

# Cognitive Impairment Following Frontal Lobe Damage and Its Relevance to Human Amnesia

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Whether frontal lobe pathology can account for some of the cognitive impairment observed in amnesic patients with Korsakoff's syndrome was investigated. Various cognitive and memory tests were given to patients with circumscribed frontal lobe lesions, patients with Korsakoff's syndrome, non-Korsakoff amnesic patients, and control Ss. Patients with frontal lobe lesions were not amnesic. Nevertheless, they exhibited 2 deficits that were also exhibited by patients with Korsakoff's syndrome but not by other amnesic patients: (a) impairment on the Wisconsin Card Sorting Test and (b) impairment on the Initiation and Perseveration subscale of the Dementia Rating Scale. Thus, frontal lobe pathology can explain some of the cognitive deficits observed in patients with Korsakoff's syndrome.

Amnesia is characterized by a severe deficit in the ability to learn new facts and events (i.e., anterograde amnesia) in the context of relatively preserved intellectual functions (for reviews see Cermak, 1982; Hirst, 1982; Mayes & Meudell, 1983; Milner, 1972; Schacter, 1985; Squire, 1986; Weiskrantz, 1987). The pattern and extent of cognitive impairment can vary considerably across different etiological groups. Patients with Korsakoff's syndrome, for example, are poor problem solvers (Oscar-Berman, 1980), have difficulty making temporal order judgments (Meudell, Mayes, Ostergaard, & Pickering, 1985; Squire, 1982) or metamemory judgments (Shimamura & Squire 1986), and fail to release from proactive interference (i.e., they do not benefit from a change in the semantic category of words during a list-learning task; Butters, 1984; Cermak, Butters & Moreines, 1974; Cermak 1976; Squire, 1982). They also perform poorly on tests of initiation and perseveration (see Squire & Shimamura, 1986) and show personality changes, such as apathy and disinhibition (Butters & Cermak, 1980; Squire & Zoukounis, 1988; Talland, 1965). These deficits have not been observed in

other, non-Korsakoff amnesic patients (Shimamura & Squire, 1986; Squire, 1982; Squire & Shimamura, 1986).

One possibility is that many or all of these deficits reflect impairments in processes integral to normal learning and memory. By this view, these deficits would be expected to occur when amnesia is sufficiently severe. Another possibility is that these deficits are dissociable from memory impairment. If so, they must be due to damage in regions other than the medial temporal area and the diencephalic midline that have been traditionally associated with amnesia.

Several findings suggest that some of the deficits associated with Korsakoff's syndrome may be due to frontal lobe pathology. Some patients with frontal lobe lesions show perseverative tendencies on problem-solving tasks (Milner, 1963), are impaired at making recency judgments (Milner, 1971; Milner, Petrides, & Smith, 1985), and fail to show release from proactive interference (specifically patients with left frontal lobe lesions; Moscovitch, 1982; but see Freedman & Cermak, 1986). In addition, some patients with frontal lobe lesions show personality changes, such as apathy and poor judgment (Blumer & Benson, 1975; Luria, 1966). Finally, quantitative radiological (i.e., computer tomography [CT]) evidence of frontal lobe atrophy has been obtained for patients with Korsakoff's syndrome (Jacobson & Lishman, 1987; Shimamura, Jernigan, & Squire, 1988).

In order to demonstrate that cognitive deficits in Korsakoff's syndrome can be dissociated from amnesia and are due to frontal lobe damage, several pieces of evidence are needed. First, patients with frontal lobe lesions should exhibit the same cognitive deficits that are exhibited by patients with Korsakoff's syndrome. Second, the same patients with frontal lobe lesions should perform normally on the standard mem-

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Table 1  
*Characteristics of Patients With Frontal Lobe Lesions and Their Control Subjects*

Group	Age	Education	WAIS-R Full Scale IQ	WAIS-R subtest scores		Lesion
				Information	Vocabulary	
Frontal						
J.D.	69	16	112	24	67	Left dorsolateral prefrontal
R.L.	71	8	118	27	60	Left dorsolateral prefrontal
J.V.	63	13	92	20	50	Right dorsolateral prefrontal
M.S.	44	18	85	18	42	Right dorsolateral and orbital prefrontal
E.M.	66	10	117	24	66	Right medial prefrontal
G.Y.	69	14	96	25	56	Bilateral frontal
M.D.	65	12	88	15	35	Bilateral frontal
<i>M</i>	63.9	13	101.1	21.9	53.7	
Control	60.8	14	112.0	22.5	55.5	
( <i>n</i> = 11)	46-69	12-18	97-137	18-26	47-65	

Note. Data for the control group are means, with ranges beneath them. Raw scores are reported for Wechsler Adult Intelligence Scale-Revised (WAIS-R) subtests.

ory tests that amnesic patients fail. Although a few studies of patients with frontal lobe lesions suggest that they can perform normally on standardized memory tests (Black, 1976; Butters, Samuels, Goodglass, & Brody, 1970; Stuss et al., 1982), other studies have found significant impairments on memory-related tasks (Corkin, 1965; Freedman & Oscar-Berman, 1986; Hecaen, 1964; Luria & Homskaya, 1964; Milner, 1982; Petrides, 1985). Third, other (non-Korsakoff) amnesic patients should also exhibit deficits on the same standard memory tests but should not exhibit the other cognitive deficits.

The present study addressed these points. The performance of patients with circumscribed frontal lobe lesions was compared with the performance of patients with alcoholic Korsakoff's syndrome, 5 other patients with amnesia, and three groups of control subjects. We tested these subjects on cognitive tasks known to be sensitive to frontal lobe dysfunction (Wisconsin Card Sorting Test, Verbal Fluency Test); on standardized memory tests that are performed poorly by amnesic patients (Wechsler Memory Scale-Revised [WMS-R], Rey Auditory Verbal Learning Test, Story Recall, Paired-Associate Learning, and Diagram Recall); and on certain tasks that are performed poorly by patients with Korsakoff's syndrome but not by other amnesic patients (the Initiation-Perseveration subscale of the Dementia Rating Scale and a test of Release From Proactive Interference).

## Method

### Subjects

*Patients with frontal lobe damage.* Seven patients with lesions of the frontal lobes were identified by a review of medical records and CT scans at the Veterans Administration Medical Center, San Diego, and the University of California, San Diego Medical Center. Patients were included who had lesions restricted to the frontal lobes and who had no other diagnosis likely to affect cognition or interfere with participation in the study (e.g., significant psychiatric

disease, alcoholism). Patients with symptoms suggesting that lesions were present outside the frontal lobes were excluded (e.g., patients with sensory deficits or patients with reports of chronic pain). Likewise, patients with lesions due to tumor removal and patients with severe traumatic injury (e.g., motor vehicle accidents) were also excluded because of the likelihood of damage beyond the frontal lobes. In no case did the patients selected for study have lesions extending into the basal forebrain. Using these criteria, we identified 5 patients with unilateral frontal lobe lesions (2 left, 3 right) and 2 patients with bilateral lesions. These 7 patients (4 men and 3 women) averaged 64 years of age at the beginning of the study, had 13 years of education, and had an average Wechsler Adult Intelligence Scale-Revised (WAIS-R) IQ of 101.1 (see Table 1 for individual scores). The average Wechsler Memory Scale (WMS) score was 107.4 (range, 86-135). Table 2 shows the former occupation and current activities of each patient. Testing occurred from October 1986 to September 1987.

*Descriptions of frontal lobe lesions.* For each patient one or more CT scans, and in one case a magnetic resonance imaging (MRI) scan, were available for analysis. The scan that best demonstrated the chronic lesion was used to reconstruct the lesion for each patient (see Figure 1). For 6 patients the scans used to reconstruct the lesions were performed more than 1 year after the injury. The lesion of the remaining patient (R.L.) was reconstructed from a scan performed 6 weeks after the injury. By using the method of H. Damasio (1983; personal communication), the head CT scan of each patient was compared with five sets of templates. The set that best matched the angle of the CT images was selected, and the lesion was then drawn onto the templates as it appeared in each corresponding CT image.

