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RAPID COMMUNICATION

The Human Perirhinal Cortex and Recognition Memory

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ABSTRACT: The importance of the perirhinal cortex for visual recognition memory performance is undisputed. However, it has not been clear whether its contribution to performance is mainly perceptual, or mainly mnemonic, or whether the perirhinal cortex contributes to both perception and memory. We determined the effects of medial temporal lobe damage that includes complete damage to the perirhinal cortex in two amnesic patients by assessing recognition memory for complex visual stimuli across delays from 0 to 40 s. These patients, as well as six other amnesic patients with damage limited to the hippocampal formation or diencephalic structures, exhibited intact recognition memory at delays of 0–2 s and a delay-dependent memory impairment at delays of 6 s and longer. Additionally, the patients with damage to the perirhinal cortex performed worse than the other amnesic patients at delays of 25 s and longer. The findings suggest that the perirhinal cortex is not important for visual perception or immediate memory. In this respect, the findings for perirhinal cortex resemble the findings for other medial temporal lobe structures, including the hippocampus. *Hippocampus 1998;8:330–339.*

KEY WORDS: medial temporal lobe; inferotemporal cortex; visual perception; short-term memory; immediate memory

Recognition memory refers to the ability to identify as familiar a stimulus that has been presented previously. In humans, monkeys, and rats, this capacity depends on the integrity of a medial temporal cortical memory system that includes the hippocampus, dentate gyrus, subicular complex, and the adjacent entorhinal, perirhinal, and parahippocampal cortices. Of these cortical regions, the perirhinal cortex has recently been the focus of considerable interest. In monkeys and rats, lesions that include the perirhinal cortex impair performance on tests of visual recognition including the delayed matching or nonmatching to sample test (Murray and Mishkin, 1986; Zola-Morgan et al., 1989, 1993; Meunier et al., 1993; Suzuki et al., 1993; Eacott et al., 1994; Mumby and Pinel, 1994; Gaffan, 1995; Buckley et al., 1997) and the visual paired comparison test (Bachevalier et al., 1993; Ennaceur et al., 1996; Ennaceur and Aggleton, 1997). Additionally, in monkeys deactivation of the inferotemporal cortex, including the perirhinal cortex, impairs visual recognition memory (Horel et al., 1987). On the basis of lesions involving the separate components of the medial temporal lobe, the contribution of the perirhinal cortex to visual recognition memory appears to be greater than that of any other single structure. In addition, single-unit recordings from the inferotemporal cortex, including the perirhinal cortex, of behaving monkeys have demonstrated response properties consistent with a role of perirhinal cortex in visual recognition memory. For example, neurons in the perirhinal cortex demonstrate an enhanced response to the matching stimulus in a delayed matching to sample task (Miller and Desimone, 1994). Additionally, neurons in this region develop responses to paired stimuli in a visual paired associates task (Sakai and Miyashita, 1991; Higuchi and Miyashita, 1996).

Although the importance of the perirhinal cortex for visual recognition memory performance is undisputed, there is uncertainty concerning its specific contribution. One view is that the perirhinal cortex is involved in the perceptual processing of visual stimuli (Eacott et al., 1994) or the visual identification of individual objects (Buckley and Gaffan, 1997). Thus, Eacott et al. (1994) reported that monkeys with lesions that included the perirhinal cortex were impaired in simultaneous matching to sample with trial-unique stimuli. Under these conditions, the matching to sample task assesses visuoperceptual ability rather than memory. However, a clear interpretation of these data is difficult for two reasons. First, on two separate administrations of this test, the deficit on simultaneous matching to sample was quite small (the operated animals performed at about 90% and 98% correct, 5% and 1% below the level of the control animals, respectively). Because statistical analyses of these data were not reported, it is unclear whether these scores reflect significant impairment. Second, with an analysis of variance that included longer delays, the

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authors reported a significant group × delay interaction, which leaves open the possibility that lesions of the perirhinal cortex impair performance in a delay-dependent manner, as would be expected if the lesions impair memory (see below).

