Memory Lost and Regained Following Bilateral Hippocampal Damage

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Abstract

■ We present a longitudinal neuropsychological study (31 examinations over a period of 18 months) of patient DF. DF demonstrated bilateral atrophy of the hippocampal formation and globus pallidus resulting from carbon monoxide poisoning. Eighteen months after the event, the volume of the hippocampal formation was reduced by 42% on the left side and 28% on the right. The patient initially presented with a severe global amnesia. Then, he showed a gradual, yet selective recovery of episodic memory function. Verbal free recall and spatial memory performance remained reduced, whereas immediate word recall and recognition memory, as well as picture learning and memory, improved to levels at the lower range of normal performance. Interestingly, nonspatial associative learning was never much impaired and recovered completely by the end of testing. These data are taken as evidence that the human hippocampal formation does not equally support different forms of episodic memory. ■

INTRODUCTION

The role of the hippocampal formation in human memory has been evaluated in several neuropsychological studies of patients with selective hippocampal damage (e.g., Kartsounis, Rudge, & Stevens, 1995; Rempel-Clower, Zola, Squire, & Amaral, 1996; Zola-Morgan, Squire, & Amaral, 1986). These studies demonstrated that (1) damage limited to the hippocampal formation is sufficient to produce anterograde memory impairment, (2) bilateral damage to field CA1 alone may cause a moderately severe memory impairment, (3) more extensive damage to the hippocampal formation and adjacent medial temporal lobe structures may produce a greater loss of anterograde memory functions, and (4) extensive and temporally graded retrograde amnesia can be the consequence of damage involving all CA fields, dentate gyrus, subiculum, and entorhinal cortex. These findings fostered the view that the hippocampal formation is crucial for encoding and consolidating new information into declarative memory (Alvarez & Squire, 1994; Squire & Alvarez, 1995). Other lesion studies (Henke & Wieser, 1996; Kroll, Knight, Metcalfe, Wolf, & Tulving, 1996; Vargha-Khadem et al., 1997), functional imaging studies in healthy subjects (e.g., Dolan & Fletcher, 1997; Gabrieli, Brewer, Desmond, & Glover, 1997; Henke, Buck, Weber, & Wieser, 1997; Henke, Weber, Kneifel, Wieser, & Buck, 1999; Maguire, Frackowiak, & Frith, 1996; Nyberg et al., 1996; Rugg, Fletcher, Frith, Frackowiak, & Dolan, 1997; Stern et al. 1996; Tulving, Markowitsch, Craik, Habib, & Houle, 1996; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994), animal ablation studies (e.g., Eichenbaum, Otto, & Cohen, 1994; Murray, 1996), and electrophysiological studies (e.g., O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978) questioned the notion that the hippocampal formation is equally important for all kinds of declarative memory functions. Instead, these findings point to one or several specific subfunctions of the hippocampal

formation in declarative memory. There is evidence that the human hippocampal formation subserves episodic memory to a greater extent than semantic memory (e.g., Vargha-Khadem et al., 1997), that the human hippocampal formation is particularly involved in learning spatial information (Bohbot et al., 1998; Maguire et al., 1996, 1998; Maguire, Frackowiak, & Frith, 1997), in novelty detection (e.g., Tulving et al., 1994, 1996), and in binding components of scenes in memory (Henke et al., 1997, 1999; Kroll et al., 1996).

If the hippocampal formation demonstrates this specialization within declarative memory for either of these mentioned subfunctions, one would expect a person who sustains sudden bilateral hippocampal damage to exhibit a distinctive pattern of episodic memory loss. The functions that depend most on the hippocampal formation should recover least. This was the logic of the present longitudinal study of patient DF.

DF became severely amnesic subsequent to carbon monoxide (CO) poisoning, which damaged his hippocampal formation and globus pallidus on both sides. We repeatedly assessed a wide range of memory functions over his recovery period of 1.5 years to map the pattern of recovery, if any, of memory functions. At the end of 1 year following the incident, high-resolution magnetic resonance imaging (MRI) measured the final volumes of DF's hippocampal formation, his parahippocampal gyri, temporal lobes, and mamillary nuclei. The volumes of these structures were compared to those of matched controls. The anatomical study confirmed the selectiveness of DF's hippocampal damage, and the repeated assessments revealed substantial differences in the recovery of subfunctions of episodic memory. DF recovered sufficiently to be retrained and secure full-time employment.

RESULTS

At the first (bedside) neuropsychological examination, 11 days after carbon monoxide poisoning, DF was alert, understood all instructions, responded adequately, but initiated no spontaneous activity. During the subsequent examinations at the home of his parents, he was very cooperative but still lacked initiative. It was not until 1.5 years after the incident that he had regained drive and interest.

DF's full-scale Wechsler Adult Intelligence Scale-Revised (WAIS-R) score assessed 1 month after the event was 88 (verbal: 93, performance: 84) and his Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) score assessed 2 months after the event was less than 50, resulting in a WAIS-WMS difference of more than 38 points. One year after the event, his WMS-R score improved to 71, leading to a WAIS-WMS difference of 17 points. This 17-point differential is near threshold (15 points) for considering that a patient has a significant memory impairment.

Anterograde Memory

Episodic Memory

Figures 1 to 6 illustrate DF's performance on tests of episodic memory.

Months 1 to 3. DF's performance in most tests of episodic memory was below the lower 10% of the control data. He performed well, however, on some verbal and nonverbal conjunction and paired-associate learning tests, particularly when these required recognition only. With cued recall of associates, his performance was still low.

Months 4 to 6. DF's performance was still below the 10% cutoff in many tests, but he transcended the cutoff again in some associative learning and conjunction tests, as well as in one picture recognition test and the free recall of the movies (i.e., the free recall of color, shape, sequence of scenes, and actors), and in some movie recognition tests, namely, recognition of settings, actor-setting associations, recognition of written movie endings, and recognition of new movie endings. DF's cued recall performance on these same dimensions, however, was below 10%. We interpret these findings as indicating that he could not profit from cueing as much as the control group.

Months 10 to 15. DF's performance was, with one exception, still under the 10% cutoff in all spatial memory tests as well as in the single-word learning and memory tests. Notably, even recognition of single words had not improved at this point. DF's performance in the single-figures learning and memory tests had improved. The nonverbal associative learning and conjunction test performance was normal, even for the delayed cued recall of the WMS-R paired-associates test. The verbal associative learning and conjunction test performance were also normal, but the cued recalls in the WMS-R paired-associates test still ranked at or under the 10% limit. DF's free recall of movie information remained unchanged. His movie recognition scores had further improved for actors and new movie endings. The cued movie recall had improved as well, namely, for color information and actors' appearance.

Month 18. DF continued to recover. Although spatial memory (with one exception) and single-word free recall still suffered severe impairment, single-figure learning, recognition, and recall had markedly improved. The exception was his good performance in the Maze Test at learning. The delayed recall of the learned path, however, remained very poor. The movie tests and several associative learning and conjunction tests were not repeated on this occasion.