For the purpose of making comparisons with amnesic patients, the patients with frontal lobe lesions are considered here as a group. Due to the small number of patients, it was not possible to address the influence of locus of damage (with the exception of effects of the side of lesion, as reported below for the Verbal Fluency Test and Dementia Rating Scale). Although the frontal cortex is functionally heterogeneous, group differences have often been observed when patients with variously placed frontal lobe lesions are considered as a group (e.g., Milner, 1982; Petrides, 1985).

J.D. had a brain abscess removed in 1973. The lesion involves primarily left dorsolateral prefrontal cortex. There is some involvement of the lateral orbitofrontal cortex. The medial frontal, premotor, and motor cortices are spared.

Table 2  
*Work History and Current Activities of Patients With Frontal Lobe Lesions*

Patient	Occupation	Current activities
J.D.	Retired, army nurse for 32 years.	Owens own home. Volunteers at local hospital, travels extensively.
R.L.	Retired, director of large city school system stock-room.	Owens own home. Cares for invalid wife, reads novels, and enjoys gardening.
J.V.	Retired, computer firm quality control executive, 10 years real estate management.	Employed as a manager of a luxury condominium complex. Lives with wife.
M.S.	Special education teacher for 14 years.	Owens own home, homemaker, lives alone. Active with hobbies and real estate holdings.
E.M.	Retired, Marine officer for 30 years.	Owens own home. Does carpentry, gardening. Is active in church. Lives with wife.
G.Y.	Retired, floor covering contractor.	Owens own home. Manages rental property, participates in "gourmet group." Lives with wife.
M.D.	Homemaker, hospital housekeeper for 10 years. Day care mother.	Owens own home, lives with daughter and grandchildren. Enjoys TV and jigsaw puzzles. Prepares all meals for family.

R.L. suffered a cerebrovascular accident (CVA) in 1985. The lesion involves primarily left dorsolateral prefrontal cortex, with slight involvement of the lateral orbital surface. The medial frontal, premotor, and motor cortices were spared.

J.V. suffered a CVA in 1969. The lesion involves primarily the right dorsolateral prefrontal cortex, with slight involvement of the premotor cortex. In addition, there is some involvement of the lateral orbital surface of the frontal lobe and the anterior portion of the insula.

M.S. has neurofibromatosis. At the age of 8 (1951), her right eye and optic nerve were removed due to a tumor of the nerve. Medical records from that period made no mention of retraction, removal, or infarction of the right frontal lobe. Nonetheless, M.S. apparently suffered damage to the right frontal lobe in conjunction with the surgery. The lesion was first observed in 1978 when the patient was evaluated for headaches. The 1978 scan was not available for reconstruction. The lesion shown in Figure 1 was obtained from a 1987 scan performed because the patient was in a motor vehicle accident. The patient did not lose consciousness or suffer a skull fracture, although the 1987 scan did show blood in the lateral ventricles. The reconstruction in Figure 1 is therefore an estimate of the chronic lesion. It involves much of the dorsolateral prefrontal cortex together with orbital frontal and inferior medial frontal cortices. The premotor cortex was slightly involved, as was the ventral anterior cingulate gyrus. The motor cortex was spared.

E.M. has a small unilateral lesion of the right frontal pole (area 10) of unknown etiology. The lesion was demonstrated on CT and MRI in 1986 when the patient was being evaluated for a complaint of memory problems of 6 months duration. The patient suffered a fall in 1971, with loss of consciousness of a few seconds to minutes. He was not hospitalized, however, and was reported to be unchanged afterward. Because the MRI scan showed no sign of damage other than the small frontal lobe lesion, which was likely due to the fall, this patient was included in the study. The reconstruction was done from the MRI scan.

G.Y. suffered a CVA of the anterior cerebral arteries secondary to surgery for an anterior communicating artery aneurysm in 1976. The lesion involves primarily the left medial frontal cortex, including anterior cingulate cortex. The lesion extends into the left premotor area and the motor cortex. The postcentral gyrus (somatosensory

cortex) on the left may also be slightly involved. On the right, the lesion involves the anterior cingulate and ventral prefrontal cortex.

M.D. suffered bifrontal CVAs secondary to surgery for a left pericallosal artery aneurysm in 1985. She has an extensive bilateral lesion of the medial frontal cortex, including the anterior cingulate cortex and the medial portion of the orbital frontal cortex.

*Control subjects for patients with frontal lobe lesions.* Eleven healthy control subjects (7 men and 4 women) were volunteers or employees at the Veterans Administration Medical Center and in one case the spouse of a study patient. A 12th subject was excluded after initial screening, because her score on the Dementia Rating Scale (123) was outside the range of the scores obtained by the frontal patients (125–139). The 11 subjects were matched to the study patients with respect to age ( $M = 60.8$  years; range = 45–68) and education (14 years; range = 12–18). The control subjects were also matched to the study patients on the basis of two WAIS-R subtest scores, Information and Vocabulary (see Table 1). These subtests are considered to assess established knowledge and are relatively resistant to impairment after focal brain injury (Goodglass & Kaplan, 1979). On these subtests the mean score for control subjects was 22.5 for information (21.9 for the patients) and 55.5 for vocabulary (53.7 for the patients). The mean WAIS-R Full Scale IQ for the control group was 112 (range = 97–137). Two of the control subjects obtained unusually high WAIS-R Full Scale IQ scores (134 and 137). The mean WAIS-R Full Scale IQ score for the remaining 9 subjects was 106.0 (range = 97–125). As discussed below, the results reported here were the same whether or not the two high-IQ control subjects were included.

*Patients with Korsakoff's syndrome.* The patients with Korsakoff's syndrome consisted of 5 men and 2 women living in supervised facilities in San Diego County (see Table 3). Data from 6 of these 7 patients have been reported elsewhere (Squire, 1982; Squire & Shimamura, 1986); these include the results for all tests summarized here except the Wisconsin Card Sorting Test, which is reported here for the first time. The 7 patients averaged 54.6 years of age at the beginning of testing and had 11.4 years of education. Their average WAIS-R IQ was 97.1, and their average WMS score was 81.3. On the WMS-R, the average index scores were as follows: Attention-Concentration, 90.1; Verbal Memory, 70.6; Visual Memory, 75.1; General Memory, 66.1; Delayed Memory, 56.7.