Buckley and Gaffan (1997) reported that a deficit on concurrent discrimination learning following lesions of the perirhinal cortex in monkeys emerged when greater demands were placed on the object-identification system, that is, when the monkeys were presented with larger numbers of problems and larger numbers of distractors. However, the monkeys were unimpaired in the condition with the most distractors. Additionally, all the monkeys in this study and other studies that were designed to determine the effects of perirhinal lesions on concurrent discrimination learning tasks sustained at least some inadvertent damage to adjacent visual association area TE (Buckley and Gaffan, 1998a,b). Even a small amount of inadvertent damage to area TE has been shown to impair performance on the concurrent discrimination learning task (Buffalo et al., 1998).

A second view is that, like other components of the medial temporal lobe, the perirhinal cortex is primarily involved in memory, that is, it is required only after perceptual processing of the stimuli has been completed. By this view, the effect of a lesion should be detectable only after some delay. In both monkeys and humans, a critical characteristic of the recognition memory impairment following medial temporal lobe damage is that long-term memory is affected selectively. Thus, immediate (short-term) memory is intact in amnesic patients with hippocampal formation damage (Cave and Squire, 1992), as well as in patient H.M., who had more extensive medial temporal lobe damage (Drachman and Arbit, 1966; Sidman et al., 1968). However, the perirhinal cortex was partially spared in patient H.M. (Corkin et al., 1997) and apparently not damaged at all in the other patients who have been studied. Similarly, monkeys with lesions of the hippocampus and adjacent cortex (Alvarez-Royo et al., 1992; Alvarez et al., 1994), as well as monkeys with larger lesions that included the hippocampus, amygdala, and adjacent cortex (Overman et al., 1990), exhibit impaired memory performance at long retention intervals and intact performance at short retention intervals. Yet the perirhinal cortex was partially spared in each of these studies. Preliminary reports of monkeys with lesions limited to the perirhinal cortex suggest that the perirhinal cortex is important for delay-dependent memory and not for visual perception or immediate memory (Buffalo et al., 1995; Zola et al., 1997).

This dissociation between intact short-term memory (good retention of items for up to a few seconds) and impaired long-term memory (poor retention of items across a delay of many seconds or minutes) is crucial for understanding the function of medial temporal lobe structures. Specifically, the finding of intact immediate memory allows the interpretation that impaired performance at long delays is a memory impairment and that the impairment is not derivative from attentional or perceptual deficits. It is not known whether this same dissociation between short-term and long-term memory impairment would be obtained following complete damage to perirhinal cortex in humans.

The purpose of the present study was to assess visual recognition memory for complex visual stimuli in amnesic patients with bilateral damage that includes the perirhinal cortex and in amnesic patients with damage that spares this region. Recognition memory for complex visual stimuli was assessed across six delay intervals ranging from 0 to 40 s. In this way, we investigated the contribution of the perirhinal cortex to both immediate memory and long-term visual recognition memory.

MATERIALS AND METHODS

Participants

Two groups of patients were studied (Tables 1 and 2). The first group consisted of two men (E.P. and G.T.) who developed profound anterograde and retrograde amnesia after herpes simplex encephalitis and who have damage to the temporal lobe bilaterally. The second group consisted of six other amnesic patients (AMN) with less severe memory impairment and more circumscribed damage than E.P. and G.T.

Patients E.P. and G.T.

Patient E.P. has extensive bilateral medial temporal lobe damage, confirmed by magnetic resonance imaging (MRI) (Squire and Knowlton, 1995), which includes the hippocampal formation, the amygdaloid complex, and the perirhinal and parahippocampal cortices. In humans, the perirhinal cortex extends from the temporal pole to approximately the rostral limit of the lateral geniculate nucleus (Amaral and Insausti, 1990). On the ventral surface, the perirhinal cortex lines the banks of the collateral sulcus and is bordered medially by the entorhinal cortex and laterally by inferotemporal cortex (Amaral and Insausti, 1990; Insausti et al., 1994). E.P.'s damage is primarily medial temporal but also involves the laterally adjacent fusiform gyrus at some levels (Figs. 1A, 2B). Aside from his profound amnesia, E.P. is also anomic, scoring 42 of 60 on the Boston Naming Test (Kaplan et al., 1983). E.P. also exhibited some behavioral evidence of frontal lobe dysfunction: on the Wisconsin Card Sorting Test, 0 categories were sorted, and there were 51% perseverative errors (Heaton, 1995); on the FAS Test of Word Fluency, 18 words were produced, which placed him below the 15th percentile (Benton and Hamsher, 1976).