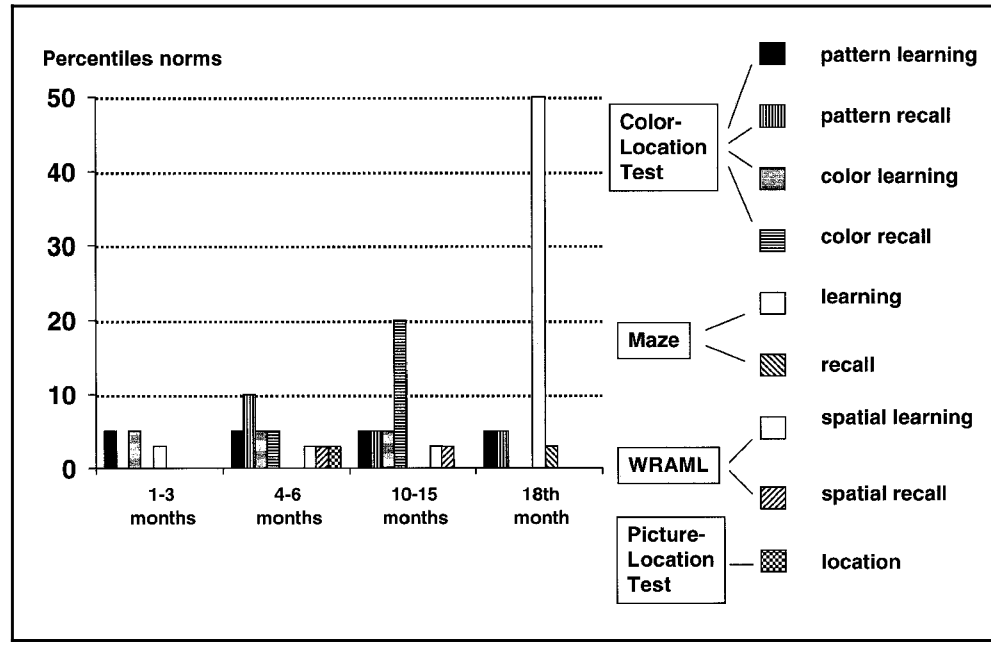

Figure 1. Spatial memory tests. DF's performance in the Color-Location Test at pattern learning with gray squares (pattern learning), pattern recall, at learning the location of colors (color learning) and at color recall, at Maze learning and recall, at WRAML spatial learning and spatial recall (Sheslow & Adams, 1990; visual learning 1 and 2), and in the Picture-Location Test at the recall of picture location (location). DF's performance is indicated in percentile ranks of the respective control group. Delayed recalls are displayed in pattern columns and immediate recalls in gray scale columns. DF's performance is indicated for four different time periods: 1 to 3 months, 4 to 6 months, 10 to 15 months, and the eighteenth month after the event.

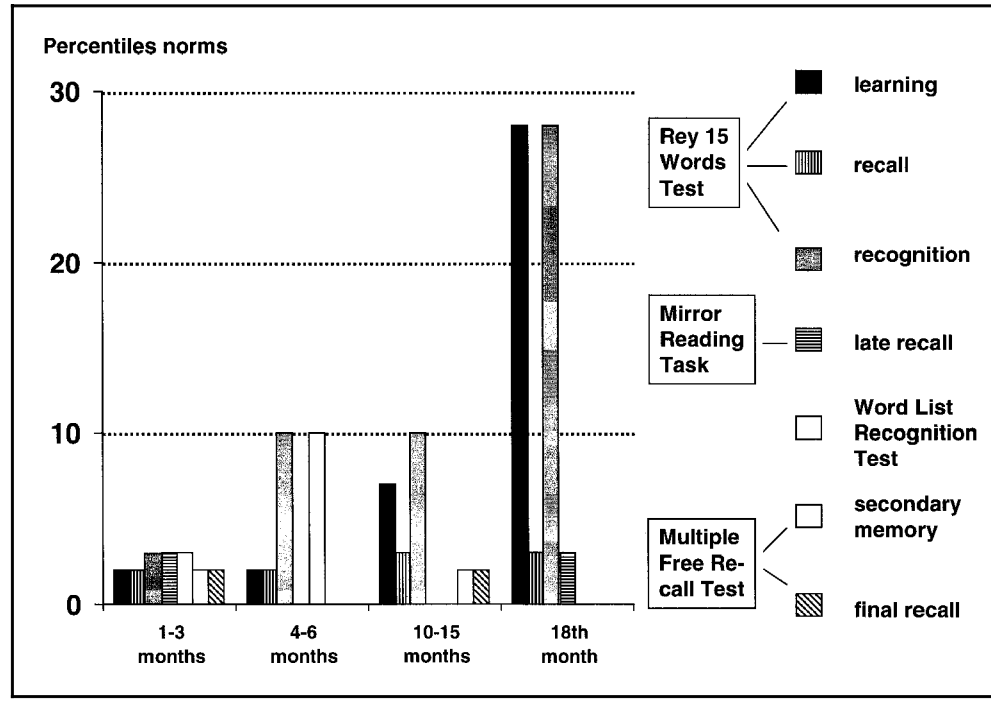

Figure 2. Memory for single words. DF's performance in the Rey 15 Words Test (Rey, 1958; auditory-verbal learning test) at the subscales learning (learning over five runs, after each run immediate recall), late recall (recall), and recognition, in the late recall of the Mirror Reading Task, in the Word List Recognition Test, and in the Multiple Free Recall Test at the subscales secondary memory and final word recall (final recall). DF's performance is indicated in percentile ranks of the respective control group. Delayed recalls are displayed in pattern columns, immediate recalls, and recognition, in gray-scale columns. Performance is indicated for four different time periods: 1 to 3 months, 4 to 6 months, 10 to 15 months, and the eighteenth month after the event.

Short-Term Memory

Short-term memory (STM) was assessed during the first 3 months after the event. Digit span and Corsi block performance (both backward and forward) were between the fiftieth and eightieth percentiles of age-matched controls. Short-term memory for words (Multiple Free Recall Test) was at the eightieth percentile of the control group.

Procedural and Implicit Memory

Figure 7 shows DF's performance in tests of procedural and implicit memory. These tests were administered during the first 3 months after the event (i.e., at a time when performance was unconfounded with explicit memory). DF's performance in all tests ranged between the twenty-fifth and the fifty-fifth percentiles of the norm data. DF's reading speed in the Mirror Reading Task was very high

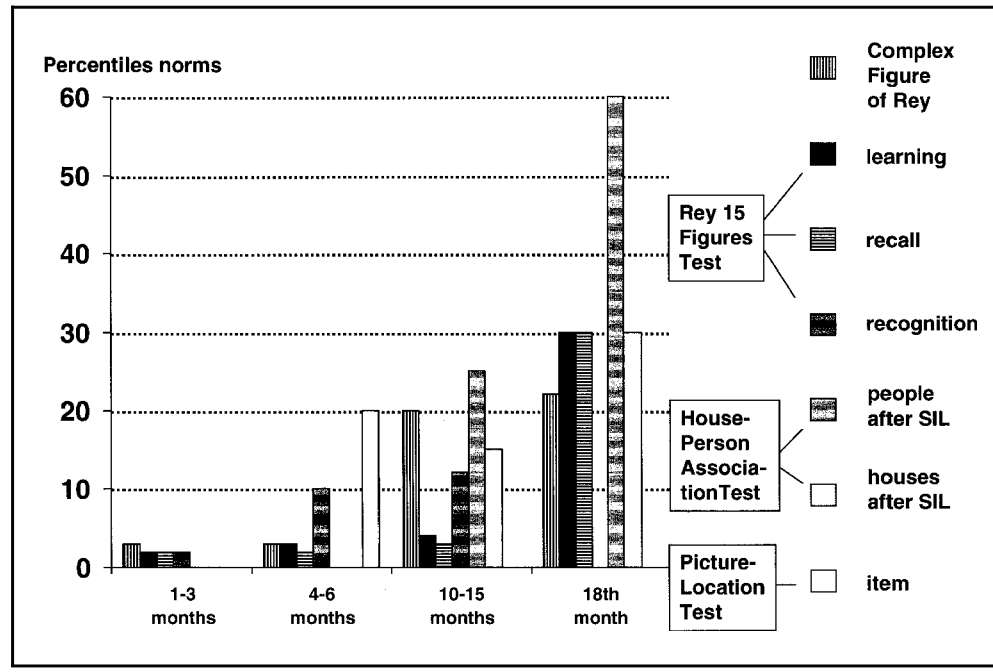

Figure 3. Memory for single figures. DF's performance in recalling the Complex Figure of Rey (Rey, 1959), in the Rey 15 Figures Test (Rey, 1958; visual learning test) at the subscales learning (learning over five runs, after each run immediate recall), late recall (recall), and recognition, in the House-Person Association Test at recognizing individuals after encoding them with the single-item learning (SIL) instruction (people after SIL) and at recognizing houses after encoding them with the single-item learning instruction (houses after SIL), and in the Picture-Location Test at recognizing the items (item). DF's performance is indicated in percentile ranks of the respective control group. Delayed recalls are displayed in pattern columns, and immediate recalls and recognition, in gray scale columns. Performance is indicated for four different time periods: 1 to 3 months, 4 to 6 months, 10 to 15 months, and the eighteenth month after the event.