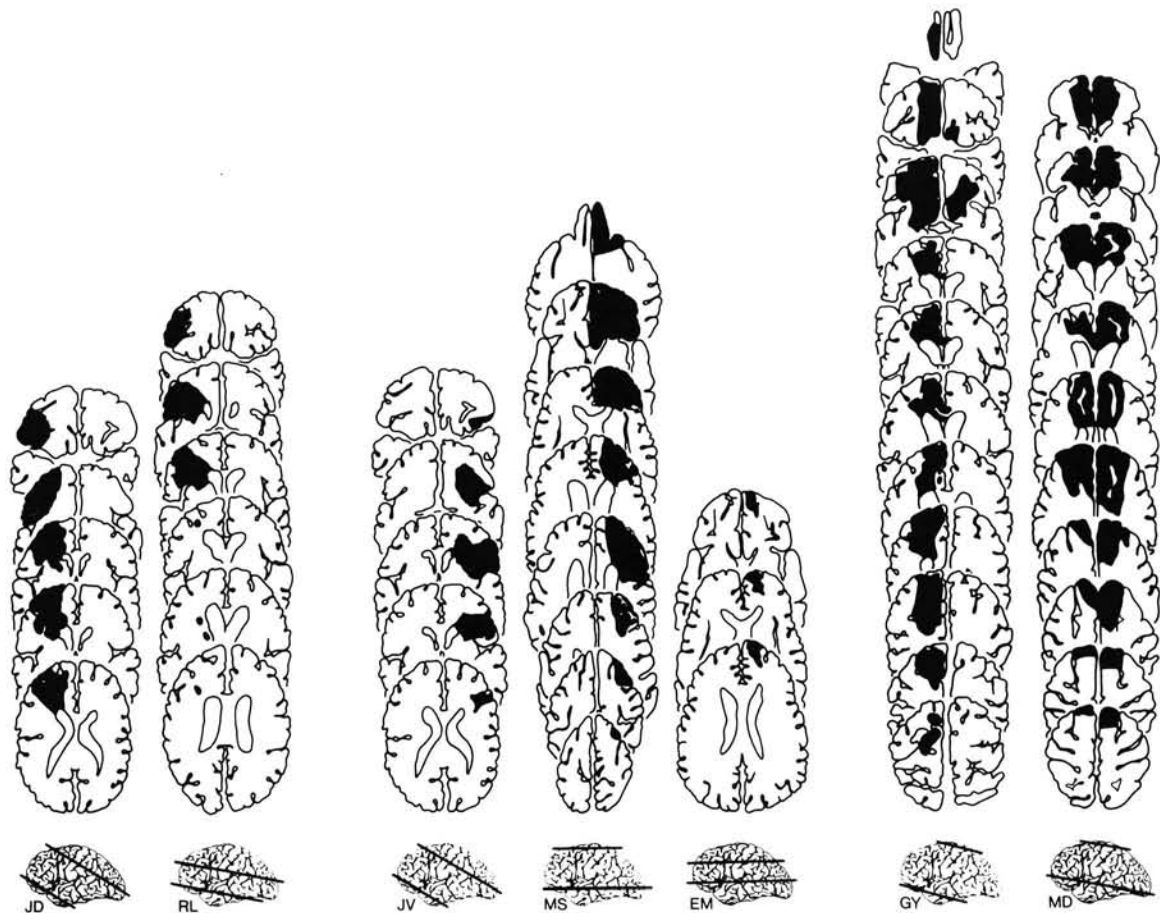


Figure 1. Reconstructions from the computer tomography or magnetic resonance imaging brain scans of frontal lobe damage (in black) for each patient in the study, by the method of H. Damasio (1983, and personal communication). (The most ventral section is shown at the top. The lateral view below each reconstruction shows the angle of the horizontal sections and the locations of the most dorsal and ventral sections.)

*Alcoholic control subjects.* Six alcoholic control subjects (2 men and 4 women) were matched to the patients with Korsakoff's syndrome with respect to age, education, and the Information and Vocabulary subtests of the WAIS-R (see Table 3). They were current

or former participants in alcohol treatment programs in San Diego County. They reported an average drinking history of 13.3 years and an average interval of 2.8 years since their last drink. Data for these subjects have been published previously and are included here for

Table 3  
*Characteristics of Amnesic Patients and Their Control Subjects*

Group	n	Age	Education	WAIS-R Full Scale IQ	Subtest scores	
					Informa- tion	Vocab- ulary
Korsakoff's syndrome	7	54.6 44-71	11.4 9-14	97.1 88-106	18.0 15-24	49.0 30-63
Alcoholic	6	55.3 53-60	12.3 11-14	—	18.8 14-24	43.8 36-52
Non-Korsakoff amnesic patients	5	53.4 47-65	15.2 13-19	109.2 92-119	22.0 16-27	57.8 39-64
Healthy control	8	50.9 44-55	14.8 12-18	—	21.9 16-26	51.8 38-65

Note. Data are means and ranges. WAIS-R = Wechsler Adult Intelligence Scale-Revised.

comparison (Squire & Shimamura, 1986); these data include the results for all tests except the Wisconsin Card Sorting Test and the Verbal Fluency Test, which are reported here for the first time. These subjects averaged 55.3 years of age, had 12.3 years of education, and had WAIS-R subtest scores of 18.8 for Information (18.0 for the Korsakoff patients) and 43.8 for Vocabulary (49.0 for the Korsakoff patients).

*Other patients with amnesia.* Five patients (4 men and 1 woman) were tested (see Table 3). Three patients (A.B., G.D., and L.H.) became amnesic after an episode of anoxia or ischemia; data for these patients have been published elsewhere (Squire & Shimamura, 1986); these include the results for all tests reported here except the Wisconsin Card Sorting Test, which is reported here for the first time. Data for 2 patients (M.G. and W.H.) have not been reported previously. W.H. became amnesic in 1986, but without a known precipitating event. Preliminary MRI scans have identified bilateral medial temporal pathology. M.G. became amnesic in 1986 following a bilateral thalamic infarction. The 5 patients averaged 54.6 years of age at the beginning of the study and had an average educational level of 15.6 years. Their average WAIS-R IQ was 109.2, and their average WMS score was 93.0. On the WMS-R, the index scores were as follows: Attention-Concentration, 105.4; Verbal Memory, 77.8; Visual Memory, 81.2; General Memory, 73.0; Delayed Memory, 55.0.

*Healthy control subjects.* Eight volunteers or employees (3 men and 5 women) of the San Diego Veterans Administration Medical Center were matched to the 5 (non-Korsakoff) amnesic patients with respect to age, education, and intelligence test subtest scores (WAIS-R, see Table 3). They had an average of 14.8 years of education and had WAIS-R subtest scores of 21.9 for Information (22.0 for the amnesic patients) and 51.8 for Vocabulary (57.8 for the amnesic patients). They had an average WMS score of 117.6 (range = 104–143). Data for these subjects were published previously (Squire & Shimamura, 1986) and are included here for comparison.

Results from a separate group of healthy control subjects are also reported here for the test of Release From Proactive Interference (from Squire, 1982). These 6 male subjects averaged 13.8 years of education and had WAIS-R subtest scores of 22.2 for Information and 58.2 for Vocabulary).

## Memory Tests

*Wechsler Memory Scale-Revised.* This newly revised scale provides for assessment of new learning ability in the verbal and visual domains (Butters et al., 1988; Wechsler, 1987). It yields five different index scores: Attention-Concentration, Verbal Memory, Visual Memory, General Memory (this index combines scores on the verbal and visual memory tests), and Delayed Memory (this index provides for assessment of memory for verbal and visual material after a delay of 30 min). The scale is constructed such that 100 is the normal score for each index and the standard deviation is 15. In this way, the index scores can be compared with the WAIS-R IQ score.

*Paired-Associate Learning.* Subjects were presented 10 noun-noun word pairs on each of three study trials. After each study trial, subjects were shown the first word of each pair and asked to recall the second word (Jones, 1974). The score was the number of pairs recalled correctly across three trials (maximum = 30 points).

*Story Recall.* Subjects were read a short prose passage containing 21 segments. Recall was tested immediately and again 12 min after presentation (Squire & Chace, 1975). The score was the number of segments recalled.

*Recall of Complex Figure.* Subjects copied the Rey-Osterrieth figure (Osterrieth, 1944) and were asked to reproduce it from memory after a 12-min delay. The score was based on the number of

segments from the diagram reproduced accurately (maximum = 36 points; Taylor, 1959).

*Word List Recall and Recognition.* Subjects were presented a list of 15 words and asked to recall as many words as possible immediately after presentation (Rey Auditory Verbal Learning Test; Lezak, 1983; Rey, 1964). Five successive study-test trials were presented, with the same words but each time in a different order. In order to test recognition memory, a different list of 15 words was used. Five successive study-test trials were presented with the same 15 study words, each time in a different order. Immediately after each list presentation, subjects were presented 30 words (the 15 study words and 15 new words), and they were asked whether or not each word was on the study list. The 15 new words were different for each 30-word test. The recall score was the percentage of words recalled on each trial. The recognition score was the total percentage of words correct on each trial, including both hits and correct rejections (chance performance = 50%). A second recognition test was also administered in order to assess yes-no recognition performance 1 week after the first five trials. All the words used in this second recognition test were different from the words used in the other recall and recognition tests. The words were matched to the ones used previously for frequency and part of speech (Thorndike & Lorge, 1944). Five study-test trials were given, just as in the first recognition test. One week following the fifth test trial, a final 30-word yes-no recognition test was given.