Patient G.T. has extensive bilateral temporal lobe damage confirmed by MRI (Figs. 1B, 3). The damage extends through the anterior 7.0 cm of his left temporal lobe and the anterior 5.0 cm of his right temporal lobe. The lesion includes bilaterally the hippocampal formation, the amygdaloid complex, the perirhinal and parahippocampal cortices, and the inferior, middle, and superior temporal gyri (Figs. 1B, 3). G.T. is also anomic, scoring 18 of 60 on the Boston Naming Test (Kaplan et al., 1983). On the FAS Test of Word Fluency, he produced 36 words, which placed him in the 65–69th percentile.

Patients E.P. and G.T. were 74 and 61 years of age, respectively, at the beginning of the study. Each had 12 years of education. Immediate and delayed (12-min) recall of a short prose passage averaged 3 and 0 segments, respectively, for patient E.P. and 0 and

TABLE 1.

Characteristics of Amnesic Patients*

Patient	Lesion	Age (years)	WAIS-R IQ	WMS-R				
				Attention	Verbal	Visual	General	Delay
E.P.	MTL[a]	74	101	94	59	92	68	56
G.T.	TL	61	92	120	57	<50	<50	<50
A.B.	HF[b]	59	104	87	62	72	54	<50
L.J.	HF	60	98	105	83	60	69	<50
R.C.	Dien	80	106	115	76	97	80	72
N.F.	Dien[c]	61	94	91	62	73	53	<50
P.N.	Dien	69	99	81	77	73	67	53
J.W.	Dien	60	98	104	65	70	57	57
Mean	(n = 6)	64.8	99.8	97.2	70.8	74.2	63.3	55.3

*The WAIS-R and the WMS-R indices yield a mean score of 100 in the normal population with a standard deviation of 15. The WMS-R does not provide scores for individuals who score below 50. Therefore, the four scores below 50 were scored as 50 for calculating a group mean. WAIS-R, Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981); WMS-R, Wechsler Memory Scale-Revised (Wechsler, 1987). MTL, medial temporal lobe; TL, temporal lobe; HF, hippocampal formation; Dien, diencephalon. Both E.P. and G.T. have bilateral damage to the perirhinal cortex and parahippocampal cortex. The other amnesic patients do not.

[a]E.P.'s damage extends somewhat beyond the medial temporal lobe (see text).

[b]The lesion site has not been confirmed radiologically but is strongly supported by the etiology of amnesia (see text).

[c]N.F. also has bilateral reduction in the size of the hippocampal formation.

0 segments, respectively, for patient G.T. (Gilbert et al., 1968; maximum number of segments, 21). Scores on other memory tests are shown in Tables 1 and 2. The scores on the Dementia Rating Scale were 118 and 106, respectively (Mattis, 1976; maximum score, 144). E.P. and G.T. lost most of their points on the memory subportion (15 and 17, respectively; maximum score, 25). Additionally, E.P. lost eight points on the conceptualization subportion, and G.T. lost 15 points on the Initiation/Perseveration subportion.

Amnesic Patients

Six amnesic patients (four men and two women) participated. Four patients with Korsakoff's syndrome had participated in quantitative MRI, which demonstrated reductions in the volume of the mammillary nuclei [for R.C., J.W., and P.N. (Squire et al., 1990); for N.F., unpublished observations]. N.F. also has bilateral reduction in the size of the hippocampal formation. Of the remaining two patients, one (L.J.) had bilateral reduction in the size of the hippocampal formation confirmed by MRI (Reed and Squire, 1998). Patient L.J. became amnesic during a 6-month period that began in 1988 with no known precipitating event. Her memory impairment has remained stable since that time. The other patient (A.B.), who is unable to participate in MRI studies, became amnesic in 1976 after an anoxic episode following cardiopulmonary arrest and is presumed to have hippocampal damage on the basis of this etiology. Other patients with amnesia due to anoxia have proved to have hippocampal formation damage at histological examination (Cummings et al., 1984; Rempel-Clower et al., 1996).

