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Preserved Visual Recognition Memory in an Amnesic Patient With Hippocampal Lesions

Emmanuel J. Barbeau,* Olivier Felician, Sven Joubert, Anna Sontheimer, Mathieu Ceccaldi, and Michel Poncet

ABSTRACT: **There is ongoing debate about whether performance on tests of recognition memory can remain preserved after hippocampal damage. In the present study, we report F.R.G., a patient who became severely amnesic following herpes simplex encephalitis. Although F.R.G. failed all tests involving recall and verbal recognition, she obtained normal performance on a wide number of tests evaluating visual recognition memory (14 of 18 different tests). Her performance was independent of various factors, such as test difficulty, duration of exposure to the stimuli, or delay separating encoding and recognition. F.R.G. also achieved normal performance on two tasks requiring that she associate pairs of visual stimuli. In addition, she demonstrated spared feeling of knowing, suggesting that her performance on recognition tests was explicit and likely to rely on familiarity. Brain imaging (MRI) revealed bilateral lesions of the hippocampus and lesions of the left parahippocampal gyrus, while the right parahippocampal gyrus remained relatively spared. The results of this study support the view that recognition memory can be preserved despite severe hippocampal damage and that familiarity is a distinct memory process that can be dissociated from recollection.** © 2005 Wiley-Liss, Inc.

KEY WORDS: **perirhinal cortex; visual recognition memory; single case study; herpes simplex encephalitis; declarative memory**

INTRODUCTION

Recognition memory is usually impaired in amnesic patients with extensive medial temporal lobes lesions (Scoville and Milner, 1957; Milner, 1972; Stefanacci et al., 2000). Recently, considerable attention has been focused on patients with lesions confined to the hippocampus. Some studies found that recognition memory was preserved in patients with such lesions, while performance on tests of recall was more severely impaired (Aggleton and Shaw, 1996; Vargha-Khadem et al., 1997; Mayes et al., 2002; Yonelinas et al., 2002). These results have been interpreted within the framework of a model that suggests that performance on recognition tests relies on two retrieval processes: recollection and familiarity (Aggleton and Brown, 1999; Yonelinas et al., 2002). With regard to neuroanatomy, recollection is assumed to depend on the hippocampus, while familiarity has been hypothesized to rely on anterior subhippocampal structures. According to this model, patients with lesions limited to the hippocampus may present with normal recognition memory because performance relies on intact processes of familiarity. According to the same model, performance on tests of recall and aspects of recognition based on recollection, i.e., mediated by the context in which a stimulus has previously been seen, should be impaired in patients with bilateral hippocampal damage.

Some of these studies, however, have been criticized on methodological grounds (Squire and Zola, 1998; Manns et al., 2003). Other studies have found impaired recognition in groups of subjects with lesions limited to the hippocampus (Reed and Squire, 1997; Manns et al., 2003). In the study by Mann et al., recollection and familiarity processes were assessed using a Remember/Know (R/K) paradigm. Both processes were found to be equally impaired in such patients. These investigators concluded that the hippocampus played a key role in recognition memory and that it was equally important for recollection and familiarity.

Therefore, whether recognition memory can remain intact after selective hippocampal damage, and whether recollection and familiarity are dissociable cognitive processes subserved by separate neuroanatomical regions, remains a matter of debate. To address this issue, we examined performance using an extensive battery of neuropsychological tests in an amnesic patient with medial temporal lobe lesions.

F.R.G., a right-handed woman, suffered from herpes simplex encephalitis at the age of 44. The disease damaged most medial temporal lobe (MTL) structures bilaterally, with the notable exception of right subhippocampal structures that were preserved. This left her densely amnesic up to the present evaluation, 4 years after the initial insult. Neuropsychological assessment revealed normal intelligence and severe anterograde amnesia. In the present study, her performance on recall and recognition tests in both the verbal and visual modalities was assessed. She was impaired in all domains of memory with the notable exception of visual recognition memory, which was largely preserved. In addition, other tests were complemented that

Service de Neurologie et de Neuropsychologie, AP-HM Timone, Laboratoire de Neurophysiologie et de Neuropsychologie, INSERM EMI-U 9926, Université Mediterranée, Marseille, France
Grant sponsor: Conseil Général des Bouches du Rhône.
*Correspondence to: Emmanuel Barbeau, Service de Neurologie et de Neuropsychologie, AP-HM Timone, 264, rue Saint-Pierre, 13385 Marseille Cedex 05, France. E-mail: emmanuel.barbeau@medecine.univ-mrs.fr
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enabled to directly assess recollection and familiarity as well as the capacity to match pairs of stimuli.

MATERIALS AND METHODS

Case Description

Patient F.R.G. had 14 years of education and was a high-level successful international saleswoman when she suffered from herpes simplex encephalitis in May 1998, at age 44. The disease left her deeply amnesic with no change in the severity of the impairment since then. She has been maintained on low doses of anti-convulsant therapy (sodium valproate, 500 mg/day) and has been seizure-free for the past 2 years. F.R.G. gave informed consent before experimentation.