## Other Tests of Cognition

*Wisconsin Card Sorting Test (Heaton, 1981).* This is a test of problem solving known to be sensitive to frontal lobe dysfunction (Milner, 1964). Subjects were asked to sort cards in a 128-card deck, matching each card to one of four key cards. The cards could always be sorted into any of three categories, that is, according to the color, form, or number of the symbols on each card. Subjects were told whether each match was correct or incorrect. However, subjects did not know in advance which category was the "correct" one, and the examiner shifted without warning to a new category after 10 consecutive correct responses by the subject. Testing continued until each category was repeated twice or until all cards were sorted. It is important to note that damage to brain areas other than the frontal lobes can impair performance on this test. An increased tendency to perseverate, together with the achievement of fewer than the normal number of categories, is characteristic of damage to the frontal lobes (Heaton, 1981). Accordingly, these measures are the focus here.

*Verbal Fluency Test (Benton & Hamsher, 1976).* Subjects were given 1 min to produce words beginning with a particular letter (exclusive of proper nouns). This procedure was repeated for the letters F, A, and S. The total number of words produced was recorded.

*Dementia Rating Scale (Coblentz et al., 1973; Mattis, 1976).* This scale provides for assessment of a spectrum of cognitive functions and yields scores in each of five categories: Attention (includes digit span, responding to simple verbal commands, imitation, detection of a figure in an array, and matching of nonverbal stimuli); Initiation-Perseveration (includes rapid verbal naming, rapid movement imitation, and copying simple figures that contain repetitive elements); Construction (includes copying simple figures); Conceptualization (includes judgments of similarity for both verbal and nonverbal stimuli, inductive reasoning, and sentence construction); and Memory (includes orientation, verbal recall and recognition memory, and figural memory). The maximum score is 144 points.

*Release From Proactive Interference (Cermak et al., 1974).* This test permits assessment of the effect on recall of changing the semantic category of the words to be remembered. Subjects saw three

words belonging to a particular category (e.g., clam, trout, salmon) and were instructed to read them aloud and remember them. Following the presentation of the three words, subjects were given a 15-s distraction task in which they read the printed names of colors. The color names were typed in multicolored print. After the distraction period, subjects attempted to recall the words. This sequence was repeated five times in succession. The fifth group of words was taken either from the same semantic category as all the other words (nonshift condition) or from a different category (shift condition). Eight sequences were given, four of which involved a category shift and four of which did not. The score was the number of words recalled on each trial and in each condition (shift and nonshift).

**IQ.** The WAIS-R IQ test was administered to the patients with frontal lobe lesions and their control group. The IQ scores for the two amnesic groups are presented in the subject section and are not discussed further.

### Procedure

The following tests were administered: WMS-R, Paired-Associate Learning, Story Recall, Recall of Complex Design, Word List Recall and Recognition, Wisconsin Card Sorting, Verbal Fluency Test, the Dementia Rating Scale, and the test of Release From Proactive Interference. All groups (patients with frontal lobe lesions, two groups of amnesic patients, and all three control groups) received the tests listed above, with the exception that only two of the three control groups (the control group for the patients with frontal lobe lesions and the alcoholic group) received the Dementia Rating Scale, the Wisconsin Card Sorting Test, and the Verbal Fluency tests. Finally, the WMS-R was administered only to the amnesic patients and to 6 of the 7 patients with frontal lobe lesions, the 7th patient being unavailable for testing.

## Results

### Wechsler Memory Scale-Revised

The average index scores for the patients with frontal lobe lesions on the WMS-R were as follows: Attention-Concentration, 83.3; Verbal Memory, 100.7; Visual Memory, 90.5; General Memory, 95.7; and Delayed Memory, 94.5. Patients with frontal lobe lesions performed well on the Delayed Memory Index as well as on other indexes of memory function, but they obtained a low score on the Attention-Concentration Index. In contrast to the patients with frontal lobe lesions, all 12 amnesic patients (patients with Korsakoff's amnesia and 5 other patients with amnesia) were severely impaired on the Delayed Memory Index (56.0) and on the other memory indexes (Verbal Memory, 73.6; Visual Memory, 77.7; General Memory, 69.0), but they scored well on the Attention-Concentration Index (96.8). To illustrate these two contrasting patterns of impairment (i.e., patients with frontal lobe lesions scored low on Attention-Concentration but high on Delayed Memory; amnesic patients exhibited the opposite pattern), we performed an analysis of variance (ANOVA) comparing the scores of patients with frontal lobe lesions and the 12 amnesic patients on the Attention-Concentration and Delayed Memory indexes. A significant group main effect was obtained,  $F(1, 16) = 4.50, p < .05$ , primarily due to the fact that the amnesic patients performed so poorly on the Delayed Memory Index. The analysis revealed a significant Group  $\times$  Index interaction,  $F(1, 16) = 57.3, p <$

$.01$ , which demonstrates that the pattern of performance on the Attention-Concentration and Memory indexes was different for patients with frontal lobe lesions and amnesic patients. This interaction was also significant when patients with frontal lobe lesions were compared only with those amnesic patients with Korsakoff's syndrome,  $F(1, 11) = 49.7, p < .01$ .

### Paired-Associate Learning, Story Recall, and Complex Figure Recall

Figure 2 shows the results for three tests of memory used to assess new learning capacity. In contrast to the amnesic patients who were severely impaired on all three tests, patients with frontal lobe lesions were not significantly different from their control subjects, all  $ts(16) < 1.60, ps > .10$ . However, it is noted that for each test the average score of the patients with frontal lobe lesions was numerically lower than the score of their control group.

### Word List Recall and Recognition

Figure 3A shows the results for patients with frontal lobe lesions and their control group. The patients with frontal lobe lesions were impaired on the recall portion of the test in comparison with their control group. A two-way ANOVA (two groups by five trials) revealed a significant effect of group for recall (49.6% vs. 66.8%),  $F(1, 16) = 6.95, p < .05$ , but not for recognition (93.6% vs. 95.8%),  $F(1, 16) = 2.08, p > .10$ . In order to evaluate whether ceiling performance was hiding a difference between groups, a second recognition test was administered (Figure 3B). This test was given in the same way as the first one except that recognition performance was also tested after a 7-day delay. The patients with frontal lobe lesions performed numerically worse than their control group across the five study-test trials of this recognition memory test (92.0% vs. 97.0%) and numerically worse on the 1-week delayed test (67.6% vs. 76.1%), but these differences fell short of significance: for the five trials,  $F(1, 16) = 4.28, p = .06$ ; for the 1-week delayed test,  $t(16) = 1.90, p = .08$ . On the two trials in which no subject in either group obtained a perfect score (the first recognition trial and the 1-week delayed test), the group difference also fell short of significance (ANOVA, two groups by two trials),  $F(1, 16) = 3.57, p = .08$ . Moreover, the Group  $\times$  Trial interaction was not significant,  $F(1, 16) = .31, p > .10$ . Thus, recognition performance of patients with frontal lobe lesions was not significantly impaired, even at the 1-week delayed test, whereas recall performance was significantly impaired.

