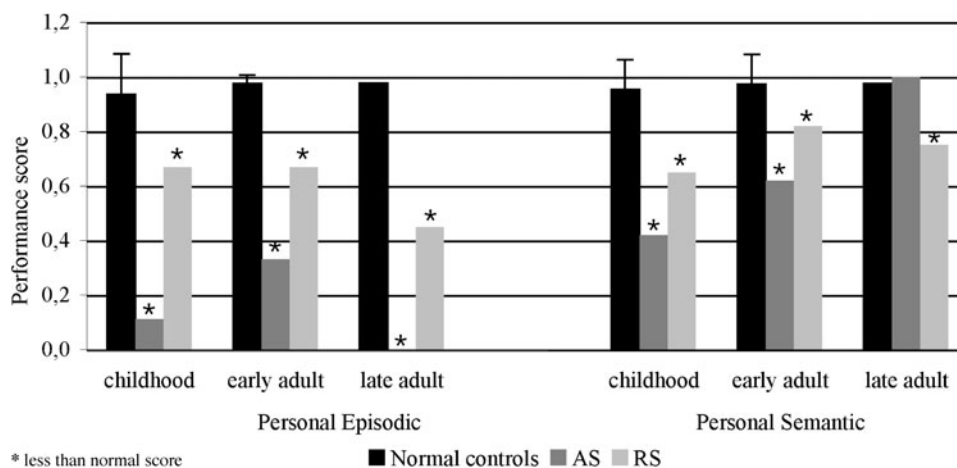


Fig. 3. Performances of A.S., R.S., and normal controls on the modified version of the Autobiographical Memory Interview. To compare performances on the Episodic and Semantic sections of the test, scores in the y axis are reported as proportion of the maximum score achievable. Bars represent the standard deviations from the mean.

to each of the cue words. Analogously to the Autobiographical Memory Interview, the scoring method for this test is based on the descriptive richness of each memory produced and its uniqueness in time and place. A score of 3 is given for a well-characterized autobiographical event specific in time and place, 2 for an event that is less characterized or more poorly temporally and spatially defined, 1 for a vague personal memory and, finally, or 0 for no response or for a response based purely on general knowledge. The two independent raters who scored performance on this test of the two patients and of the healthy controls achieved a full agreement (Cohen's Kappa = 1).

On this test, A.S. scored 24 and R.S. 38. In particular, A.S. was unable to recall any detailed event specific in time and place, while R.S. was only able to recall two such events, one from her own childhood–adolescence and one from her own early adult life. Performances of the two patients were significantly worse than the healthy controls' average (110; $SD = 24.5$; A.S.: $t = 3.34$; $p < .01$; R.S.: $t = 2.8$; $p < .05$), with A.S. only slightly worse than R.S. (3.5 and 2.9 SDs below the mean of healthy controls, respectively).

Italian Questionnaire for Remote Events

This Italian version of the test devised by Sanders and Warrington (1971) for the assessment of memory for public events was developed by Costa et al. (1989) and Budriesi et al. (2002). The events included in the questionnaire had been extensively covered by newspaper and TV news programs in the period in which they occurred. There were eight events for each of eight 4-year periods from 1966 to 1997, for a total of 64 items. For each item concerning general news, politics and sports, the subject is questioned about a detail concerning a single event (e.g., "In July, 1992, not long after the killing of Judge Giovanni Falcone, Judge

Paolo Borsellino was killed with his escort while he was paying a visit to his mother. In which city did it happen?") and is requested to indicate the correct response out of four alternatives (e.g., Caltanissetta, Catania, Reggio Calabria, Palermo). A score of 1 is assigned for each correct response. Because the subject should have been at least 16 years old when the event occurred, A.S. was administered the items from 1970 to 1997 and R.S. only items concerning the years from 1986 to 1997.

As shown in Figure 4, A.S.'s recognition scores were not different from those of healthy controls for all periods examined (t consistently < 1.6 ; $p = ns$); instead, R.S. scored significantly worse than the healthy participants for the '90 to '93 and the '94 to '97 periods ($t = 2.9$ and 2.3 , respectively; $p < .01$ in both cases) but similar to controls for the '86 to '89 period ($t = 1.4$; $p = n.s.$). Averaging the performance across all the periods examined, R.S. obtained significantly worse scores than A.S. (1.6 and 0.1 SDs below the mean of controls, respectively).