The six patients averaged 64.8 years of age at the time of the study. They averaged 13 years of education and had an average Wechsler Adult Intelligence Scale-Revised (WAIS-R) IQ of 99.8. Individual IQ and Wechsler Memory Scale-Revised (WMS-R) index scores appear in Table 1. Scores for other memory tests appear in Table 2. Note that the scores on the word recall test in Table 2 are above zero because on this test of immediate recall, several items can be retrieved from immediate memory. Immediate and delayed (12-min) recall of a short prose passage averaged 4.7 and 0 segments, respectively (21 segments total; Gilbert et al., 1968). The mean score on the Dementia Rating Scale (Mattis, 1976) was 130.7 (maximum possible, 144; range, 125–134). Most of the points lost on this test were from the memory subportion (mean, 7.3 points lost). The average score on the Boston Naming Test was 56.2 (maximum possible, 60; range, 55–57). Scores for normal subjects on these same tests can be found elsewhere (Janowsky et al., 1989; Squire et al., 1990).

Control group

The participants in the control group were employees or volunteers at the San Diego Veterans Affairs Medical Center or were recruited from the retirement community of the University of California, San Diego. The group consisted of five men and three women who matched the amnesic patients with respect to the mean and range of their ages, years of education, and scores on the Information and Vocabulary subtests of the WAIS-R (Wechsler, 1981). They averaged 67.5 years of age (range, 52–76), 12.9

TABLE 2.

Performance on Standard Memory Tests by Amnesic Patients*

Patient	Diagram recall	Paired associates (%)			Word recall	Word recognition (%)	50 words	50 faces
E.P.	0	0	0	0	24	65	24	28
G.T.	0	0	0	0	20	70	27	27
A.B.	4	1	1	1	33	83	32	33
L.J.	3	0	0	0	40	93	33	29
R.C.	3	0	0	3	19	85	37	30
N.F.	4	0	0	2	36	76	28	27
P.N.	2	1	1	1	29	83	31	31
J.W.	4	0	0	2	28	96	29	34
Mean (n = 6)	3.3	0.3	0.3	1.5	30.8	86.0	31.7	30.7
Control (n = 8) Mean	20.6	6	7.6	8.9	71.3	97.7	41.1	38.1

*The diagram recall score was based on delayed (12-min) reproduction of the Rey-Osterrieth Complex Figure (Osterrieth, 1944; maximum score, 36). The average score for copying the figure was 28.8, a normal score (Kritchevsky et al., 1988). The paired-associate scores were the number of word pairs recalled on three successive trials (maximum score, 10 / trial). The word recall score was the percentage of words identified correctly on five successive study-test trials (Rey, 1964). The word recognition score was the percentage of words identified correctly by yes-no recognition across five successive study-test trials. The scores for words and faces were based on a 24-h recognition test of 50 words or 50 faces (modified from Warrington, 1984; maximum score, 50; chance, 25). G.T.'s scores were obtained after delay of 5 min, not 24 hrs. The mean scores for normal controls shown for these tests are from Squire and Shimamura (1986).