Figure 3C shows the impaired recall and recognition performance of the amnesic patients with respect to their control groups. Compared with alcoholic subjects, patients with Korsakoff's syndrome exhibited impaired recall,  $F(1, 11) = 34.0, p < .01$ , and recognition,  $F(1, 11) = 10.2, p < .01$ . Moreover, compared with healthy control subjects, the 5 non-Korsakoff amnesic patients exhibited impaired recall,  $F(1, 11) = 15.1, p < .01$ , and recognition,  $F(1, 11) = 23.5, p < .01$ . Interestingly, compared with the 5 non-Korsakoff

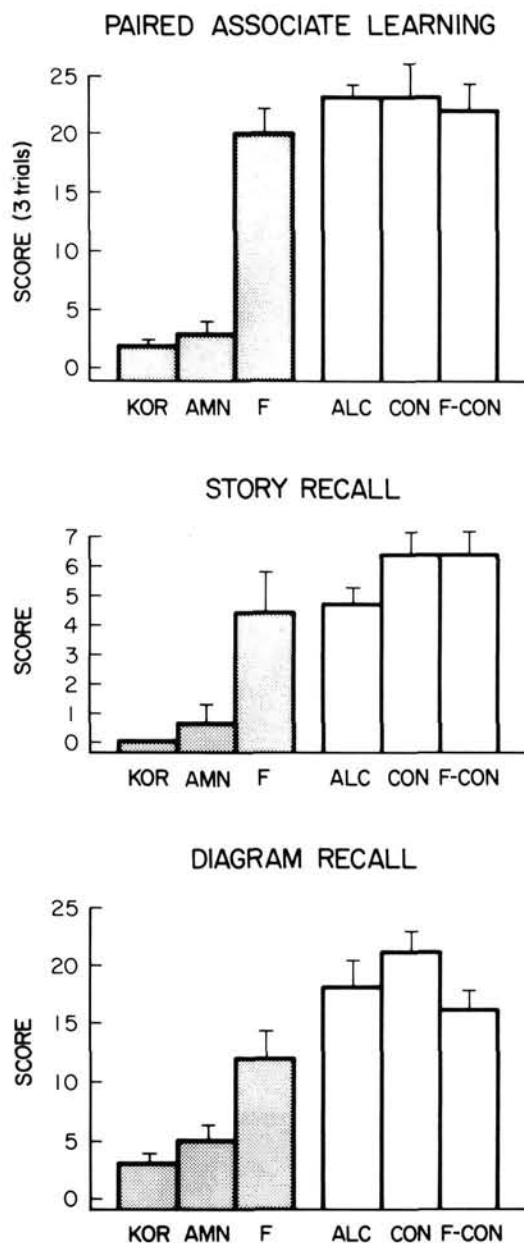


Figure 2. Performance of patients with frontal lobe lesions, amnesic patients, and control subjects on three tests sensitive to anterograde amnesia. (KOR = 7 patients with Korsakoff's syndrome; AMN = 5 other patients with amnesia; F = 7 patients with frontal lobe lesions; ALC = 6 alcoholic control subjects matched to the Korsakoff patients; CON = 8 healthy control subjects matched to the other amnesic patients; F-CON = 11 control subjects matched to the patients with frontal lobe lesions. Brackets show SE.)

patients, the 7 patients with Korsakoff's syndrome performed more poorly on recall,  $F(1, 10) = 17.8$ ,  $p < .01$ , but similarly on recognition,  $F(1, 10) = .63$ ,  $p > .10$ . Previously reported data for 6 of the 7 patients with Korsakoff's syndrome and 3 of the 5 other patients with amnesia did not suggest this possible difference between recall and recognition (Squire & Shimamura, 1986).

### Wisconsin Card Sorting Test

Table 4 shows the results for the patients with frontal lobe lesions, the amnesic patients, and two control groups. As would be expected, patients with frontal lobe lesions performed poorly on this task, achieving only 2.1 categories out of 6. Although the control group performed better (4.0 categories), the difference fell short of significance,  $t(16) = 2.12$ ,  $p = .06$ . They also committed a greater percentage of perseverative errors ( $M_s = 41.6$  and  $20.2$ , respectively), a measure that is often inversely correlated with the number of categories achieved. According to normative data for this age group, 5 of the 7 patients with frontal lobe lesions achieved fewer than the expected number of categories, and 6 of 7 patients produced more than the expected percentage of perseverative errors (Heaton, 1981). The low number of categories achieved and the high perseverative error score are characteristic of patients with frontal lobe lesions. Patients with Korsakoff's syndrome also achieved fewer categories than their control subjects ( $M_s = 3.3$  for the patients with Korsakoff patients vs.  $4.8$  for the alcoholics),  $t(11) = 1.96$ ,  $p = .08$ , and they were more perseverative ( $M_s = 25.4\%$  for the patients with Korsakoff's syndrome vs.  $16.9\%$  for the alcoholics). Finally, the patients with Korsakoff's syndrome achieved significantly fewer categories than the 5 other patients with amnesia ( $M_s = 3.3$  vs.  $5.4$ ),  $t(10) = 2.64$ ,  $p < .05$ .

### Verbal Fluency

Figure 4 shows results for the patients with frontal lobe lesions, amnesic patients, and three control groups on the test of verbal fluency. Patients with lesions of the frontal lobes produced fewer words than their control group but not significantly so (mean number of words produced was  $29.7$  for patients with frontal lobe lesions,  $37.5$  for control subjects). However, patients with left or bilateral lesions of the frontal lobes did produce significantly fewer words ( $M = 21.5$ ) than the control group,  $t(13) = 2.47$ ,  $p < .05$ , whereas patients with right frontal lobe lesions performed similarly ( $M = 40.7$ ). The amnesic patients did not differ from their control subjects.

### Dementia Rating Scale

Figure 5 shows the results for patients with frontal lobe lesions, amnesic patients, and control subjects on the Dementia Rating Scale. Patients with frontal lobe lesions performed normally on this test except on the Initiation-Perseveration subscale. The mean score for patients with left or bilateral frontal lobe lesions was  $78\%$  (range =  $70\%$ – $86\%$ ). The mean score for patients with right frontal lobe lesions was  $97\%$  (all 3 patients with right frontal lesions achieved this score). The overall mean for patients with frontal lobe lesions was  $86\%$ . The control subjects obtained a mean score of  $99\%$  (range =  $89\%$ – $100\%$ ). The overall scores obtained by patients with frontal lobe lesions on this subscale ( $86\%$ ) was lower than the score ( $99\%$ ) obtained by control subjects,  $t(16) = 3.49$ ,  $p < .01$ . The patients with Korsakoff's syndrome were also impaired on the Initiation-Perseveration subscale