New Words Test

This test was constructed *ad hoc* to evaluate knowledge of the meaning of words that entered the Italian vocabulary in the last forty years. In a preliminary study, we selected 226 words from the Zanichelli Italian Language Dictionary (2006), introduced into the Italian lexicon between 1960 and 2000. Ten college students were given a booklet containing definitions and were required to write down the corresponding words. The final form of the test, comprising 30 words for each decade from 1960–69 to 1990–2000, was based on the college students' performance accuracy on the individual items (i.e., at least 8 of 10).

Figure 5 reports the performance accuracy of the two patients and the group of healthy controls on this test. A.S.'s performance scores were significantly below the average of

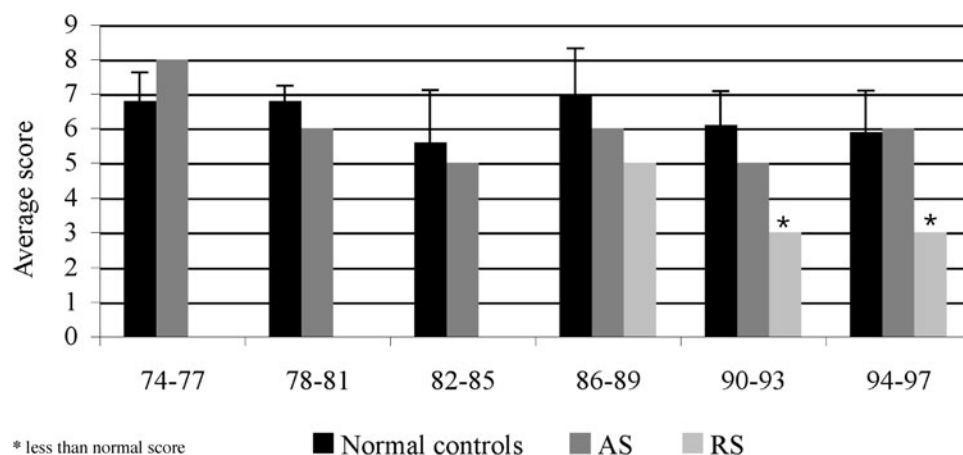


Fig. 4. Average performances of A.S., R.S., and the group of normal controls on the eight items included in each of the 4-year periods of the Italian Questionnaire for Remote Events. Since they had different ages at the time the events occurred, A.S., R.S., and the healthy controls were given questions pertaining to three and six 4-year periods, respectively. Bars represent standard deviations from the mean.

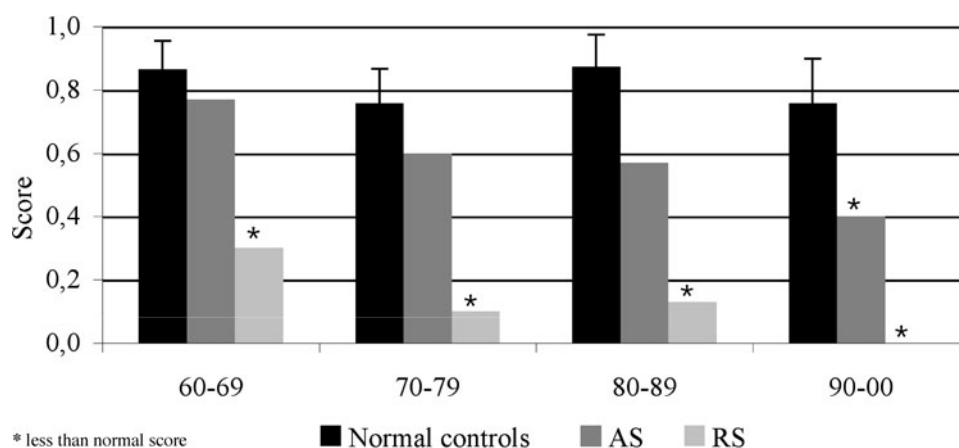


Fig. 5. Average proportion of correct responses of A.S., R.S., and the group of normal controls on the New Words test as a function of the decade of entry of the words in the Italian lexicon. Bars represent standard deviations from the mean.