Recognition Tests

To evaluate recognition memory, we used standard tests (e.g., subtests from the Wechsler memory Scale III, Wechsler, 2001), as well as specific tests developed in our laboratory. The latter tests consisted of either yes/no tasks in which targets presented one after the other had to be recognized among distracters, or of forced-choice tests (equivalent to delayed matching to sample tests) in which pairs of stimuli were presented, one target along with a distracter. Forced-choice tests are thought to be easier because subjects can benefit from both the previously encountered stimuli (familiarity detection) and from the novel distracter (novelty detection) to make their judgments. Words were selected from the Brulex database (Content et al., 1990) and were matched for frequency and length. Pictures were colorful cliparts representing single objects selected from standard databases. All stimuli were trial-unique, unless noted otherwise. Eprime v1.1 (Psychology Software Tools, 2001) was used to run computerized tests. Performance on the recognition tests was expressed in percentage: number of correct answers [hits + correctly rejected items]/total answers.

Random scores and a difficulty index, such as proposed by Holdstock et al. (2002), were calculated for each test. The difficulty index is a percentage score that indicates where a control subject's mean score stands between chance and a perfect score. The following equation was used:

$$\text{Difficulty} = (s - c)/(p - c),$$

where s is the control subject's mean score, c is chance performance and p is a perfect score. A high score indicates an easy test. For details of the various visual recognition memory tests, see Table 3.

Normative Data and Analysis

Six female control subjects matched for age (mean age: 49.8, SD = 4.4; approximate IQ using the Binois–Pichot vocabulary test; Binois and Pichot, 1959: 99.7, SD = 7.1) provided normative data for the memory tests developed in our laboratory. All subjects were fully informed of the nature of the study and written consent was obtained. Subjects were rewarded for their participation. Some tests were normalized with 20 or more control subjects matched in age (indicated in Table 3) to heighten the statistical power of the normative data.

For the purpose of statistical comparison, F.R.G.'s performance was converted to *Z*-scores (number of SDs above or below control subjects' mean). F.R.G.'s performance was considered impaired if it was >1.96 SDs below the control mean (type 1 error, $P = 0.05$, two-tailed, Holdstock et al., 2002). Because of the small samples, a nonparametric test (two-tailed Mann–Whitney U-test) was carried out to compare means using SPSS v10.0 (SPSS, 1999).

Brain Imaging

F.R.G.'s brain was imaged during the course of the evaluation (i.e., 4 years after the disease's onset) with a 1.5-T Magneton (Siemens, Erlangen). A T2 fluid-attenuated inversion recovery (FLAIR) sequence was acquired in the sagittal plane aligned on the axis of the hippocampus, using a standard head coil and tilted coronal gradient echo sequence (TR = 8,040 ms, TE = 113 ms, TI = 2,200 ms, FOV = 210 × 280, matrix = 308 × 512, slice thickness = 5 mm, slices gap = 1.5 mm).

RESULTS

F.R.G.'s intellectual efficiency was within normal range (WAIS-III IQ = 94; m = 100, SD = 15; Wechsler, 2000), as

TABLE 1.

F.R.G.'s Performance on Standard Tests of Delayed Recall

Test/description	*Z*-score
Test of verbal recall	
1 Auditory Verbal Learning Test (Rey, 1958)	−4.00[a]
2 Free and Cued Selective Reminding Test (Grober et al., 1988)	−4.89[a]
3 Logical memory II subtest (WMS-R) (Wechsler, 1991)	−3.66[a]
4 Verbal paired associates II subtest (WMS-III) (Wechsler, 2001)	−2.33[a]
Tests of visual recall	
5 Rey Osterreich complex figure (Rey, 1959)	−3.07[a]
6 Figure reproduction II subtest (WMS-R) (Wechsler, 1991)	−3.30[a]
7 Shapes subtest (Doors and People test) (Baddeley et al., 1994)	−2.88[a]
8 Family scenes II subtest (WMS-III) (Wechsler, 2001)	−3.00[a]

[a]Impaired.

well as working memory, executive functioning, visuoperceptive skills, and praxic abilities. A mild semantic agnosia was observed. In fact, she showed mild difficulties completing tasks that required to match visual or verbal semantic pairs (Howard and Patterson, 1992) or to identify objects from their silhouettes (Warrington and James, 1985). She was able to name 75 out of 80 line drawings of common objects (one item above cut-off score, Deloche and Hannequin, 1997). The relative preservation of her other cognitive skills contrasted sharply with her dramatically poor episodic memory. Her amnestic syndrome was severe: she forgot everything that had been said a few minutes before, and she could not recall anything that she had done 1 h earlier. It took her several months before she was able to remember the names of the examiners she was seeing twice a week. She had lost most of her autonomy, mainly because of spatial disorientation in new environments. For daily activities, she used a notepad where she wrote everything she had done or was planning to do. Her WMS-R delayed MQ was 57 (m = 100, SD = 15, Wechsler, 1991).