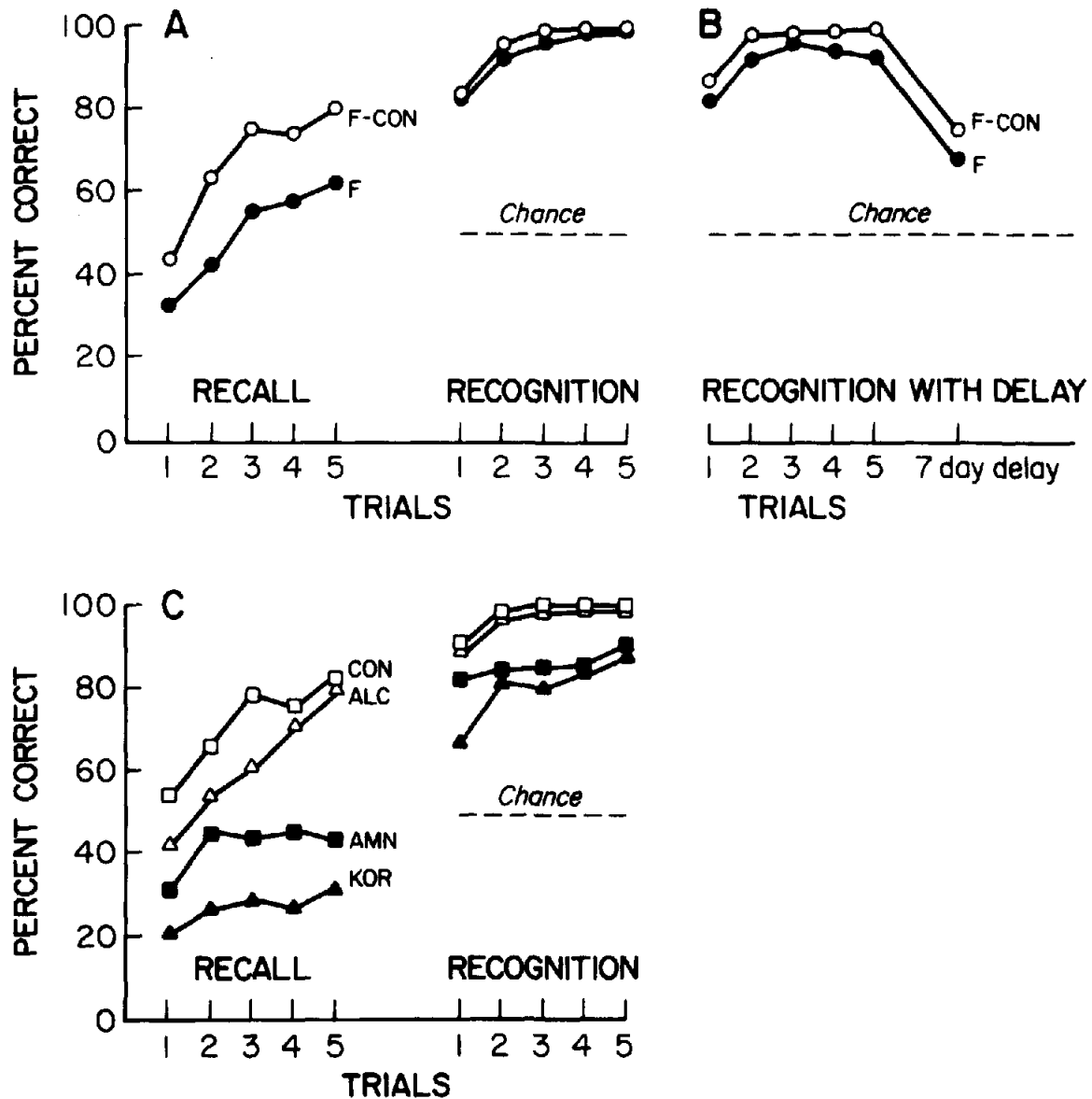


Figure 3. Performance of patients with frontal lobe lesions, amnesic patients, and control subjects on the Rey Auditory Verbal Learning Test. (A: Recall performance for 15 words during five study-test trials and yes-no recognition performance for 15 study words and 15 distractor words during five study-test trials. F = 7 patients with frontal lobe lesions; F-CON = 11 control subjects. B: A second test of yes-no recognition performance by patients with frontal lobe lesions and control subjects for 15 study words and 15 distractor words. The delayed test trial was given 7 days after the five study-test trials. C: Recall and recognition performance as in A. KOR = 7 patients with Korsakoff's syndrome; AMN = 5 other patients with amnesia; ALC = 6 alcoholic control subjects; CON = 8 healthy control subjects.)

compared with the alcoholic control subjects ( $M = 88\%$ , range = 78%–97%, for patients with Korsakoff's syndrome;  $M = 98\%$ , range = 95%–100% for alcoholic control subjects,  $t(11) = 3.79$ ,  $p < .01$ ). Finally, on the Memory subscale, both amnesic groups performed more poorly than the alcoholic control group ( $M_s = 72\%$ , 75%, and 100%, for the patients with Korsakoff's syndrome, the 5 other patients with amnesia, and alcoholic control subjects, respectively;  $t_s > 3.80$ ,  $p_s < .01$ ).

#### Release From Proactive Interference

Figure 6 shows the results for patients with frontal lobe lesions, patients with amnesia due to Korsakoff's syndrome, the 5 other patients with amnesia, and healthy control subjects. Patients with frontal lobe lesions performed similarly to the non-Korsakoff amnesic patients and the healthy control subjects. As with the other groups, their performance was significantly better on the fifth test trial when the se-

mantic category of the words was shifted, compared with the fifth test trial of the nonshift condition,  $t(6) = 5.28, p < .01$ . Patients with Korsakoff's syndrome did not show this advantage of category shift,  $t(6) = 0, p > .1$ .

## IQ

All subtests of the WAIS-R IQ Test were administered to the patients with frontal lobe lesions, their control group, and to both groups of amnesic patients. The patients with frontal lobe lesions had IQs within the normal range (Table 1), which did not differ significantly from the IQs obtained by their control group,  $t(16) = 1.58, p > .10$ . However, the patients did perform more poorly than their control group on three subtests of the WAIS-R: Digit Span,  $t(16) = 3.04, p < .01$ , Picture Arrangement,  $t(16) = 2.8, p < .01$ , and Block Design,  $t(16) = 2.3, p < .05$  (see Table 5). Despite matching groups on the Information and Vocabulary subtests of the WAIS-R, 2 subjects in the frontal control group obtained rather high Full Scale IQ scores (134 and 137). When these 2 subjects were excluded, the mean WAIS-R IQ of the remaining 9 control subjects more closely matched the mean WAIS-R IQ of the patients with frontal lobe lesions (106.0 vs. 101.1). Nevertheless, differences between the two groups on WAIS-R subtests remained for Picture Arrangement and Digit Span.

In order to ensure that none of the differences reported in this study between the patients with frontal lobe lesions and the subjects in their control group could be attributed to global intellectual differences, all the data were reevaluated excluding the 2 control subjects who obtained high IQ scores. With two exceptions, all the results remained the same when these 2 high-IQ control subjects were excluded. First, because the two high-IQ subjects performed rather poorly on the Wisconsin Card Sorting Test, the deficit observed in patients with frontal lobe lesions became even clearer in this test. Now the patients were impaired on the number of categories achieved  $t(14) = 2.87, p < .02$ . Second, on the test of verbal

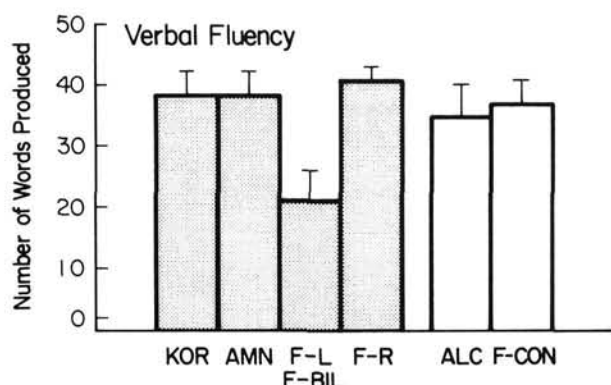


Figure 4. Performance of patients with frontal lobe lesions, amnesic patients, and control subjects on the Verbal Fluency Test. (The score is the total number of words produced in 1 min that begin with the letters F, A, or S. KOR = 7 patients with Korsakoff's syndrome; AMN = 5 other patients with amnesia; F-L, F-BIL = 2 patients with left and 2 patients with bilateral frontal lobe lesions; F-R = 3 patients with right frontal lobe lesions; ALC = 6 alcoholic control subjects; F-CON = 11 control subjects. Brackets show SE.)

learning the disparity between recall and recognition performance became more striking. Recall performance of the patients with frontal lobe lesions remained markedly impaired relative to their control group,  $F(1, 14) = 5.38, p < .05$ , whereas recognition performance was quite intact. Recognition performance by patients with frontal lobe lesions was normal on the first set of five recognition trials,  $F(1, 14) = 1.24, p > .10$ , as well as on the second set of five recognition trials,  $F(1, 14) = 3.10, p = .10$ , and on the delayed recognition test,  $t(14) = 1.69, p > .10$ . In addition, the performance of patients with frontal lobe lesions was normal on the first trial and on the week-delayed trial of the recognition test when performance was not at ceiling: ANOVA, two groups by two trials,  $F(1, 14) = 2.45, p > .10$ .