NCs only in the last decade examined ($t = 2.45$; $p < .02$). By contrast, R.S. performed significantly worse than NCs in all periods examined ($t = 5.93$; 5.72 ; 7.05 , and 4.97 for the 4 decades, respectively; $p < .001$ in all cases). Overall, R.S.'s performance on this test was considerably poorer than A.S.'s performance (6.3 and 2.0 *SDs* below the mean of controls, respectively).

DISCUSSION

In this study, we investigated the retrograde memory deficit of two amnesic patients suffering from damage to the MTL structures and temporopolar cortex as a result of herpes simplex encephalitis. The morpho-volumetric analysis computed on cerebral MR images of the patient R.S. highlighted the presence of a significant bilateral volumetric reduction at the level the perirhinal and entorhinal cortices of the MTL but much more severe on the left side for the hippocampus, parahippocampal cortex and temporopolar cortex. For patient A.S., a visual inspection of the clinical MR images clearly revealed the presence of damage at the level of MTL and temporopolar structures in the right hemisphere, with minor lesions in the left hippocampus and temporopolar cortex. In both patients, the cerebral damage extended beyond the temporomesial and temporopolar structures. Indeed, R.S. presented atrophic changes throughout the left hemisphere, including the frontoparietal region; in A.S., instead, the damage also involved the orbitoventral region of the right frontal lobe. In summary, these two patients showed parenchymal damage which, consistent with what is generally observed in postencephalitic patients, was particularly severe at the level of mesial and anterior temporal lobe regions but that also involved other neocortical and subcortical structures. However, the two patients differed as to the prevalent side of cerebral damage: A.S.'s lesion was predominantly located in the right hemisphere; R.S.'s damage, instead, was bilateral but prevalent on the left side.

The two patients underwent a global cognitive evaluation which highlighted the presence of severe anterograde memory impairment for both verbal and visuospatial material. A.S. had also some difficulties on tests of executive functioning and constructional praxis. This finding, together with the behavioral abnormalities this patient demonstrated particularly in the early phases of the disease, is likely related to the involvement of frontal lobe structures documented by MRI. On the other side, R.S. performed very poorly on the verbal subtests of the WAIS, consistent with her prevalent semantic memory disturbance.

On the retrograde memory battery, the two patients' performances were indicative of a relatively different pattern of impairment. In particular, A.S. was dramatically poor in recollecting specific autobiographical episodes from his own premorbid life, and in both tests of autobiographical memory he was unable to produce any detailed event, producing only vague episodes or general personal knowledge. On the Autobiographical Memory Interview, A.S.'s performance on the Personal Semantic section was still worse than that of the healthy subjects but significantly better than his performance on the Personal Episodic section. In fact, he scored approximately 3 *SDs* and 15 *SDs* below the mean of healthy controls, respectively. Finally, on tests of public (nonautobiographical) semantic knowledge, A.S.'s performances were substantially normal, with normal scores on all periods examined by the Public Events Test and on the first 3 decades of the New Words Test (he was difficulties only in recollecting words entered the Italian lexicon in the past decade). In summary, A.S. disclosed a pattern of impairment that was substantially consistent with the hypothesis of a specific role played by the right hemisphere in autobiographical episodic memory. Indeed, following damage almost exclusively confined to the anterior portion of the right temporal lobe and the ventral region of the right frontal lobe, this patient showed a clear dissociation between almost complete absence of recollection of autobiographical episodic

memories and substantially preserved memory of public semantic knowledge. Performance accuracy on questions pertaining to personal (i.e., autobiographical) semantic knowledge was intermediate between that achieved on tests of personal episodic and public semantic knowledge; this suggests a less pronounced lateralization of this kind of retrograde memory which, although concerned with autobiographical material, conveys information not linked to any particular spatial-temporal context.