Assessment of Recall

Further assessment of her abilities to recall newly acquired information revealed a severe impairment on four standard tests of verbal recall and four standard tests of visual recall (Table 1). For instance, although F.R.G. was able to copy the Rey Ostereich figure perfectly (Rey, 1959), she scored only 6/36 in immediate recall and couldn't remember any single element after a 20-min delay. Similarly, in the verbal modality, she was unable to recall any of the 16 words she had learned after a 20-min delay. Performance remained invariably altered despite reinforced encoding through repetition (Baddeley et al., 1994; Rey, 1958), cued recall (Grober et al., 1988), or on the examiner's suggestion to use self-generated strategies.

Assessment of Verbal Recognition Memory

Verbal recognition memory was then assessed using three standard tests as well as three other tests developed in our laboratory. F.R.G. was severely impaired on all tests (Table 2). She consistently failed to recognize previously learned words and made numerous false alarms. Overall, verbal recognition memory was impaired regardless of the nature of the test (yes/no or forced-choice), type of stimuli (nouns of concrete objects, abstract words and pseudo-words), word length, delay between study and test (10 min or immediate), modality of presentation of the words (auditory or visual), and frequency of exposure to stimuli before recognition (up to five presentations).

Assessment of Visual Recognition Memory

F.R.G. was then tested on five standard tests of visual recognition memory. Surprisingly, she obtained normal scores on four of these tests. To carry out a more in-depth investigation of these results, she underwent an additional battery of 13 visual recognition tests developed in our laboratory (details and results in Table 3). Overall, F.R.G. obtained Z-scores equal to or above the mean on eight of the 18 visual recognition memory tests. She was below the mean but not significantly impaired on six of these tests. Finally, she was significantly impaired on only four of the tests.

TABLE 2.

F.R.G.'s Performance on Tests of Verbal Recognition Memory (1)- False alarms were not included (6 false alarms, Z-score = −7.93). (2)- False alarms were not included (7 false alarms, Z-score = −6.70). (4)- Test developed in our laboratory. 25 targets, 25 distracters, one minute interference task. (6)- Same test as 5. One-h delay. Trial unique distracters. Although F.R.G. obtained a seemingly better Z-score, she performed only four items above chance level (raw score = 28/48) and made 20 errors.

	Tests of verbal recognition	Z-score
1	Auditory Verbal Learning Test (Rey, 1958) — Recognition subtest	−10.50[a]
2	Free and Cued Selective Reminding Test (Grober et al., 1988) — Recognition subtest	−5.57[a]
3	Forced-choice words test (RMT) (Warrington, 1984)	−4.12[a]
4	Yes/No word test	−2.17[a]
5	Forced-choice word test immediate	−4.21[a]
6	Forced-choice word test delayed	−2.03[a]

[a]Impaired.

Her performance was not affected by the duration of stimulus presentation (test 15 of Table 3, free stimulus presentation delay during study and test: Z-scores = +0.17; test 16, limited to 800 ms: Z-scores = +2.08; test 17, limited to 400 ms: Z-scores = +0.14) or by the delay between study and test (tests 8 and 18, performed with a one-week delay: Z-scores = −0.33 and +2.33, respectively).

It could be argued that performance was preserved on some tests because they were easier than others. However, we did not find any statistical relationship between F.R.G.'s Z-scores and a difficulty index (Holdstock et al., 2002) that was computed for each test (Pearson correlation = −0.44, two-tailed P = 0.06). The correlation actually showed a tendency for an inverse relation.

F.R.G. was impaired on four tests of visual recognition memory, although her performance remained well above chance. All four tests consisted of items belonging to specific semantic categories such as animals, fruits, vegetables, and faces. In contrast, F.R.G. succeeded better than controls on all four tests that used abstract patterns for stimuli (mean Z-score = +1.18, SD = 1.19). This leads us to suggest that the nature of the stimuli, rather than the difficulty of the task, influenced F.R.G.'s performance. It is possible that F.R.G. presents with a mild agnosia for biological entities that could have interfered with her recognition. It is also worth mentioning that the control subjects' performance for biological categories is subject to very small standard deviations (e.g., only 2% in the

TABLE 3.