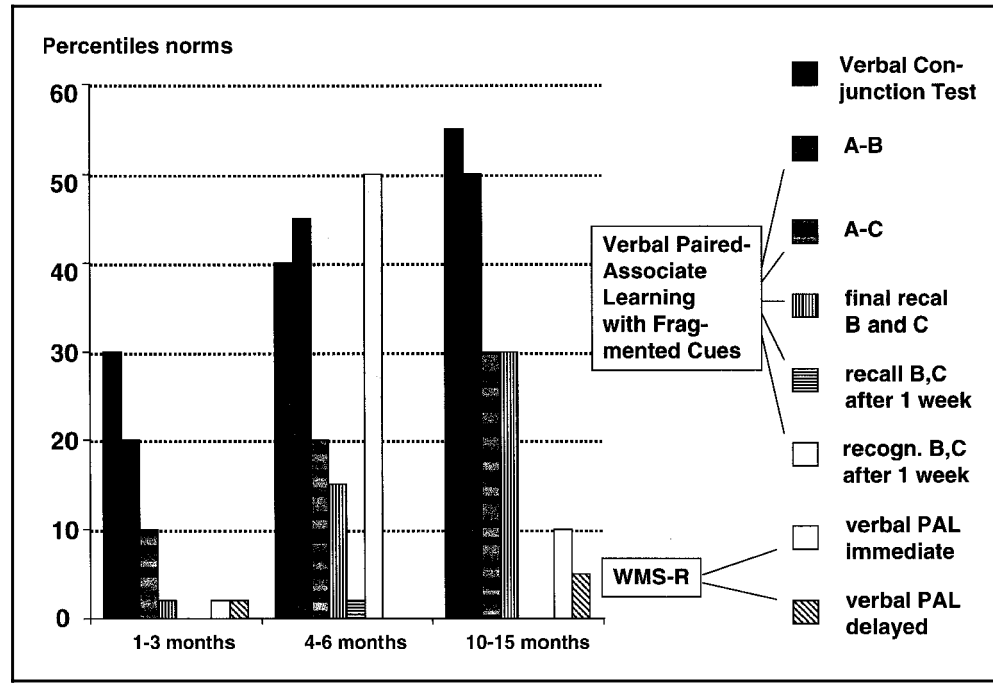

Figure 4. Verbal paired-associate learning and conjunction tests. DF's performance in the Verbal Conjunction Test, in the Verbal Paired-Associate Learning with Fragmented Cues Test at recalling the A-B associations (A-B), at recalling the A-C associations (A-C), at the delayed recall of both the B's and C's to each A (final recall B and C), at recalling B's and C's to each A after 1 week (recall B,C after 1 week), and recognizing the B's and C's after 1 week (recognize B,C after 1 week), in the Wechsler Memory Scale-Revised (WMS-R, Wechsler, 1987) verbal paired-associate learning test at immediate recall (verbal PAL immediate) and at delayed recall (verbal PAL delayed). DF's performance is indicated in percentile ranks of the respective control group. Delayed cued recalls are displayed in pattern columns, immediate cued recalls, and recognition in gray scale columns. Performance is indicated for three different time periods: 1 to 3 months, 4 to 6 months, and 10 to 15 months after the event.

on the first run, but it got even better on the second run. Similarly, his bimanual coordination in the Motor Learning Task was good initially and improved further. DF exhibited normal facilitation in tests of visual priming (Word Fragment Completion 6 and 30, Gollin Fragmented Pictures Test, Within-Modal Priming Test) and in Crossmodal Priming (auditory to visual). Norms for the Gollin Fragmented Pictures Test are based on the performance of a group of amnesic patients with various etiologies (unpublished data).

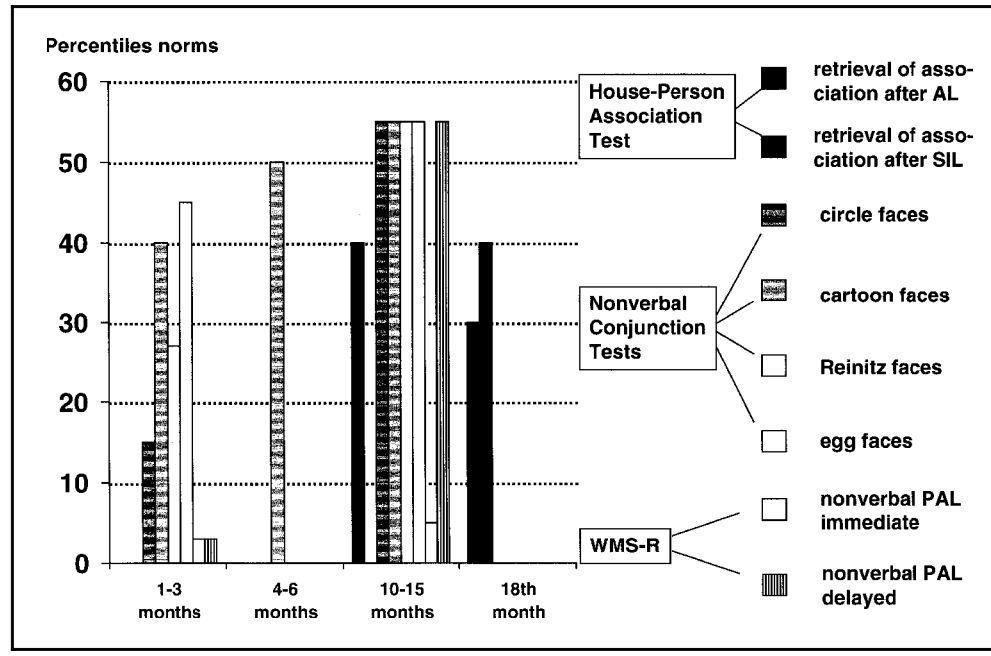

Figure 5. Nonverbal paired-associate learning and conjunction tests. DF's performance in the House-Person Association Test at retrieving associations after establishing them with the associative learning (AL) strategy and at retrieving associations after learning with the single-item learning (SIL) strategy, in the recognition part of the Nonverbal Conjunction Tests with circle faces, cartoon faces, Reinitz faces, and egg faces and in the Wechsler Memory Scale-Revised (WMS-R, Wechsler, 1987) nonverbal paired-associate learning test at immediate recall (nonverbal PAL immediate) and at delayed recall (nonverbal PAL delayed). DF's performance is indicated in percentile ranks of the respective control group. Delayed cued recalls are displayed in pattern columns, and immediate cued recalls and recognition, in gray scale columns. Performance is indicated for four different time periods: 1 to 3 months, 4 to 6 months, 10 to 15 months, and the eighteenth month after the event.

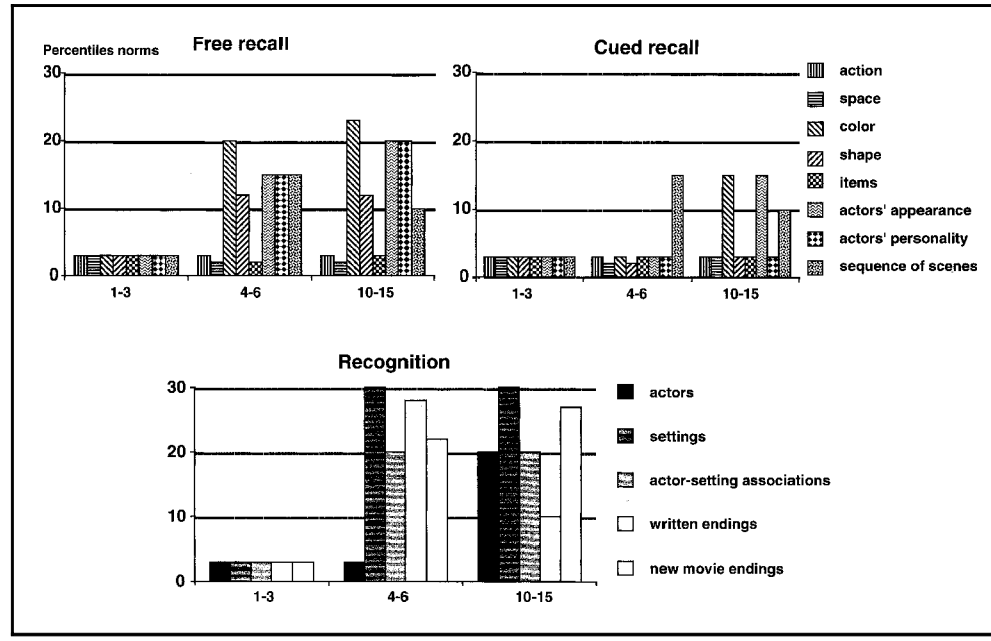

Figure 6. Movie tests. The top two graphs show DF's free and cued recalls of the three movies organized into the categories "action," "space," "color," "shape," "items" (e.g., furniture, tools), "actors' appearance," "actors' personality," and "sequence of scenes". The bottom graph shows DF's recognition organized into the categories "actors," "settings," "actor-setting associations," "written endings," and "new movie endings." DF's performance is indicated in percentile ranks of the control group. Recalls are displayed in pattern columns, and recognition, in gray scale columns. Performance is indicated for three different time periods: 1 to 3 months, 4 to 6 months, and 10 to 15 months after the event.