## Discussion

In the present study, tests sensitive to frontal lobe dysfunction, tests of global intellectual function, and tests of memory were administered to patients with frontal lobe lesions, two groups of amnesic patients, and control subjects. The objective was to determine whether frontal lobe pathology might account for the cognitive impairments exhibited by patients with Korsakoff's syndrome but not by other amnesic patients. The main findings were that (a) patients with frontal lobe lesions were not amnesic; they performed quite well on most of the memory tests. (b) Although they also performed well on many tests of global intellectual function, the patients with frontal lobe lesions shared with the patients with Korsakoff's syndrome deficits on two tests that were not exhibited by other (non-Korsakoff) amnesic patients: impaired performance on the Wisconsin Card Sorting Test and impaired performance on the Initiation-Perseveration subscale of the Dementia Rating Scale.

On several tests of memory (the WMS, WMS-R, Story Recall, Complex Figure Recall, Paired-Associate Learning, and the recognition portion of the Word List Recall and Recognition Test), patients with frontal lobe lesions per-

Table 4  
Wisconsin Card Sorting Test Scores

Group	Categories	% perseverative error
Frontal		
J.D.	5	25
R.L.	3	31
J.V.	4	22
M.S.	0	98
E.M.	2	10
G.Y.	1	42
M.D.	0	63
<i>M</i>	2.1	41.6
Frontal control	4.0	20.2
	3-6	7-26
Korsakoff	3.3	25.4
	0-5	12-56
Alcoholic	4.8	16.9
	3-6	10-24
Non-Korsakoff	5.4	14.4
amnesic patients	4-6	9-22

Note. Data for amnesics and control groups are means, with ranges beneath them.

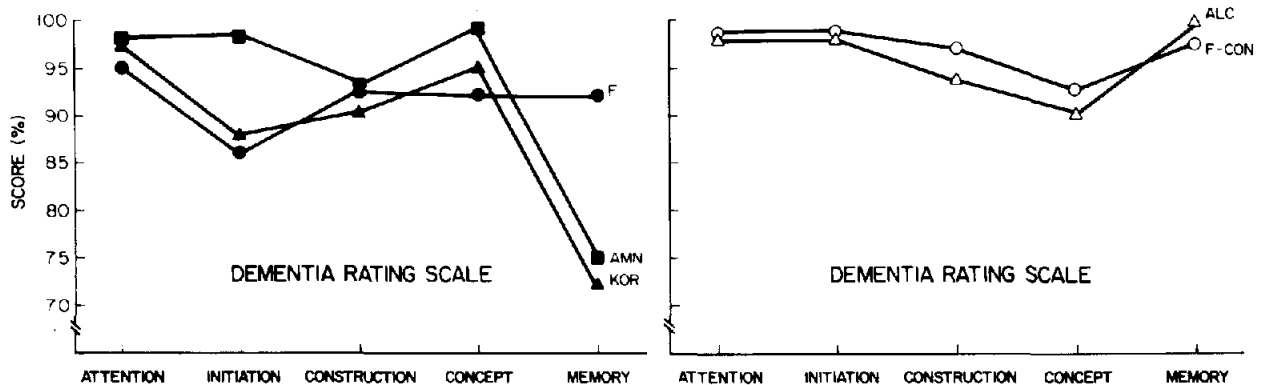


Figure 5. Performance on the Dementia Rating Scale by patients with frontal lobe lesions (F = 7), amnesic patients (KOR = 7 patients with Korsakoff's syndrome; AMN = 5 other patients with amnesia), and control subjects (ALC = 6 alcoholic control subjects, F-CON = 11 control subjects matched to the patients with frontal lobe lesions).

formed well. By contrast, both groups of amnesic patients were severely impaired on all these tests. These results make it clear that the patients with frontal lobe lesions cannot be characterized as globally or severely amnesic.

Patients with frontal lobe lesions also performed within the normal range on tests of global intellectual ability, as measured by the WAIS-R. However, they did perform poorly on the Digit Span, Picture Arrangement, and Block Design subtests. These results confirm that lesions of the frontal lobes do not substantially reduce Full Scale IQ scores (Stuss & Benson, 1986), although deficits can occur on specific subtests (Drewe, 1974; McFie & Thompson, 1972). Despite overall good performance on the WAIS-R, the patients with frontal lobe damage were impaired on the Wisconsin Card Sorting Test and on the Initiation-Perseveration subscale of the Dementia Rating Scale. These findings would be expected on the basis of results of previous studies of patients with frontal lobe lesions. The important finding was that the patients with Korsakoff's syndrome also exhibited these two deficits and that the 5 non-Korsakoff amnesic patients did not. These findings suggest that some of the cognitive deficits exhibited by patients with Korsakoff's syndrome (the Wisconsin Card Sorting Test deficit and the Initiation-Perseveration deficit) may be due to frontal lobe pathology.

Frontal lobe pathology may also contribute to the memory disorder exhibited by patients with Korsakoff's syndrome. The relevant finding was that patients with frontal lobe lesions appeared to be disproportionately impaired in recall despite good recognition performance. This conclusion must remain tentative, however. First, recognition performance was close to 100% on many of the trials. Second, on the second recognition test (Figure 3B), the patients with frontal lobe lesions did perform numerically worse than the control subjects.

Patients with Korsakoff's syndrome may also have exhibited a disproportionate deficit in recall, but this possibility requires further study. The present results show that both recall and recognition were severely impaired, but recall was somewhat more impaired than would have been expected given the level of recognition impairment. These findings suggest that frontal lobe pathology may contribute to im-

paired free recall performance in patients with Korsakoff's syndrome. Because recognition tests, such as the ones used here, are so often vulnerable to ceiling effects, this possibility requires further study.

It is possible that performance on free recall tests especially requires self-organization of information and retrieval strategies and that frontal lobe dysfunction impairs these abilities. Recognition memory performance may depend less on self-organization and retrieval strategies than performance on tests of free recall. A disproportionate deficit on tests of free recall has been reported previously for amnesic patients, some of whom performed well on the Wisconsin Card Sorting Test and other tests of frontal lobe function (Hirst et al., 1986) and for patients with frontal lobe damage (Jetter, Poser, Freeman, & Markowitsch, 1986). Further study is needed to determine the conditions under which recall may be disproportionately impaired.

Despite the similarities between patients with frontal lobe lesions and patients with Korsakoff's syndrome, one test was performed poorly only by the patients with frontal lobe lesions. Specifically, the Verbal Fluency Test was sensitive to left and bilateral frontal lobe lesions but not to Korsakoff's syndrome. Fluency tests may be less sensitive to frontal lobe pathology than some of the other tests used here (e.g., Wisconsin Card Sorting), or the patients with Korsakoff's syndrome may not have sufficient frontal lobe pathology to exhibit fluency deficits. An alternative is that particular areas of the frontal lobe important for performance on the fluency test may have been damaged in the patients with frontal lobe lesions but not in the patients with Korsakoff's syndrome. Note that the impairment exhibited by patients with Korsakoff's syndrome on a similar test, the Initiation-Perseveration subscale of the Dementia Rating Scale, probably occurred because this test not only involves a different measure of fluency (the ability to generate categorized material) but also contains separate measures of perseverative tendency.