F.R.G.'s Performance on Tests of Visual Recognition Memory

	Test/description	Stimulus type	Paradigm type[a]	Presentation[b]	Repetition[c]	Delay[d]
1	Doors and People Test—Part A (Baddeley et al., 1994)	Doors	FC	Paper	1	Im
2	Doors and People Test—Part B (Baddely et al., 1994)	Doors	FC	Paper	1	Im
3	WMS-III face recognition subtest immediate (Wechsler, 2001)	Faces	Y/N	Paper	1	Im
4	Same test as 3, delayed	Faces	Y/N	Paper	2	25 min
5	RMT Recognition Memory Test (Warrington, 1984)	Faces	FC	Paper	1	Im
6	Delayed-Matching to Sample with trial-unique distracters task, 3 min (Barbeau et al., 2004)	32 objects; 16 abstract	FC	Paper	1	3 min
7	Same test as 6, delayed 60 min	32 objects; 16 abstract	FC	Paper	2	1 hr
8	Same test as 6, delayed 1 wk	32 objects; 16 abstract	FC	Paper	3	1 wk
9	Forced-choice test with 3 distracters per targets	32 objects; 16 abstract	FC	Comp.	1	10 min
10	Yes/No recognition test with 25 targets and 25 distracters	Animals	Y/N	Comp.	1	2 min
11	Yes/No recognition test with 25 targets and 25 distracters	Buildings	Y/N	Comp.	1	2 min
12	Yes/No recognition test with 25 targets and 25 distracters	Scenes	Y/N	Comp.	1	2 min
13	Yes/No recognition test with 25 targets and 25 distracters	Fruits and vegetables	Y/N	Comp.	1	2 min
14	Yes/No recognition test with 25 targets and 25 distracters	Tools	Y/N	Comp.	1	2 min
15	Yes/No recognition test with 15 targets and 30 distracters; free learning and recognition delay	Abstract pattern	Y/N	Comp.	1	1 min
16	Yes/No recognition test with 15 targets and 30 distracters; 800-ms learning and recognition delay	Abstract pattern	Y/N	Comp.	1	1 min
17	Yes/No recognition with 15 targets and 30 distracters; 400-ms learning and recognition delay	Abstract pattern	Y/N	Comp.	1	1 min
18	Forced-choice test with long delay between study and test	Abstract pattern	Y/N	Paper	1	1 wk

[a]Y/N, yes/no recognition memory task; FC, forced-choice recognition memory task.
[b]Paper or computerized.
[c]Number of times targets have been previously seen before test (due to the same test being used at different delays, always with trial-unique distracters).
[d]Delay between study and test; Im, immediate.
[e]Number of possible choices of stimuli per studied item.
[f]Number of control subjects.

Test choice[e]	Controls[f]	Difficulty[g]	List length[h]	F.R.G.'s performance (mean ± SD)	P/RS ratio[i]	*Z*-score
4	>=20	0.89	12	36.9%	3.67	−0.33
4	>=20	0.50	12	4.8%	1.67	−1.66
2	>=20	0.50	48	Scaled score: 6 (10 ± 3)	1.21	−1.33
2	>=20	0.46	48	Scaled score: 10 (10 ± 3)	1.46	0.00
2	>=20	0.77	50	2%	1.36	−2.85[j]
2	>=20	0.84	48	92% (99% ± 2%)	1.83	−3.50[j]
2	>=20	0.96	48	98% (99% ± 2%)	1.96	−0.50
2	>=20	0.92	48	96% (97% ± 3%)	1.92	−0.33
4	6	0.73	48	88% (80% ± 13%)	2.63	+0.62
2	6	0.81	50	76% (91% ± 5%)	1.52	−3.03[j]
2	6	0.57	50	72% (78% ± 5%)	1.44	−1.20
2	6	0.65	50	84% (83% ± 6%)	1.68	+0.23
2	6	0.86	50	78% (93% ± 2%)	1.56	−6.12[j]
2	6	0.77	50	92% (89% ± 5%)	1.76	+0.65
3	6	0.72	45	87% (86% ± 7%)	1.72	+0.17
3	6	0.57	45	91% (79% ± 6%)	1.82	+2.08
3	6	0.50	45	76% (75% ± 7%)	1.51	+0.14
2	6	0.31	48	78% (66% ± 5%)	1.54	+2.33

[g]Percentage score indicating at what level between chance and a perfect score the control subjects' mean score stands (Holdstock et al., 2002).
[h]Length of the study list.
[i]Performance to random score ratio (e.g., if a random score is 10 and the F.R.G. score is 16, P/RS ratio = 1.6. A P/RS ratio < 1 indicates that F.R.G. performs at random.
[j]Impaired.