Retrograde Memory

Semantic Memory

DF's knowledge of animals, plants, tools, American cars, rock music, past and recent famous faces, famous names, and geography was examined using tests that we designed and others (e.g., Test des semantischen Altgedächtnisses, provided by K. Schmidtke, see Markowitsch et al., 1993) during the first three months after the incident. DF's knowledge in these categories was adequate with respect to his educational background.

Episodic Memory

DF's withdrawn lifestyle and his limited interest in public affairs made it difficult for us to find adequate formal tests to assess his retrograde memory. He scored

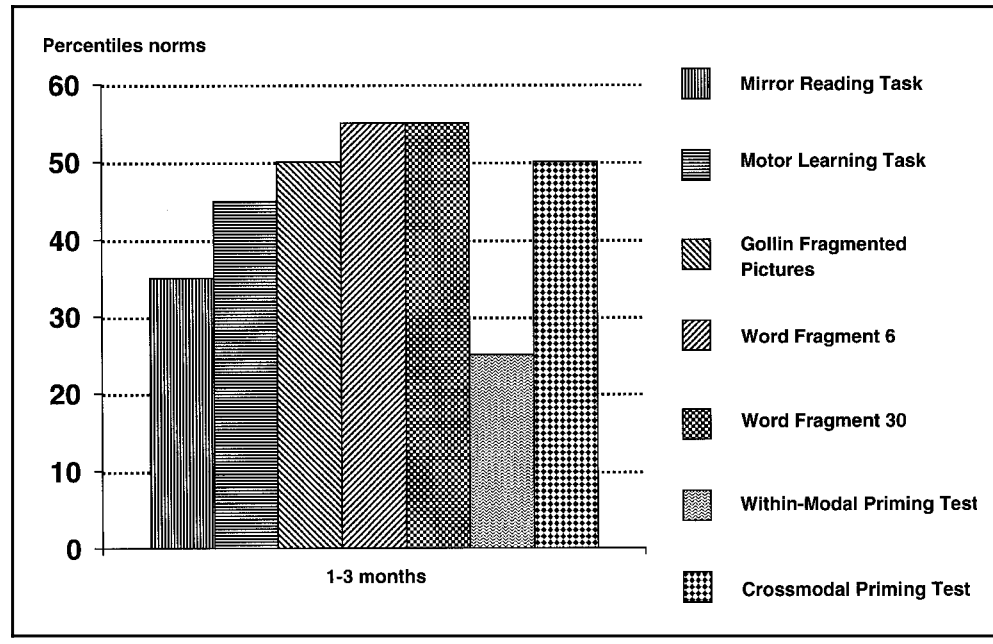

Figure 7. Procedural and priming tests. Displayed is DF's performance in the Mirror Reading Task, the Motor Learning Task, the Gollin Fragmented Pictures Test, the Word Fragment Completion 6 and 30 Tests (Word Fragment 6, Word Fragment 30), and the Within-Modal and Crossmodal Priming Test. DF's performance is indicated in percentile ranks of the respective control group. These tests were conducted during the 3 months after the event.

low on the Headlines Memory Questionnaire (developed by A. Shimamura and updated by Kroll, Markowitsch, Knight, & von Cramon, 1997) and the Transient Events Questionnaire (Cermak, 1994; O'Connor, Kaplan, & Cermak, 1990), but this may well be merely a reflection of his previous lack of interest in public affairs. We repeatedly interviewed DF on autobiographical events that occurred during the 10 years preceding his brain damage and compared his answers to his parents' reports. We employed the technique devised by Crovitz and Schiffman (1974) (recalling specific personal memories in response to cue words, e.g., birthday, movie) for the study of DF's autobiographical memory. DF was instructed to try to recall the most recent specific experience that incorporated the stimulus word. He remembered occurrences (events with friends, birthdays, parties, vacations, bad days, trips, etc.) up to a year preceding CO poisoning. We also gave DF the "former residences" test described by Beatty, Salmon, Bernstein, and Butters (1987) to test his autobiographical memory. He was able to draw precise floor plans of homes he had lived in, including the home he inhabited at the time of the incident. His parents verified the accuracy of his drawings. Specific questioning confirmed that DF's memory for events from the year preceding the incident, especially those from 3 months before, was patchy. Although he was able to remember many facts about the O. J. Simpson trial and significant events in his own life, he did not remember other episodes. Thus, DF appears to suffer a patchy retrograde amnesia covering roughly the year preceding his brain damage.

Other Cognitive Skills

Frontal lobe functions were assessed with the Wisconsin Card Sorting Test (Grant & Berg, 1948), the Tower-of-Hanoi Test (Glosser & Goodglass, 1990, but with four rings), Halstead Category Test of the Halstead-Reitan Battery (Halstead, 1947; Reitan & Davison, 1974), Stroop (Perret, 1974; Stroop, 1935), verbal and nonverbal fluency tests (Regard, Strauss, & Knapp, 1982), a concept-finding test (Kramer, 1970), Luria's motor sequencing tasks (Luria, 1973), and attention/concentration (WMS-R subtest). DF increased his scores to a normal level in all of these tests except for the verbal fluency tests and motor sequencing by the end of the second month after the event. Verbal fluency was initially very reduced and remained at the low end of the normal spectrum. Unimanual sequencing was slow and prone to errors with both hands throughout the period of testing. We attributed these sequencing problems to the damage of the patient's globus pallidus.

Spatial abilities were examined with the Spatial Subtest of the Differential Aptitude Test (Bennett, Seashore, & Wesman, 1972). DF performed in the upper 80% rank. DF also performed very well on a test of mental rotation ("Spatial"; Thurstone & Thurstone, 1962). *Language:* DF's writing, reading, sentence repetition (Benton & Hamsher, 1976), naming (Boston Naming Test; Goodglass, Kaplan, & Weintraub, 1983), and language comprehension (Token Test; De Renzi & Vignolo, 1962) were normal. *Other functions:* DF exhibited no neglect or extinction phenomenon, no agnosia and no apraxia.

Neuropathological Findings—MRI Imaging

The relative volume of DF's left hippocampal formation (left hippocampal formation/left temporal cortex) was 5.06%, whereas the mean (M) of the controls was 8.8% with a mean-minus-2-standard deviations (M-2STD DEV) cutoff at 7.38%. Thus, DF's relative left hippocampal volume was 42.5% smaller than the mean of the controls. The relative volume of DF's right hippocampal formation (right hippocampal formation/right temporal cortex) was 6.32%; the mean of the controls was 8.86% with a M-2STD DEV cutoff at 7.02%. DF's relative right hippocampal volume was therefore 28.7% smaller than the mean of the controls. The relative volumes (divided by the temporal cortex) of DF's left and right parahippocampal gyri lay within the M and M-2STD DEV range (left parahippocampal gyrus: DF = 10.17%; $M_{controls}$ = 14.77%, M-2STD DEV = 7.81%; right parahippocampal gyrus: DF = 9.95%, $M_{controls}$ = 14.74, M-2STD DEV = 5.09%). The absolute volume of DF's right and left mammillary nuclei were larger than those of the control subject in whom the mammillary nuclei were visible on the MR images and who has the largest brain structures of the controls. This indicates that DF's mammillary nuclei are likely to be of normal size. Importantly, DF's absolute temporal cortex volumes were comparable to those of the controls. The absolute total volume of DF's left hippocampal formation was 1.89 cm^3 ($M_{controls}$ = 3.47 cm^3) and the volume of his right hippocampal formation was 2.31 cm^3 ($M_{controls}$ = 3.64 cm^3) (see Table 1 for the absolute volumes of all structures of interest). Figure 8 shows the relative hippocampal areas over the length of the left and right hippocampal formation. Displayed are the relative left and right hippocampal areas (hippocampal formation/temporal cortex) in DF and the controls at every other slice position from rostral to caudal. DF's relative left hippocampal areas are smaller than the M-2STD DEV cutoff over the middle two-thirds of the rostrocaudal extent of the hippocampal formation, whereas his right relative hippocampal areas are close to the M- 2STD DEV cutoff in about the same middle two-thirds of the length of the hippocampal formation.