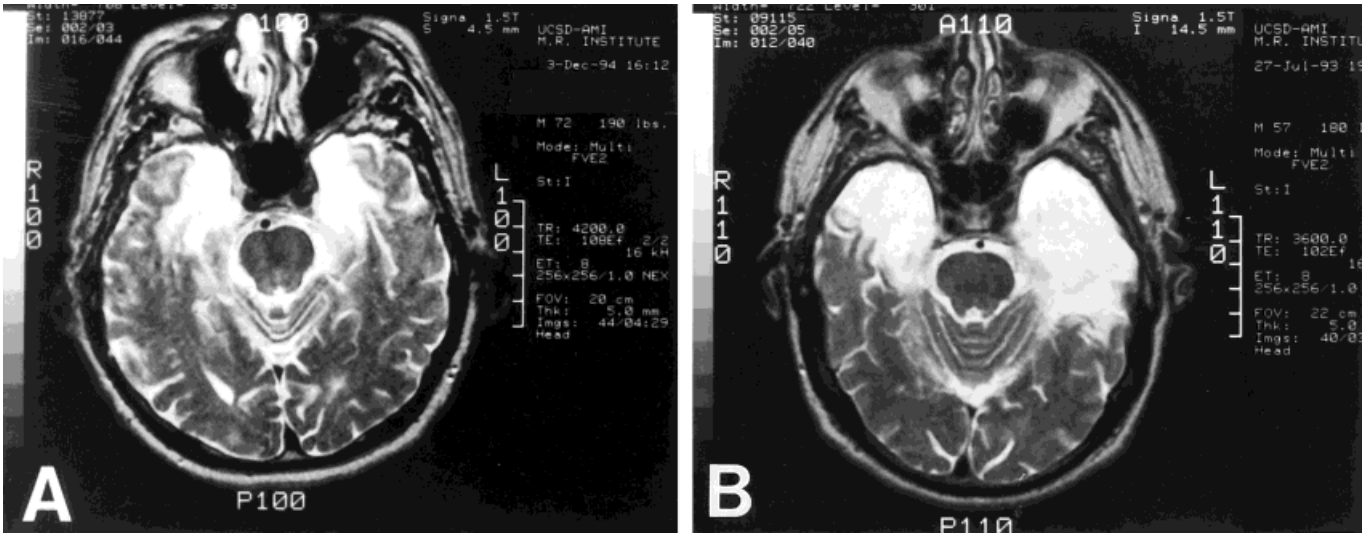


FIGURE 1. For E.P. (A), an axial T_2-weighted image through the temporal lobe shows the extent of bilateral medial temporal lobe damage, which extends caudally from the temporal pole and damages bilaterally the perirhinal cortex, the entorhinal cortex, the parahippocampal cortex, the amygdaloid complex, and the hippocampal region (CA fields, dentate gyrus, and subicular complex). The lesion extends laterally to include the fusiform gyrus at some levels. Finally, reduced volume of the insular cortex and inferotemporal gyrus is apparent bilaterally, although it is unclear whether this differs from atrophy due to normal aging. R, right; L, left. For G.T. (B), an axial T_2-weighted image through the temporal lobe shows the damage extending through the anterior 7.0 cm of his left temporal lobe and through the anterior 5.0 cm of his right temporal lobe. The lesion includes bilaterally the amygdaloid complex, hippocampus, entorhinal, perirhinal, and parahippocampal cortices as well as the inferior, middle, and superior temporal gyri. There is also bilateral damage in the insular cortex, medial and orbitofrontal cortex, and cingulate gyrus. R, right; L, left.

years of education, and 20 and 53.4 on the Information and Vocabulary subtests, respectively (amnesic patients, 18.8 and 52.8, respectively). Immediate and delayed recall of the short prose passage averaged 6.6 and 5.1 segments, respectively.

Procedure

Subjects were seated in front of a laptop computer in a darkened testing room. For each trial, four complex designs were presented one at a time at the top of the screen (Fig. 4). Each of the four designs was presented for 1 s with a 1-s interstimulus interval. Then, after a delay of either 0, 2, 6, 10, 25, or 40 s, another design (the test stimulus) was presented at the bottom of the computer screen. The subjects were asked to press the "yes" button if they thought that the test stimulus was the same as one they had just seen and to press the "no" button if they thought that the test stimulus was not one they had just seen. Subjects were allowed 1.5 s to respond. [Four patients (A.B., P.N., E.P. and G.T.) who were unable to respond consistently within 1.5 s during practice sessions were given 4 s to respond during testing.] If the subject made a correct response, a high tone was sounded, and they pressed the space bar to go to the next trial. If they made an incorrect response, a low tone was sounded, they waited for 5 s, and then pressed the space bar to go to the next trial. The computer generated new designs for every trial, following the algorithm of Miyashita et al. (1991).