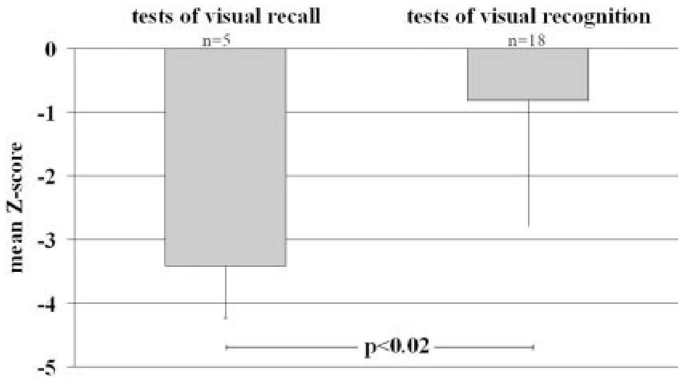

FIGURE 1. F.R.G.'s performance on tests of visual recall and visual recognition. A significant difference is observed ($P < 0.02$).

fruits and vegetables recognition memory test). Consequently, any deviation from the mean score results in a high *Z*-score. Nonetheless, the fact that she failed one of the face recognition tests is more surprising (test 5; Warrington, 1984), and leads us to wonder whether her performance here reflected a true difficulty in recognizing faces or if it was due to a temporary attentional gap during this particular test. The fact that F.R.G. obtained perfectly normal scores on another very similar test of face recognition (test 4, WMS-III face recognition subtest) seems to support the latter interpretation.

To evaluate whether there was a dissociation between F.R.G.'s recall and recognition, mean performance on the eight tests of recall was computed (mean *Z*-score = −3.39, SD = 0.79) and compared with mean performance on the 18 tests of visual recognition memory (mean *Z*-score = −0.81, SD = 2.06). A significant difference was observed ($P < 0.01$). In an attempt to explore further the validity of this dissociation within the visual modality, F.R.G. underwent a complementary test in which recall and recognition were assessed using the same stimuli (Yonelinas et al., 2002). She was asked to draw and remember abstract shapes (Signoret, 1991). After a 10-min delay, she was asked to recall as many of them as possible and later to recognize them among a series of distracters. There was a clear difference between her *Z*-score on the recall subtest (−4.87) and on the recognition subtest (0.13). Furthermore, there was a significant difference between F.R.G.'s performance on the five tests of visual recall (Table 1 and this last test, mean *Z*-score = −3.42, SD = 0.82) and the 18 tests of visual recognition ($P < 0.02$). These results argue in favor of a dissociation between recall and recognition in the visual modality (Fig. 1).

Within the domain of recognition memory, a second dissociation was evidenced. F.R.G.'s performance on the six verbal recognition memory tests (mean *Z*-score of −4.77, SD = 3.11) was significantly poorer than her performance on the six most difficult visual recognition memory tests (*Z*-score = −0.29, SD = 1.48, $P < 0.01$), despite the fact that the verbal tests tended to be easier than the visual tests (mean verbal difficulty index: 0.67, SD = 0.19, visual: 0.47, SD = 0.09, $P = 0.053$).

Remembering, Knowing, and Feeling of Knowing

Yonelinas (2002) reviewed different methods that can be used to measure recollection and familiarity processes. Two general approaches were identified: task-dissociations methods (e.g., recall/recognition comparison, such as used in the previous section, response speed method), or process-estimation methods (e.g., R/K paradigm, ROC procedure). Demonstrating a dissociation between recollection and familiarity using both a process-estimation approach and a task-dissociation approach would thus considerably strengthen the claim of a dissociation between these processes in F.R.G.

To test this, F.R.G. thus underwent an R/K paradigm using pictures. Detailed instructions were given to F.R.G. and control subjects, similar to those used by Wheeler and Stuss (2003). Each subject was presented with a piece of paper on which the definitions of R and K responses were printed. During the experiment, F.R.G. told the experimenter that she remembered all the items she had correctly recognized (R responses). For each item, when she was asked to explain why she had made an R judgment, she typically answered that she remembered seeing all the details present on each picture quite vividly. Yet, contrary to controls, she was never able to provide any contextual information indicating that she actually remembered the context in which she had learned these pictures (e.g., what she was thinking of during the encoding procedure, from which encoding list target pictures originated). When provided with additional explanations and using basic examples, it became apparent that she had difficulties understanding the notion of "context," and that this explained why she had chosen so many R responses.

Under these circumstances, it was important to evaluate F.R.G.'s own awareness of her performance, considering that her answers might have been based on an automatic, implicit, process (e.g., a judgment based on preference) without a conscious, explicit, feeling of knowing (Mandler et al., 1987). She was asked in a separate test to judge whether she felt certain, rather certain or uncertain of her responses (whether stimuli were correctly recognized or correctly rejected). Results indicate that she felt certain or rather certain 90% of the time, a rate similar to that of control subjects (mean = 94%, SD = 7%). Taken together, these results suggest that F.R.G. has a true sense of knowing (K) such as indicated by her ability to evaluate her awareness of her own performance, but that her ability to remember (R) is, in fact, impaired. These results are is thus in keeping with the dissociation observed in F.R.G. between recognition and recall.