DISCUSSION

After bilateral hippocampal and globus pallidus damage due to CO poisoning, DF was initially severely amnesic, but his memory functions showed selective recovery over 1.5 years. His recovery allowed him to be retrained and secure full-time employment. DF also suffered from inertia (i.e., a lack to initiate spontaneous activities). This is a common symptom subsequent to CO poisoning and atrophy of the globus pallidus (Ali-Cherif et al., 1984). Yet, DF recovered from inertia as well. As of this writing, he lives independently and on his own.

What is perhaps most remarkable about the course of recovery of his memory is that some episodic memory subfunctions recovered more than others. Although nonspatial associative learning, single-item immediate recall, single-item recognition, and nonverbal free recall recovered almost completely, verbal free recall and spatial memory functions remained as reduced as immediately after the event. DF's spatial perceptual abilities were intact, as were all other cognitive and perceptual functions. The differential recovery of anterograde episodic memory suggests that these episodic memory functions have different degrees of dependence upon the damaged brain areas. One possible criticism of our interpretation of DF's pattern of performance is that he was merely manifesting differential carryover effects on the repeatedly applied tests. In response to this criticism, it should be noted that DF did not exhibit episodic learning in any of our tests except for the conjunction tests during the first 3 months. Nor did he show any improvement over retesting during the first 3 months. Therefore, it seems unlikely that the results of the subsequent test sessions during months 4 through 6 would be more than marginally compromised by earlier test administrations. Thereafter, no performance increase occurred in either the spatial memory tests or verbal free recall tests, and thus, there was no carryover on these tests. In other tests, carryover effects may add to a genuine improvement of function, but cannot explain the huge performance differences between tests. To show any, as opposed to no, nonprocedural carryover effects, DF must have been

Table 1. Volumes of the Structures of Interest in DF and the Three Controls

	Left HF[a]	*Right HF*	*Left PG*[b]	*Right PG*	*Left TL*[c]	*Right TL*	*Left MN*[d]	*Right MN*
Control JR	3.35 cm^3	3.44 cm^3	6.65 cm^3	7.23 cm^3	35.56 cm^3	35.73 cm^3		
Control DT	3.95 cm^3	3.77 cm^3	5.94 cm^3	5.37 cm^3	49.14 cm^3	48.08 cm^3	0.11 cm^3	0.11 cm^3
Control DD	3.12 cm^3	3.72 cm^3	4.73 cm^3	5.24 cm^3	34.94 cm^3	40.76 cm^3		
Patient DF	1.89 cm^3	2.31 cm^3	3.79 cm^3	3.63 cm^3	37.32 cm^3	36.52 cm^3	0.13 cm^3	0.13 cm^3

[a] Hippocampal formation.
[b] Parahippocampal gyrus.
[c] Temporal lobe.
[d] Mammillary nuclei.

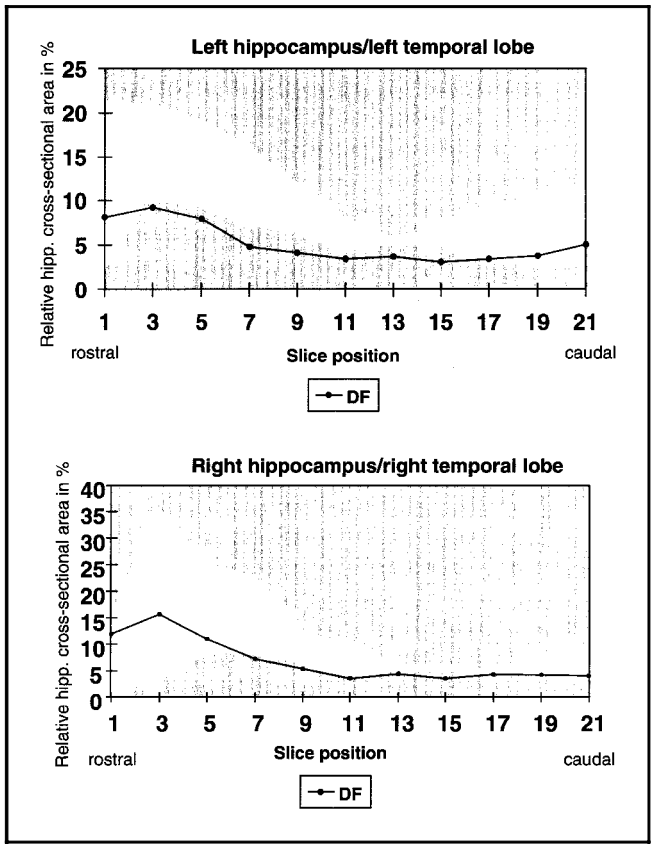

Figure 8. Hippocampal measures. Relative hippocampal cross-sectional area at every other slice position (1, 3, 5, etc.) from rostral to caudal. The left side is displayed on top, and the right, on the bottom. Hippocampal areas are indicated in percentage of the temporal cortex area at each position. DF's measures (in black) are shown in relation to the mean plus or minus two standard deviations range of the controls (white area).

able to learn the presented material—but that in itself would be evidence favoring the differential recovery interpretation.

Although the globus pallidus might be involved in cognitive functions (Brown, Schneider, & Lidsky, 1997; White, 1997), it is not known to have a role in the processing of episodic memories. Therefore, the damage to the hippocampal formation is more likely to have caused DF's episodic memory deficits than the damage to the globus pallidus. Assuming that those memory functions that depend most on the damaged structures recovered the least, our data indicate that spatial memory and verbal free recall depend most on the damaged hippocampal areas, whereas other episodic memory functions can be supported by healthy neuronal populations within and outside of the hippocampal formation. MRIs acquired 1 year after the event illustrated long-lasting damage to the globus pallidus and hippocampal formation, both bilaterally.

The fundamental mechanism of action of CO involves binding with hemoglobin, which forms carboxyhemoglobin. CO poisoning produces tissue hypoxia by competing with oxygen for binding sites on hemoglobin. CO has an affinity approximately 250 times that of oxygen (Ginsberg, 1985). Furthermore, CO decreases the oxygen affinity of the remaining binding sites. Although anoxia causes nonspecific degenerative neuropathological changes, the hippocampus appears to be more vulnerable to anoxic injury than other brain regions. Hopkins, Weaver, and Kesner (1993) found that individuals who develop memory impairments subsequent to CO poisoning have significantly smaller hippocampi compared to controls. Bilateral necrosis of the globus pallidus is another pathological hallmark of CO intoxication (Ali-Cherif et al., 1984; Chang, Han, Kim, Wie, & Han, 1992; Klawans, Stein, Tanner, & Goetz, 1982; Sawa, Watson, Terbrugge, & Chiu, 1981). Other commonly affected areas include the cerebral cortex, cerebellum, and substantia nigra (Ginsberg, 1985).

Although uncomplicated hypoxia is associated with cerebral vasodilatation and increased cerebral perfusion, the coexistence of cardiomyopathy with associated hypotension and systemic acidosis has been proposed as an additional important mechanism of CO toxicity. Hypotension prevents the rise in cerebral perfusion needed to offset the decline in delivery of oxygen and glucose. This complication leads to ischemia superimposed on hypoxia—a state that has far more deleterious effects on the nervous system than hypoxia alone. A state of hypoxia and ischemia induces white matter pathology, which uncomplicated hypoxia is insufficient to provoke (Ginsberg, 1985).