Unlike A.S., R.S.'s pattern of impairment was less indicative of a dissociation between distinct components of retrograde memory. This patient scored below the range of normal controls on all tests of the retrograde memory battery. However, if we directly compare the qualitative pattern of impairment disclosed by the two patients, some clues emerge pointing to a double dissociation between performance on episodic and semantic tasks. Although both patients scored poorly on the autobiographical episodic memory tests, A.S.'s deficit was much more severe than R.S.'s. This was particularly evident in the episodic section of the Autobiographical Memory Interview, where R.S. and A.S. scored approximately 7 *SDs* and 15 *SDs* below the mean of normal controls, respectively. Conversely, on the tests tapping public semantic knowledge R.S.'s scores were consistently abnormal, whereas A.S.'s performances were substantially preserved. Finally, the performance accuracy of the two patients on the semantic section of the Autobiographical Memory Interview did not significantly differ. Across the three life periods examined by the questionnaire, both A.S. and R.S. scored approximately 3 *SDs* below the mean of normal controls. In summary, R.S. disclosed a pervasive impairment of all the components into which retrograde memory is articulated, but with a relatively more severe deficit in the public semantic than in the personal episodic component. Furthermore, with the caution due to a relative (rather than absolute) performance dissociation, the pattern of impairment exhibited by R.S. appears to be coherent with the hypothesis that the left hemisphere (particularly in the anterior portions of the temporal lobe) plays a specific role in the storage of semantic memories. Indeed, the morpho-volumetric analysis of cerebral MR images revealed that R.S. had bilateral damage to anterior temporal regions, but with substantially more severe atrophic changes on the left side.

In conclusion, the two patients described in this study provide support for the view that the mesial and polar structures of the right and left temporal lobes play a distinct role in the domain of retrograde memory, the first being particularly involved in the storage and retrieval of personal episodic memories, the second mainly underlying the recollection of public semantic knowledge. Regarding personal semantic knowledge, our results seem to indicate less pronounced lateralization of the temporal structures involved, possibly because of the double component, autobiographical and semantic, supporting this kind of memory. Although caution is needed in generalizing the results deriving from only two patients, the presently reported evidence add to a

growing literature (mainly based on lesional data) on the asymmetric representation of episodic and semantic retrograde memories in the human brain.

Possible mechanisms underlying the relative dominance of the right and left temporal structures for the autobiographical episodic and public semantic retrograde memory, respectively, have been generally traced to the more basic specialization of the two cerebral hemispheres in the domains of language and visual imagery. In particular, according to Goldberg and Costa (1981) semantic memory is mainly mediated by the left hemisphere because of the intrinsically propositional nature of its contents, which makes the verbal code the most suited to memory storage. By contrast, the right hemisphere supports autobiographical episodic memory because of the close relationship between visual imagery (mainly mediated by the right hemisphere; Gardini et al., 2005) and the subjective experience of auto-noetic consciousness, which supports the ephory of previously experienced autobiographical events (Calabrese et al., 1996; Piolino et al., 2007). As a further, not necessarily alternative, mechanism underlying the functional relationship between the right hemisphere and episodic memory, it has also been suggested that the main role played by this hemisphere in mediating emotional experiences (Markowitsch et al., 2000) makes it more suited to storing and successively retrieving emotionally rich personal events rather than generally neutral semantic facts (Calabrese et al., 1996). As for our two patients, a relationship between semantic incompetence and poor linguistic abilities was evident in R.S. Indeed, in both spontaneous speech and formal testing, this patient had difficulty in the verbal processing of previously acquired information, which is likely the reason for her very poor performances on semantic tasks. Much less clear is whether A.S.'s poor episodic memory was due to deficient visual imagery abilities or emotional processing. Indeed, even though a sort of emotional flattening was noted in this patient throughout the period of our observation, no formal investigation was made of his visual imagery and emotional processing abilities and no attempt was made to separately assess memory for emotionally rich versus neutral autobiographical and public semantic memories.

In conclusion, the two cases presented here provide further support for the view of an opposite specialization of the temporal structures in the right and left hemispheres in the domain of autobiographical episodic and public semantic retrograde memory. Although a close relationship between impaired language abilities and loss of semantic competences was evident in R.S., we were unable to provide a clear account for A.S.'s prevalent loss of autobiographical episodic memory as a consequence of predominantly lateralized right side damage. Investigation of linguistic, visual imagery, and emotional processing abilities in patients with lateralized temporal damage, and evidence of a relative dissociation between distinct components of retrograde memory may provide relevant insights about this issue in the future.

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