Paired Associates Tests

Some studies have suggested a link between preserved recognition memory and preserved stimulus–stimulus association

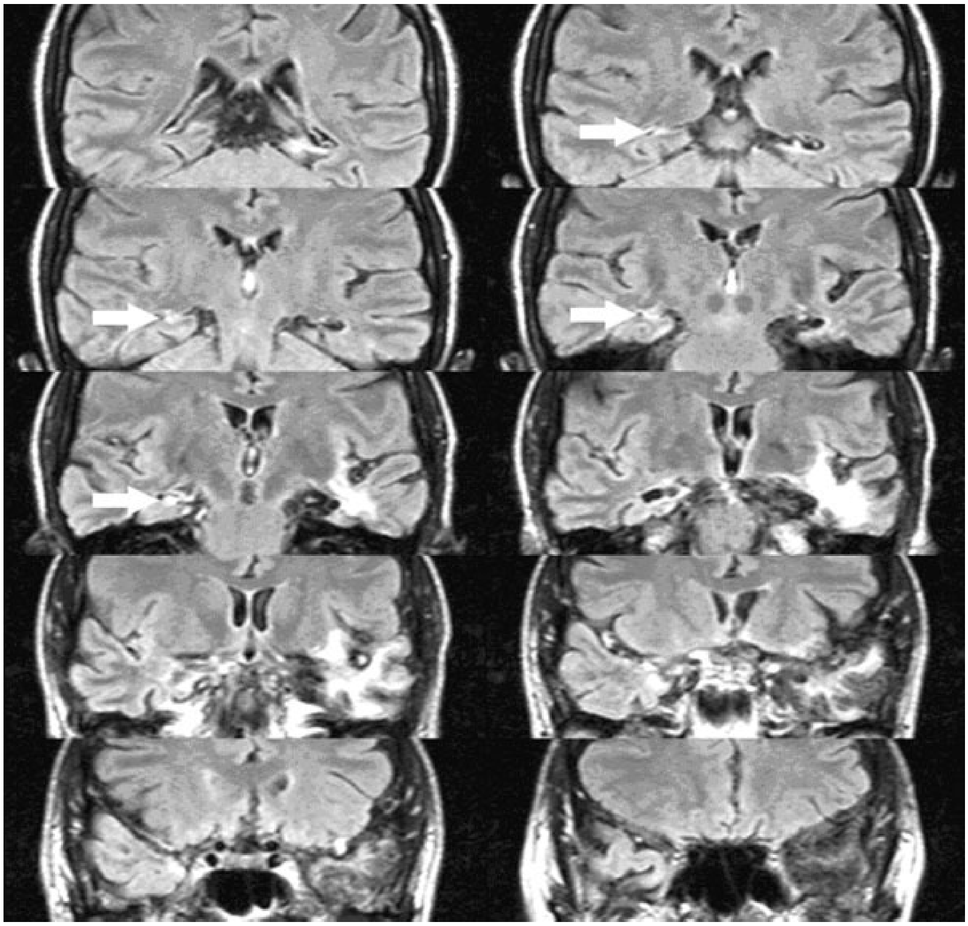

FIGURE 2. FLAIR images of F.R.G.'s medial temporal lobes. Sections from posterior (top) to anterior (bottom) temporal lobes. White arrows show hypersignals in the right posterior hippocampus. Right is left (radiographic convention).

within a sensory modality (Eichenbaum et al., 1996; Vargha-Khadem et al., 1997; Mayes et al., 2001). We thus developed a task in which 12 pairs of abstract patterns had to be learned. Following a 2-min interfering task, one stimulus was shown along with two others, one of them belonging to the pair and the other belonging to another learned pair. Subjects had to choose the correct member of the pair. Trials were repeated until 100% correct responses were obtained. F.R.G. performed as well as control subjects, reaching criterion by trial 7 ($P > 0.5$ for all trials). This preserved ability to learn pairs of visual stimuli was confirmed by F.R.G.'s performance on a standard test, the WMS-R delayed visual paired associates subtest (Z-score $= -0.36$). Interestingly, this was the only delayed subtest of the WMS-R scale in which she achieved normal performance.

In addition to investigating F.R.G.'s abilities on visual–visual stimulus association tasks, she underwent a series of verbal–verbal, visual–verbal, or verbal–visual paired associates tests using similar arrangements as the one just described or using standard tests such as the WMS-III verbal paired associate subtest (in the recognition part). She was consistently impaired on all these tests, even after 10 trials. She failed every trial, and her best overall performance was -5.2 SDs below controls.

Brain Imaging

High-resolution magnetic resonance imaging (MRI) revealed intact frontal, parietal, and occipital lobes, but extensive lesions of medial temporal lobes, consistent with the pattern of lesions usually observed in herpes simplex encephalitis (Stefanacci et al., 2000; Kopelman, 2002).