DF had no cardiac arrhythmias or hypotension and no acidosis at the time he was hospitalized. We presume, therefore, that he probably belongs within the category of uncomplicated cases. Unfortunately, a positron emission tomographic (PET) examination, which would have helped to discover eventual additional cell loss and/or neuronal dysfunction in the temporal lobes, the diencephalon and parieto-occipitally (Markowitsch, Weber-Luxeburger, Ewald, Kessler, & Heiss, 1997), has not been carried out. The absolute volumes of DF's temporal lobes were, however, comparable to those of the matched controls. Accepting that DF's amnesia was induced by his bilateral hippocampal damage, the very selective recovery of his episodic memory functions suggests a functional specialization of the hippocampal formation within episodic memory. The rat hippocampal formation (Nadel, 1991; O'Keefe & Nadel, 1978) is believed to play a particularly prominent role in spatial learning. Nonhuman primate studies indicate that the primate hippocampal formation is also involved in spatial memory (Angeli, Murray, & Mishkin, 1993; Gaffan, 1994; Gaffan & Saunders, 1985; Parkinson, Murray, & Mishkin, 1988). A selective mnemonic role for the human hippocampus could not readily be observed. Patients with focal damage to the hippocampal formation do exhibit spatial learning problems (Bohbot et al., 1998), yet these may constitute an instance of a broader category of memory that re-

quires the hippocampus (Cave & Squire, 1991). Accordingly, hippocampal and parahippocampal activations in functional imaging studies have been obtained during both spatial (Maguire et al., 1996, 1997, 1998) and nonspatial memory tasks (Lepage, Habib, & Tulving, 1998; Schacter & Wagner, 1999) including verbal (Dolan & Fletcher, 1997; Henke et al., 1999; Kopelman, Stevens, Foli, & Grasby, 1998; Rugg et al., 1997; Schacter, Alpert, Savage, Rauch, & Albert, 1996; Wagner et al., 1998) and nonverbal memory taks (Haxby et al., 1996; Henke et al., 1997; Kapur, Friston, Young, Frith, & Frackowiak, 1995; Martin, Wiggs, & Weisberg, 1997; Schacter et al., 1995; Stern et al., 1996).

The present study of DF shows that the hippocampal formation is not only involved in spatial memory, but that it is *indispensable* for spatial learning and memory. Interestingly, even though DF's left hippocampus is more affected than his right hippocampus, spatial memory was severely reduced. The greater left hippocampal damage, however, might explain why the verbal, rather than the nonverbal, free recall did not recover. This is consistent with the classic view of the left temporal lobe structures as being more specialized for verbal memory than the right temporal lobe structures. The fact that DF's recognition scores were much better, even for verbal material, than his free recall is most likely due to the heterogeneous nature of recognition tests. Recognition depends partly on nonepisodic information retrieval (priming or semantic memory—the "know" aspect of recognition) and partly on episodic retrieval (the "remember" aspect of recognition). Thus, DF might have profited from semantic and/or implicit memory during recognition. His better performance in the recognition than in the free recall tests therefore indicates that he had suffered a selective episodic memory impairment. This further substantiates the notion that the hippocampal formations support episodic rather than semantic memory. Notably, DF performed normally in all priming tests and appeared to have a normal retrograde semantic memory. The alternative interpretation that an additional prefrontal dysfunction could have debilitated DF's free recall more than recognition can be excluded on grounds of his good scores on several tests sensitive to frontal lobe damage.

DF's good performance early after the event in the nonspatial associative learning tasks came as a surprise because of recent PET findings demonstrating that the right human hippocampal formation was specifically activated by nonspatial associative as opposed to single-item learning (Henke et al., 1997, 1999) and findings in amnesic patients with hippocampal damage showing that these patients have a pronounced deficit in binding the components of pictures and words in memory (Kroll et al., 1996). How can the absence of a nonspatial associative learning deficit in DF be explained? Nonspatial associative learning might simply not depend on the hippocampal formation. Alternatively, nonspatial associative learning might rely on both the parahippocampal gyrus and the hippocampal formation (Bunsey & Eichenbaum, 1993; Henke et al., 1997), whereas spatial associative learning might depend more on the hippocampal formation itself. Because DF's parahippocampal gyri are apparently normal or near normal in size, this may explain his good nonspatial associative learning. Because DF's good associative learning scores stem from recognition tests, it is also possible that he profited from semantic memory in these tasks.

The issue of whether spatial learning is a typical function of the human hippocampal formation alone or whether it is the kind of learning that is most vulnerable to medial temporal or diencephalic damage is not yet resolved. It is conceivable that item information in conjunction with space and/or time information is most difficult to remember and most vulnerable to damage at several brain locations. In monkeys, for example, anterior and medial thalamic lesions as well as mammillary body lesions lead to impairments of object-in-place memory (e.g., Parker & Gaffan, 1997a, 1997b). Rats with anterior thalamic lesions are also impaired at using allocentric cues but perform well on an egocentric discrimination task (Aggleton, Hunt, Nagle, & Neave, 1996).

The differential contribution of the various subregions of the hippocampal formation, the surrounding structures, and the diencephalic nuclei to the type of episodic and semantic memory are at the core of current memory research. This case report indicates that episodic memory relies more on the function of the hippocampus than does semantic memory and that there is a functional specialization of the hippocampus within episodic memory for spatial learning.

METHOD

Patient Report

DF is a 28-year-old, Caucasian right-handed man with an unremarkable past medical history except for an addiction to gambling and depressed moods that were undiagnosed and untreated. He was an excellent student in high school, worked in different jobs, and managed a fast-food restaurant. DF did not experience any memory problems until the age of 25 after ischemic brain damage secondary to CO poisoning with automobile exhaust gases. He was oxygenated via face mask until the arrival at the hospital. Upon arrival the patient was intubated and hyperventilated. He was comatose with a Glasgow coma scale of 5, a carboxyhemoglobin level of 54 (normal <2), and a sinus tachycardia with a regular rate in the 150s. His heart rate, thereafter, remained regular between 111 and 140. His blood pressure was 156/88. DF presented in decorticate posturing and with positive Babinski signs bilaterally. He received intravenous man-

nitol to treat cerebral edema. Urine analysis and toxicity screen were completely negative, except for diphenhydramine (a nonprescription antihistamine). Postintubation arterial blood gases showed a ph of 7.5, pO2 of 366, pCO2 of 25.6, and HCO3 of 20. By the evening of admission, he was still stuporous but could be awakened. He was administered hyperbaric oxygen (HBO) treatments twice daily for a total of 10 dives at 3 atmospheres of pressure (44 ft). The treatment of CO poisoning is reoxygenation, because hyperoxia shortens the half-life of CO in the blood stream, and the increased solubility of oxygen under pressure accelerates this process. In the neurological examination 5 days after the event, DF was alert and cooperative, without any paralysis or sensory impairment. He was entirely disoriented to time, place, and circumstances. His speech was intact, but he exhibited a profound psychomotor retardation, inertia, and bradykinesia but only mild rigidity. He was able to walk. Balance and posture were intact. His movements were slow and he manifested no affect, animation, or exploratory behavior. DF had no seizures and no other complications secondary to CO poisoning. An MRI scan performed 5 days after the incident revealed symmetric T2 hyperintensity within the globus pallidus bilaterally and ill-defined high signals on T2-weighted images within the hippocampal formation bilaterally extending from the amygdala to the splenium of the corpus callosum. The remainder of the brain parenchyma demonstrated normal morphologic features and signals. The cerebrospinal fluid-containing spaces and vascular structures appeared normal.

DF was discharged 2 weeks after hospitalization and went to live with his parents. Inertia remained profound, and he initiated almost no spontaneous activity but was compliant when some activity was instructed. Color and light perimetry indicated normal results. At the neurological follow-up 6 months after the incident, DF was alert, animated, and cooperative. There was no longer any psychomotor retardation and no evidence of anxiety, depression, or thought disorder. Extraocular movements, all cranial nerve functions, and motor strength were normal. There was no cogwheeling or rigidity. Coordination, finger dexterity, and sensory functions were preserved. The glabellar tap reflex was disinhibited, but there were no other pathological reflexes. Gait was normal, and balance and postural reflexes were intact. A second MRI examination 1 year after the incident was performed for hippocampal volumetry and the assessment of morphological or signal intensity abnormalities. T1- and T2-weighted images were acquired and evaluated by two neuroradiologists independently. There was hyperintensity on T2-weighted images in the globus pallidus. The hippocampal formation seemed slightly reduced in size (Figure 9) but did not exhibit widening of