Each testing session consisted of three blocks (32 trials/block) with each block assigned to a different delay interval. For each block, there were 16 "yes" trials and 16 "no" trials. For the 16 "yes" trials, the test stimulus equally often matched the design that had been presented in the first, second, third, and fourth positions (four trials for each of the four presentation positions). Each of the eight control subjects and each of the six amnesic patients participated in four test sessions for a total of 2 blocks (64 trials) at each of the six delays (384 total trials). The order in which the testing blocks were given within and across test sessions was counterbalanced across subjects. To obtain a more accurate measure of individual ability for patients E.P. and G.T., they received 12 and 9 sessions, respectively. E.P. received six blocks (192 trials) at each of the six delays (0, 2, 6, 10, 25, and 40 s) for a total of 1,152 trials. G.T. received a total of 832 trials. He received six blocks (192 trials) at each of the four shorter delays (0, 2, 6, and 10 s) but only one block (32 trials) at each of the two longer delays (25 and 40 s) because of his extremely poor performance at these delays.

RESULTS

Delay Effects

Discrimination accuracy scores (d'; Green and Swets, 1966) for the six delays are presented for the eight control subjects, six amnesic patients, and patients E.P. and G.T. in Figure 5A. Scores were collapsed across presentation positions and averaged for the

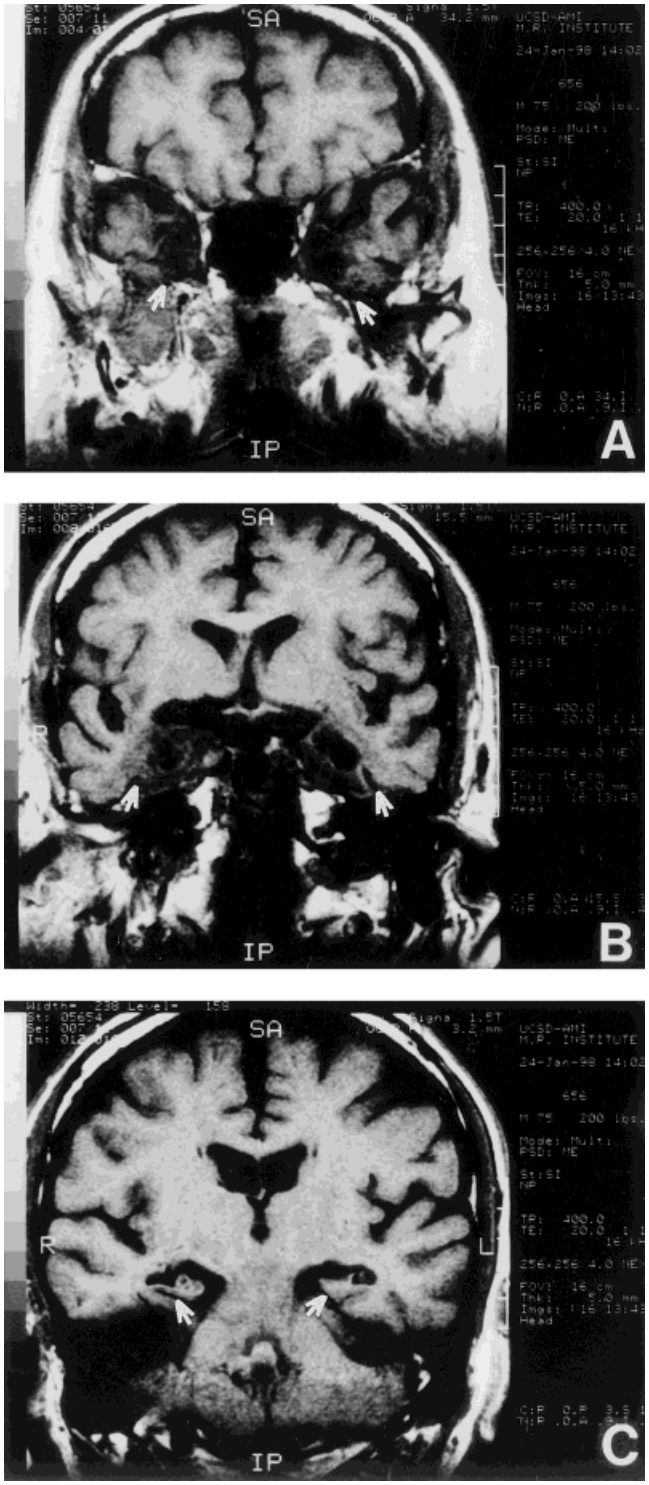


FIGURE 2. For E.P., three coronal T_1-weighted images, 2.0 cm apart, through the temporal lobe are arranged from rostral (A) to caudal (C). Damaged tissue is indicated by darker signal and includes all tissue medial to the arrowheads. Slice thickness = 5.0 mm. A: At the level of the temporal polar region, the damage is restricted to the medial aspects of the temporal poles bilaterally. B: At the level of the amygdala, the damage includes all of the amygdala, entorhinal cortex, and perirhinal cortex, as well as the laterally adjacent fusiform gyrus bilaterally. C: More caudally, at the level of the hippocampus, the damage spares the fusiform gyrus and is restricted to the medial portion of the temporal lobes bilaterally. The damage includes the hippocampal region and the parahippocampal gyrus, which at this level is parahippocampal cortex.