As can be seen in Figure 2, the left hippocampus suffered complete destruction, from its anterior to most posterior parts. The left parahippocampal gyrus was also entirely damaged, with the exception of minimal residual tissue in the most posterior portion. On the right side, the hippocampal head was completely damaged. Large signal abnormalities are observed in the posterior hippocampal sections (white arrows; Fig. 2). In contrast, the right parahippocampal gyrus was far better preserved, with small hypersignals found only in the most anterior part.

Presumably because of the nature of the disease, the quality of the contrast between gray and white matter was not high enough to carry out reliable brain volumetry of medial temporal lobe structures in F.R.G. In addition, brain volumetry would have had to take into account signal abnormalities. The value of such signals is controversial, as there is evidence to suggest that structures with hyperintensities are dysfunctional (Marusic et al., 2002; Wen et al., 2004).

DISCUSSION

The present study shows that some amnesic patients can have normal recognition despite impaired recall. F.R.G. was impaired on all tests involving recall and verbal recognition, but achieved normal performance on most tests of visual recognition memory. Her visual recognition memory was consistently spared, irrespective of the duration of exposure to the stimuli and the delay between study and test. In addition, her level of performance was independent of test difficulty. Preservation was not limited to recognition of single items but also included visual paired associates.

To our knowledge, such a dissociation in performance between tests of recall and recognition has only been clearly established in four patients, three adolescents who sustained hippocampal lesions during early childhood (Vargha-Khadem et al., 1997) and in patient Y.R., who suffered from hippocampal lesions at an adult age (Mayes et al., 2002). The report of F.R.G., who shows a similar pattern of dissociation, thus provides additional evidence in favor of these studies.

It has been proposed that recognition memory relies on two independent retrieval processes: a familiarity and a recollection process (Yonelinas, 2002). Here, F.R.G.'s recollection process, assessed through tests of recall, was severely impaired in both the verbal and visual modalities. To substantiate further the claim that F.R.G. relied on familiarity during visual recognition memory tasks, she was submitted to a R/K paradigm. Results indicate that she had difficulties understanding the procedure despite repeated attempts to explain the task to her. Such behavior in a deeply amnesic patient has already been detailed in the case study of Jon (Baddeley et al., 2001). Jon also made R judgments more often than control subjects, because when he looked at a word during a recognition task, he had an immediate and a clear mental image of the word printed on the stimulus card, which would result in him selecting an R answer. Such a behavior was interpreted as being related to perceptual fluency, which is associated with implicit rather than explicit memory. The authors suggested that the fact that Jon could not master the R/K rule was consistent with the notion that Jon's recollection process was impaired. Here, F.R.G.'s behavior was very similar to Jon's, in that her R answers appeared to rely more strongly on a sense of perceptual familiarity of the stimuli rather than on the actual reminiscence of the episodic context. F.R.G.'s intellectual efficiency was within normal range and she otherwise never showed any difficulties in understanding instructions during the rest of the neuropsychological assessment. In our view, Baddeley and collaborators' interpretation, which suggests a true impairment of recollection in Jon, could also apply to F.R.G.'s behavior. In addition, F.R.G. showed preserved feeling of knowing for the stimuli that were correctly recognized or rejected. F.R.G. thus seemed to present with an explicit ability to judge her performance. In conclusion, when considering her profound amnesia, results of this study suggest that familiarity may largely support her preserved performance in visual recognition memory tasks.

In the monkey, lesions of a specific subhippocampal structure, the perirhinal cortex, severely impair recognition memory (Meunier et al., 1993; Murray and Richmond, 2001), to a greater extent than hippocampal lesions (Squire and Zola, 1996). This observation brought some investigators to consider the perirhinal cortex as having a key role in recognition memory (Meunier et al., 1993) and on familiarity based-recognition (Aggleton and Brown, 1999).

Within the context of the current study, it is a possibility that the perirhinal cortex played an effective role in F.R.G.'s relatively intact visual recognition memory. In addition to achieving normal performance on most tasks of visual recognition memory, F.R.G. also demonstrated the ability to learn new associations between pairs of visual stimuli. Similar findings have been evidenced in other patients with lesions limited to the hippocampus (Vargha-Khadem et al., 1997; Mayes et al., 2001). Moreover, lesions of anterior subhippocampal structures in the rat (Eichenbaum et al., 1996) and of the perirhinal cortex in the monkey (Higuchi and Miyashita, 1996; Buckley and Gaffan, 1998) have been shown to impair performance on such tasks. Taken as a whole, these data collected both in humans and in animals suggest that this area plays a critical role in paired associate visual tasks. It is noteworthy to mention that F.R.G. failed all tasks that required associating stimuli from different modalities (visual–verbal or verbal–visual). This finding is consistent with data obtained in other patients with lesions limited to the hippocampus, who were found consistently impaired in visuospatial and face–voice association tasks (Vargha-Khadem et al., 1997), as well as in recognition tasks requiring to associate different kinds of information (Mayes et al., 2004).