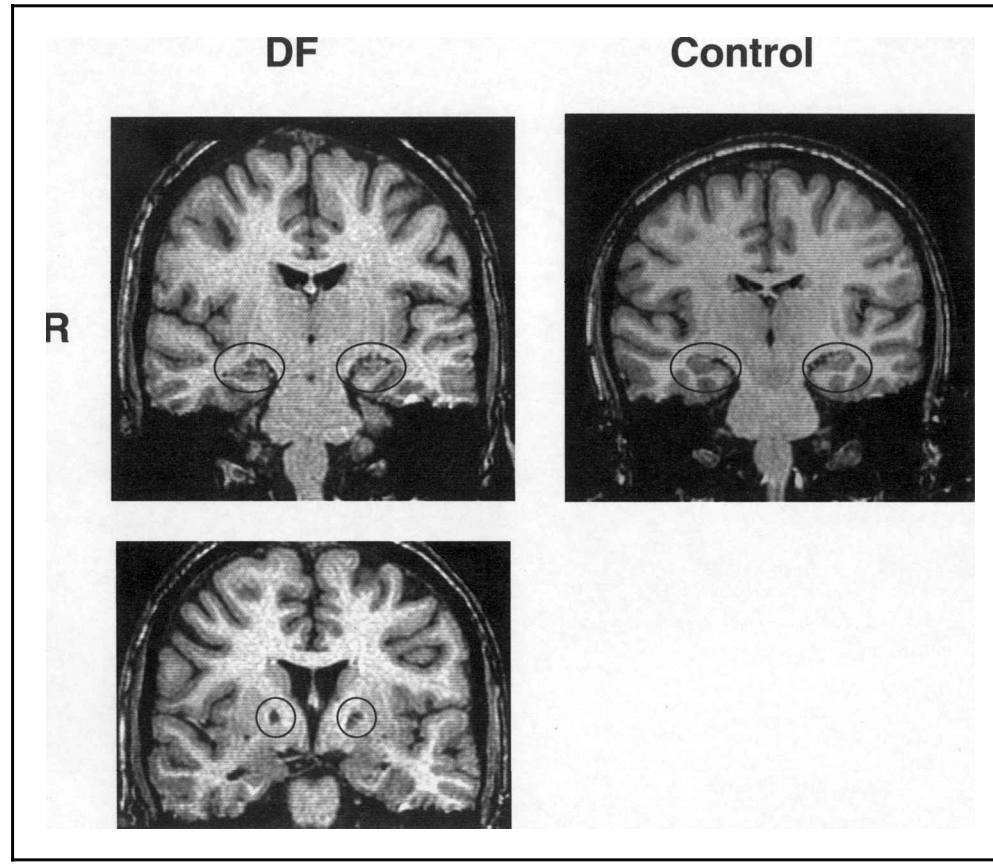

Figure 9. MRIs of the brains of DF and a control. T1-weighted (TR, 33 msec; TE, 12 msec; matrix, 256 × 192;FOV, 22 × 16 cm; NEX, 0.75) images of 1.5-mm-thick slices through the hippocampal formation of DF and one control (on top, hippocampal formation = circled), and through the globus pallidus of DF (bottom, globus pallidus = circled). The top photographs show rostral slices through the hippocampal formation that were used for making volume measurements. The area of the hippocampal formation is smaller in DF compared to the control, more so on the left than on the right side. In contrast, the average area of the temporal lobe was equal in the two subjects. The photograph shows the left side of the brain on the right side of the figure.

the sulci. The rest of the brain appeared normal. The elevated signal in the hippocampal formation on the MRI scans taken 5 days after admission is interpreted as an edema.

Neuropsychological Procedure

We continually followed DF over 18 months postintoxication, repeatedly applying the same tests (no parallel versions) of retrograde and anterograde episodic memory, semantic memory, short-term memory, and implicit and procedural memory. The construction and normalization of at least four comparable parallel test versions was considered impractical. DF's language, frontal lobe, and visual and motor functions were also assessed during the first 2 months after the event. Our first neuropsychological examination was bedside, 11 days after carbon monoxide poisoning. All other examinations took place at the home of DF's parents. Those neuropsychological tests for which no age-matched norms were available were administered to 14 age-matched (M = 24, range: 20 to 29) and education-matched (high-school education only) control subjects (eight male, six female) who live in the same city as DF. Unlike DF, the control subjects took each test only once.

Neuropsychological Tests

Some of the memory tests used in this study are well known and commercially available. The tests developed specifically for DF and those not widely known are described in the following.

Spatial Memory Tests

Picture-Location Test

Subjects first see a series of 10 stimuli; each stimulus consisted of four pictures, one in each quadrant of the screen, such that they fill the entire screen. All four pictures of a set belong to a single category (e.g., bee, grasshopper, ant, butterfly), two are in color and two, in black and white. The encoding task is to ostensibly rank them by their relative size in reality (not screen size). The memory test begins immediately following the ranking test. Subjects are asked two questions for each of the original sets. First, four pictures appear on the screen and subjects indicate which one was previously shown. One of the alternatives (the target) is exactly the same as one of the studied pictures, another alternative is very similar to the target (e.g., rotated or a colored picture if the target was black and white), a third alternative is from the same subcategory as the target (e.g., a different kind of butterfly), and the fourth alternative has the same relationship to the third as the second has to the target. After that choice is made, one picture of the original set (not the one tested previously) appears in the center of the screen and subjects attempt to recall the quadrant in which it was originally shown.

Color-Location Test

There are four learning trials and a late recall of a display of either gray or color squares on a grid of 8 by 11 squares. The displays consist of either 8, 10, or 12 squares that are either all gray or all colored (for a total of six types of test trials) and randomly distributed on the grid. During learning, subjects study the display and then arrange the colored or gray squares on an empty grid to reproduce the studied template. This procedure is repeated three times with the same square arrangement. Then, the next display is given for learning. The recall tests of all the displays are given 1 h later. The procedure with gray squares assesses memory for patterns and their spatial configuration, whereas the procedure with color squares requires these abilities plus memory for what color occupied what location within the pattern (i.e., color-place association learning).

Maze (Perret, 1973, p. 44)

Of several possible paths, subjects have to find a specific path (which only the experimenter knows) from a starting point to an end point within a visual maze. There are 10 crossings between the start and the end points, and subjects have to decide which direction to take at each crossing. Verbal feedback is given after each decision, and subjects have to correct the choice accordingly. The procedure is repeated until the correct path is chosen in three consecutive runs. We have added a free recall test after a delay of 1 h where subjects are required to draw the path from the start to the end on a blank sheet of paper.

Single-Item Learning Tests

Word List Recognition Test

Fifteen nouns are presented on a screen, for 3 sec each, during which subjects rate the pleasantness of the noun. After a short delay of 1 min, subjects are given a recognition test consisting of the 15 studied words and 30 nonstudied words (15 of which were semantically related to the studied words). Subjects respond "old" or "new" for each word.

Multiple Free Recall Test (Dobbins, Kroll, Tulving, Knight, & Gazzaniga, 1998)

Subjects read through twenty 16-word lists. After each list, subjects are asked to recall as many of the words in the list as possible, beginning with the most recent words (i.e., words from the end of the list). Words from the end of the list are considered to be from primary memory and the remaining words, from secondary mem-

ory. Ten of the lists are presented at a fast rate and 10 at a slow rate; 10 lists consist of abstract words and 10, of concrete words (5 of each are presented at each of the two rates). After all 20 lists, subjects are asked to recall as many of the words as possible from all 20 lists.

Binding Tests

Movie Test

Subjects view three silent 4-min movies. These movies depict daily scenes with a sudden unexpected, but realistic, ending. Subjects are instructed to pay close attention to the action, the actors, and the settings in the movies to remember the movies later. After a delay of an hour, subjects engage in free recall of the movies. After that, they are cued to remember specific aspects about the movies, namely, the appearance and the personality of the actors, the appearance of the settings, and the action. Then, subjects receive multiple choice forms to select a specific setting (e.g., the movie bathroom out of six photographs of bathrooms); to choose, among portraits of the seen actors, the portrait of the actor who played a certain part; to choose the correct actor-setting combinations; and to select the correct written description of the ending for each movie. Finally, the movies are presented again, but this time with new endings attached to the old beginnings. These new endings depict expected outcomes of the stories. Subjects are instructed to pay attention to potential changes in the movies.

House-Person Association Test (Henke et al., 1997)

A set of 40 pairs of photographs of houses and individuals is presented for paired-associate or single-item learning. The immediately following recognition test is a house recognition test (studied and new houses), a person recognition test (studied and new individuals), or a paired-associates retrieval test (old and new house-person combinations; new combinations consisting of studied material).