Finally, one deficit associated with Korsakoff's syndrome that could not be attributed solely to frontal lobe dysfunction was failure to release from proactive interference. It has been suggested that this phenomenon is due to left frontal lobe dysfunction (Moscovitch, 1982). Nevertheless, the patients

## RELEASE FROM PROACTIVE INTERFERENCE

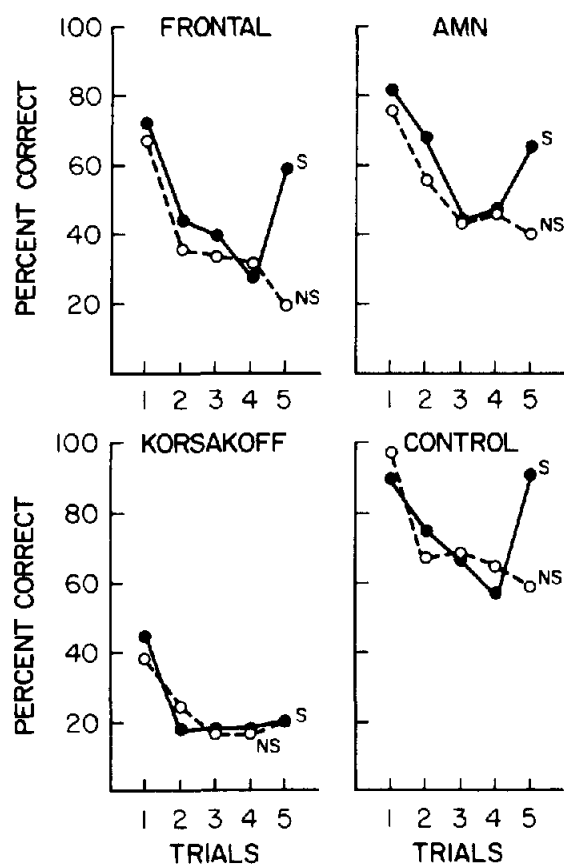


Figure 6. Release from proactive interference by 7 patients with frontal lobe lesions, 5 patients with (non-Korsakoff) amnesia (AMN), 7 patients with Korsakoff's syndrome, and 8 healthy control subjects. S = shift condition; NS = nonshift condition.

with frontal lobe lesions tested in the present study did exhibit release from proactive interference. One possibility is that the impairment observed in Korsakoff's syndrome is the result of combined damage to frontal and diencephalic regions, as suggested by Freedman and Cermak (1986).

Taken together, the findings from our study suggest that certain features of Korsakoff's syndrome may be attributed to frontal lobe dysfunction. Specifically, patients with Korsakoff's syndrome and patients with frontal lobe pathology exhibited an impairment on the Wisconsin Card Sorting Test, an impairment on the Initiation-Perseveration subscale of the Dementia Rating Scale, and possibly a disproportionate deficit in recall performance. The finding of frontal lobe dysfunction in our patients with Korsakoff's syndrome was corroborated by recent radiological (CT) findings of frontal atrophy in patients with Korsakoff's syndrome (Shimamura, Jernigan, & Squire, 1988). The cognitive impairments observed both in patients with Korsakoff's syndrome and in patients with frontal lobe lesions were not observed in the 5 other patients with amnesia. Two other cognitive deficits

Table 5  
Subtest Scores of Wechsler Adult Intelligence Scores-Revised

Group	n	Digit Span	Picture Arrangement	Block Design
Frontal				
J.D.		14	9	29
R.L.		15	4	29
J.V.		14	5	18
M.S.		8	6	14
E.M.		14	16	33
G.Y.		10	4	11
M.D.		12	2	13
M		12.4	6.5	21.0
Frontal control	11	17.4	12.3	31.4
Korsakoff	7	12.4	6.9	19.4
Non-Korsakoff amnesic patients	5	16.2	14.0	31.8
		11-21	7-19	25-39

Note. All scores are raw scores. The maximum possible for Digit Span is 28; for Picture Arrangement, 20; and for Block Design, 51.

observed in patients with Korsakoff's syndrome but not the other patients with amnesia have now been observed in patients with frontal lobe lesions (metamemory and impaired temporal order judgments). These will be reported elsewhere (Janowsky, Shimamura, & Squire, 1989; Shimamura, Janowsky, & Squire, 1988).

One possible explanation of the findings is that diencephalic damage causes or contributes to the cognitive deficits that distinguish Korsakoff's syndrome from other etiologies of amnesia. By this view, diencephalic damage, which is prominent in Korsakoff's syndrome, produces some of the same deficits that are observed in patients with circumscribed frontal lobe lesions. This possibility seems unlikely. First, patient M.G., who has bilateral thalamic lesions, did not exhibit signs of frontal lobe damage in the present study. Second, it should be noted that patient N.A., who has severe amnesia for verbal material due to a unilateral left diencephalic lesion (Kaushal, Zetlin, & Squire, 1981; Squire, Amaral, Zola-Morgan, Kritchevsky, & Press, in press), does not exhibit signs of frontal lobe damage. Specifically, he performed normally on the Wisconsin Card Sorting Test (six categories) and on the Initiation-Perseveration subscale of the Dementia Rating Scale (100% correct; Squire & Shimamura, 1986). Moreover, his recall and recognition score on the Rey Auditory Verbal Learning Test was similar to the scores obtained by the patients with amnesia due to anoxia and ischemia (percentage correct on recall 67, 40, 53, 47, 40; percentage correct on recognition 77, 93, 97, 100, 100; Squire & Shimamura, 1986). In addition, he showed normal release from proactive interference (Squire, 1982).

The good memory performance of our patients with frontal lobe lesions can be contrasted with the performance of patients with lesions of the basal forebrain. Some of these patients exhibit persisting memory impairment, together with signs of frontal lobe dysfunction such as inappropriate affect and inattention (Alexander & Freedman, 1984; A. Damasio,

Graff-Radford, Eslinger, Damasio, & Kassell, 1985; Phillips, Sangalang, & Sterns, 1987). The memory impairment in these patients occurs after damage to basal forebrain structures and does not require direct damage to prefrontal cortex (Alexander & Freedman, 1984; Phillips, Sangalang, & Sterns, 1987). The syndrome therefore appears to depend on the disruption of normal function in the basal forebrain. Thus, studies of patients with basal forebrain damage may help to further delineate the brain regions that contribute to memory performance.

Finally, the present findings are relevant to discussions about the forms of memory impairment that can occur in neurological patients and to questions about the appropriate definition of amnesia. One possibility is to consider amnesia as a broad impairment of learning and memory that results from lesions of the diencephalon, the medial temporal region, the frontal lobes, and possibly other regions. That is to say, one could suppose that the complete amnesic syndrome includes a broad spectrum of cognitive deficits that influence memory performance, for example, deficits in attention, encoding, memory storage, and retrieval. Another possibility is to suppose that there is a core amnesic disorder on which other cognitive deficits can be superimposed. In this view, certain functions are specifically linked to memory, but other, qualitatively different (nonmemory) disorders can also occur in the same patient.

The present findings suggest that a compromise can be made between the two positions just outlined (see Schacter, 1987; Shimamura, in press; Squire, 1987; for further discussion of this issue). Confusion over whether a patient is amnesic need not arise as long as it is recognized that memory impairment can take different forms and be composed of a variety of symptoms. The term *amnesia* might be best reserved for *severe* and *selective* disorders of memory. Patients identified as amnesic should exhibit scores within the normal range on tests of intelligence and language. Patients with circumscribed damage to frontal lobes are not amnesic, because the memory performance of these patients is generally good.

The severe deficits in recall and recognition that are the hallmarks of amnesia are associated with selective, bilateral lesions in the medial temporal region, the diencephalic midline, and in some cases with basal forebrain lesions. Among such amnesic patients one can expect the memory deficit to take different forms, depending on the extent of the underlying neuropathology in these regions and on the extent of neuropathology in other regions. In this study, patients with Korsakoff's syndrome, for example, had a severe memory disorder that seemed to include additionally a disproportionate deficit in recall as well as other cognitive deficits. These additional deficits were linked to frontal lobe dysfunction, because they were also observed in patients with frontal lobe lesions who were not globally amnesic. Furthermore, other non-Korsakoff amnesic patients did not exhibit these deficits. Consequently, severe, global amnesia can occur without the appearance of frontal symptoms. At the same time, frontal symptoms do more than superimpose independent cognitive deficits. Frontal symptoms contribute to the memory disorder itself and influence its character.

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