In summary, F.R.G.'s ability to perform well on tests of visual recognition memory and to learn new visual–visual associations is consistent with the fact that her perirhinal cortex was largely functional. In contrast, F.R.G.'s inability to recall verbal and visual information as well as her impaired performance to cross-modal tasks suggest that hippocampi were largely dysfunctional. These hypotheses derived from experimental findings are largely supported by neuroimaging data, which evidenced widespread lesions to the hippocampii and relative preservation of the right perirhinal cortex.

Neural Correlates of Visual Recognition Memory in the Human

The major difference between F.R.G. and previously reported patients presenting a pattern of dissociation between performance on tests of recognition and recall concerns the extent of hippocampal injury and the nature of the disease. The adolescents described by Vargua-Khadem et al. (1997) and Y.R. had approximately 50% reduction of hippocampal volume when compared with controls, which leaves open the possibility that the remaining tissue may have been sufficient to support intact recognition. For example, a functional MRI study performed with Jon, one of the three adolescents, revealed an activation of both hippocampii during memory tasks (although the pattern of activation differed from that of controls, Maguire et al., 2001), thus highlighting the functional role of residual tissue in the hippocampus. Y.R. and the three adolescents suffered from probable anoxia, ischemic injury or epilepsy. In contrast, F.R.G. suffered from herpes simplex encephalitis, a disease that severely damages brain tissues, often resulting in necrosis and tissue loss. Both hippocampii were severely damaged. The entire left hippocampus and the head of the right hippocampus were completely destroyed. Widespread hypersignals were also observed in the right posterior hippocampus, thus strongly suggesting a functional deficit in this area. The right posterior hippocampus has been thought to play a special role in spatial cognition (Maguire et al., 2000, 2003). The fact that F.R.G. presented with severe spatial disorientation in new environments lends further strength to the idea that this structure is dysfunctional in our patient. In summary, the fact that F.R.G. suffered from severe bilateral hippocampal lesions raises the possibility that certain processes underlying recognition memory in the human (i.e., familiarity) may not rely on this structure at all. Similar findings have been reported in the monkey (Murray and Mishkin, 1998), although the issue remains controversial (Zola et al., 2000). Still, as there remains some uncertainty about the extent of damage in F.R.G.'s right posterior hippocampus, this study does not definitely rule out the absence of a role of the hippocampus in recognition memory.

F.R.G.'s visual memory was preserved, but she was impaired in the verbal domain. Her right parahippocampal gyrus was partially preserved, while the left was fully damaged. In line with previous studies (Kimura, 1963; Milner, 1968), this dissociation between verbal and visual material further illustrates the respective roles of left and right MTL in the human and suggests that the right parahippocampal gyrus may be preferentially involved in visual recognition.

Recognition Memory and the Hippocampus

Some amnesic patients with lesions restricted to the hippocampii have been shown to be impaired on both recall and recognition (Reed and Squire, 1997; Manns et al., 2003). These findings contrast with the results reported in this study. A counterintuitive way to reconcile these findings has been suggested by authors working on the monkey (Murray and Mishkin, 1998; Baxter and Murray, 2001), who found an inverse correlation between the extent of hippocampal damage and its effect on recognition tasks: the smaller the lesion, the greater the impairment of recognition memory. Similar results have been reported in rats, in which hippocampal lesions actually improved performance on an odor–odor paired associate task (Eichenbaum et al., 1996). A putative explanation for this phenomenon is that the hippocampus underlies a competing memory process (e.g., recognition based on recollection rather than on familiarity, the latter depending on sub-hippocampal structures). According to this view, when the hippocampus is damaged, irrelevant competing information would impair overall memory performance whereas larger lesions would prevent competing information from altering performance. For instance, the hippocampal volumes of six amnesic patients (Manns et al., 2003) reported to be impaired on recognition memory tasks following a small hippocampal lesion (H−R− group) had a volume reduction of 29%, 45%, 40%, 10%, 28%, and 0% (mean: about 25%). In contrast, patients with hippocampal lesions who had preserved recognition (H−R+ group) had a volume reduction of 39%, 50%, 57% (Vargha-Khadem et al., 1997; Baddeley et al., 2001) and 45% (Mayes et al., 2002) (mean: about 48%). F.R.G.'s left hippocampal volume was most likely reduced by 100% and the right hippocampus was also severely damaged. Overall, therefore, there is a trend for the H−R− group to have less hippocampal damage than the H−R+ group, although the difference in volumes of the two groups is statistically nonsignificant because of the small number of subjects. The possibility that small hippocampal lesions may impede normal recognition, while larger lesions release a direct recognition memory system deserves some consideration.

In conclusion, our results demonstrate that performance on recognition tests can be largely preserved in some deeply amnesic patients. Such data are important for our conception of current models of memory and for our understanding of the neural correlates of such processes. Finally, these findings may also contribute to the development of specific cognitive rehabilitation strategies designed for amnesic patients with preserved recognition memory.

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