Nonverbal Conjunction Tests (Kroll et al., 1996)

Different stimulus sets are used consisting of different kinds of face drawings. The stimuli in each set were presented for three study trials, and a recognition test was given on that set before the next set was studied. The eight test faces in each set are related to the study faces in the following ways: Two of the test faces are identical to two of the study faces, two test faces are "conjunctions" of the features of two of the study faces (e.g., the eyes of one of the study faces and the nose of another), two test faces have one of the features of a study face and one new feature that has not appeared before, and two test faces are completely new. Before each study phase, subjects are warned to pay close attention to how the components of the faces are combined. They are shown examples of a "new" test face that consists of components of "old" study faces. "Old" responses to repeated faces are hits; all other "old" responses are false alarms.

Verbal Conjunction Test (Kroll et al., 1996)

Three lists of common two-syllable nouns are constructed such that each word presented falls into one of four categories: It appears in the list for the first time, one of its syllables appears the second time in the list, the word appears the second time in the list, each of the syllables appeared in the list before, but it is the first time that they appear together. There is an equal number of repeated words, repeated syllables, and conjunction words in each of three retention intervals in a continuous recognition test. Subjects read the word aloud from the screen and judge whether or not the word has occurred previously in the list. "Old" responses to repeated words are hits; all other "old" responses are false alarms.

Verbal Paired-Associate Learning with Fragmented Cues (adapted from Baddeley, 1992)

Subjects read a list of word pairs. On the first test trial, the first ("A," or stimulus) word of each pair is given together with word fragments of the second ("B," or response) word. Subjects have to name the response word. On the second trial, a more fragmented response cue is given. On the third trial, only the stimulus is given. Then, the procedure starts over with new ("C") responses to be learned to the same stimuli ("A-C" associations). At the end, both responses ("B" and "C") are requested to each stimulus.

Implicit Memory Tests

Word Fragment Completion 6 and 30

A list of 6 or 30 nouns is presented for study, each word appearing on the screen for 3 sec. Subjects read words out loud and rate them for pleasantness. Later, a list of fragmented nouns is presented for 6 sec each; half were on the study list. Subjects say the first word that comes to mind to complete the fragments. The 6/12 word study/test list procedure is repeated three times (total four runs), with new words each time. The 30/60 word study/test list procedure is given once. After each six-word study list, subjects are asked to recall as many words as possible after a short delay. After completion of each fragment completion test with the six-word study list, subjects are read back the twelve words from the test list and asked if the word was old (from the study list) or new (from the test list only).

Within-Modal/Crossmodal Priming (Roediger & Blaxton, 1987)

For within-modal priming, subjects read a list of 20 eight-letter words and are then shown a list of 40 word fragments (20 studied words, 20 new words) and given 10 sec per fragment to say the first word that comes to mind that fits the fragments. For crossmodal priming, the experimenter reads a list of 20 eight-letter words to subjects and then visually presents the list of 40 word fragments (20 old and 20 new words) to subjects. There were two such lists for each type of priming presented in the sequence: Within – Cross – Within – Cross.

Gollin Fragmented Pictures Test

We use a version of our own devising (Henke, Landis, & Markowitsch, 1993) consisting of 21 pictures of animals and objects. Each item is progressively fragmented in 10 steps from a complete to an extremely fragmented representation. Thus, for each item there is a set of 10 cards. There are two runs with the same 21 sets; in each run, the 10 representations of an item are given consecutively, starting with the most fragmented representation. The task is to verbally identify the item in a state that is as fragmented as possible. Earlier (= more fragmented representation) identification of items in the second run than the first one without concomitant conscious recognition of the item is interpreted as evidence for visual priming.

Mirror Reading Task

The procedure is loosely based on that described in Regard and Landis (1988) and Cohen and Squire (1980). The same five columns, each consisting of 16 mirror-reflected four-letter nouns, are presented in two runs separated by 1 h. In both runs, subjects are requested to read one column at a time as correctly and as fast as possible. Reading time and reading errors are recorded. In run 1, after reading a column, subjects recall the words of the column just read. Before run 2, subjects are required to recall words from all columns read in run 1. The difference in reading time of each column between runs 2 and 1 is taken as a measure for procedural learning, whereas the word recalls are taken as measures of explicit verbal memory.

Motor Learning Task

This is a bimanual motor coordination task with visual feedback. The task is to rotate a button with the right hand and another button with the left hand in a precisely coordinated manner so that the resulting line that appears on the monitor ascends smoothly from the left lower corner to the right upper corner of a screen. Time and accuracy are recorded.

Anatomical Methods

MR Scanning

One year after CO poisoning, a high-resolution protocol was used for MR imaging the brain of DF and three age-, sex-, and handedness-matched controls using a GE Signa (General Electric, Milwaukee) 1.5 Tesla whole body scanner. This protocol provides detailed images of the hippocampal formation, the parahippocampal gyrus, the temporal lobe, and the mammillary nuclei. In earlier investigations (Press, Amaral, & Squire, 1989; Squire, Amaral, & Press, 1990) it was found that the best resolution of the hippocampal formation can be obtained by imaging the hippocampal formation perpendicular to its long axis. To locate the hippocampal formation, an initial T1-weighted sequence was performed acquiring twelve 5-mm-thick images with 2.5-mm interslice gaps in the sagittal plane [repetition time (TR), 400 msec; echo time (TE), 10 msec; matrix, 256 × 192, field of view (FOV), 24 × 24 cm; number of excitations (NEX), 1]. Following the localization sequence, high-resolution coronal images were acquired using a T1-weighted sequence (TR, 33 msec; TE, 12 msec; matrix, 256 × 192; FOV, 22 × 16 cm; NEX, 0.75). One-hundred twenty-four 1.5-mm-thick sections were acquired with no interslice gaps from the frontal to the occipital lobe. Between 21 (3.15 cm) and 24 (= 3.6 cm) sections of the hippocampus were acquired. Thus, the rostrocaudal extent of the intraventricular portion of the hippocampal formation was approximately 3 to 3.5 cm in length.

To examine DF's whole brain for regions of abnormal morphology, one additional T2-weighted sequence was performed. Sixty-eight, 5-mm-thick contiguous images were obtained in the coronal plane (TR, 3000 msec; TE, 133 msec; matrix, 256 × 192; FOV, 20 × 20 cm; NEX, 3). This sequence provided images from the frontal through the occipital lobe.

Image Analysis

On each section through the hippocampal formation, the area of the hippocampal formation, the parahippocampal gyrus, the temporal lobe, and the mammillary nuclei were measured according to methods previously described (Press et al., 1989; Squire et al., 1990). The 21 to 24 sections displaying the hippocampal formation, starting with the pes hippocampi rostrally, were used for measurements of the four structures of interest on both sides. The regions included in each of the temporal structures are illustrated and described elsewhere (Squire et al., 1990). The contours of the four structures of interest were traced from the magnified MRI films using a microfilm viewer (Dokumator DL 2 from Jena) and then digitized with a digitizing tablet (SummaSketch 3 by Summagraphics). The areas were then computed using image measurement software (SigmaScan by Jandel Corporation). The contour of the hippocampal for-

mation extended from a point at the lateral, inferior border of the temporal horn of the lateral ventricle, continued medially, and included the fimbria, dentate gyrus, hippocampus proper, and subiculum (see Figure 1 in Squire et al., 1990). The contour of the parahippocampal gyrus extended from the same point on the lateral ventricle used for the hippocampal measurements, continued along the medial border of the collateral sulcus, and ran around the medial border of the parahippocampal gyrus to terminate at the hippocampal formation. The contour of the temporal lobe originated at the same point described above, extended along the lateral border of the collateral sulcus, wound around the temporal cortex following the cortical surface into the sulci to the inferior limiting sulcus of the insular cortex, and then want back to the starting point cutting through the temporal stem. The contours of the mammillary nuclei were measured on the four consecutive slices in which they were visible. In one control case, the mammillary nuclei were not clearly visible, and, in another control, they were visible on only two consecutive slices. Therefore, the volume of DF's mammillary nuclei were compared to that of only one control. The total volume of each of the four structures of interest was computed by multiplying the measured areas by the slice thickness and adding the products across slices. Hippocampal areas and volumes were divided by the respective measures of the temporal cortex to correct for interindividual differences in brain size. The temporal cortex was selected as reference because it is also a structure supporting memory functions.

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