short, middle, and long delays. A two-way repeated measures ANOVA comparing the performance of the control group and the amnesic group across the three delay intervals (short, middle, and long) revealed a marginally significant effect of group [$F(1,12) = 4.23$; $P < 0.07$], a significant effect of delay [$F(2, 24) = 8.48$; $P < 0.01$], and a significant group × delay interaction [$F(2, 24) = 5.82$; $P < 0.01$]. The amnesic patients performed similarly to the control subjects at the short delays ($P > 0.50$). However, at the middle and long delays, the amnesic patients were significantly impaired (middle delays, $P < 0.05$; long delays, $P < 0.01$).

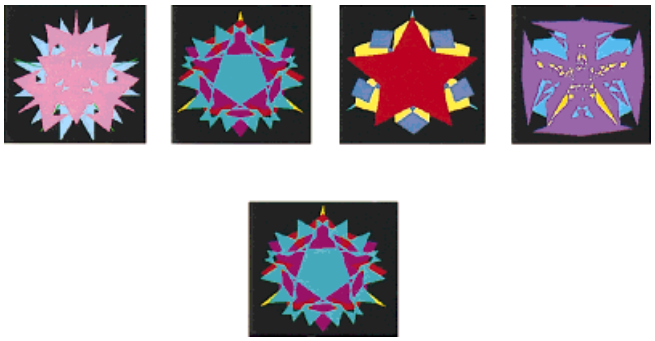


FIGURE 4. The structure of a single trial. Four complex designs were presented one at a time at the top of the computer screen. Each design was presented for 1 s, with a 1-s interstimulus interval. Then, after a variable delay (0, 2, 6, 10, 25, or 40 s), the test stimulus was presented at the bottom of the computer screen and the subjects decided (yes or no) whether or not the test stimulus was one of the designs they had just seen.

At the short delays, patients E.P. and G.T. both performed as well as the control subjects and the other amnesic patients (E.P., 1.09; G.T., 1.10; CON, 1.03; AMN, 1.06). By contrast, at the middle delays, patients E.P. and G.T. performed worse than the control subjects (E.P., 0.75; G.T., 0.18; CON, 0.99); additionally, at the middle delays, patient G.T. performed worse than the other amnesic patients (AMN, 0.55). Indeed, G.T.'s performance (0.18) was worse than the performance of all the other subjects and not significantly above chance ($P > 0.20$). Patient E.P. (0.75) performed significantly above chance ($P < 0.02$) but more poorly than six of the eight CON subjects and more poorly than one of the six AMN patients. At the long delays, both patients E.P. and G.T. performed more poorly than all the other subjects (E.P., 0.17; G.T., 0.15; CON, 0.92; AMN, 0.41), although patient E.P. did score measurably above chance ($P < 0.02$). Patient G.T. was tested only once at the long delays. He obtained 17 correct trials out of 32, which was no better than chance (binary test; $P > 0.10$).

Figure 5B shows percent correct scores for the six delays. The findings were the same when the data were analyzed using percent

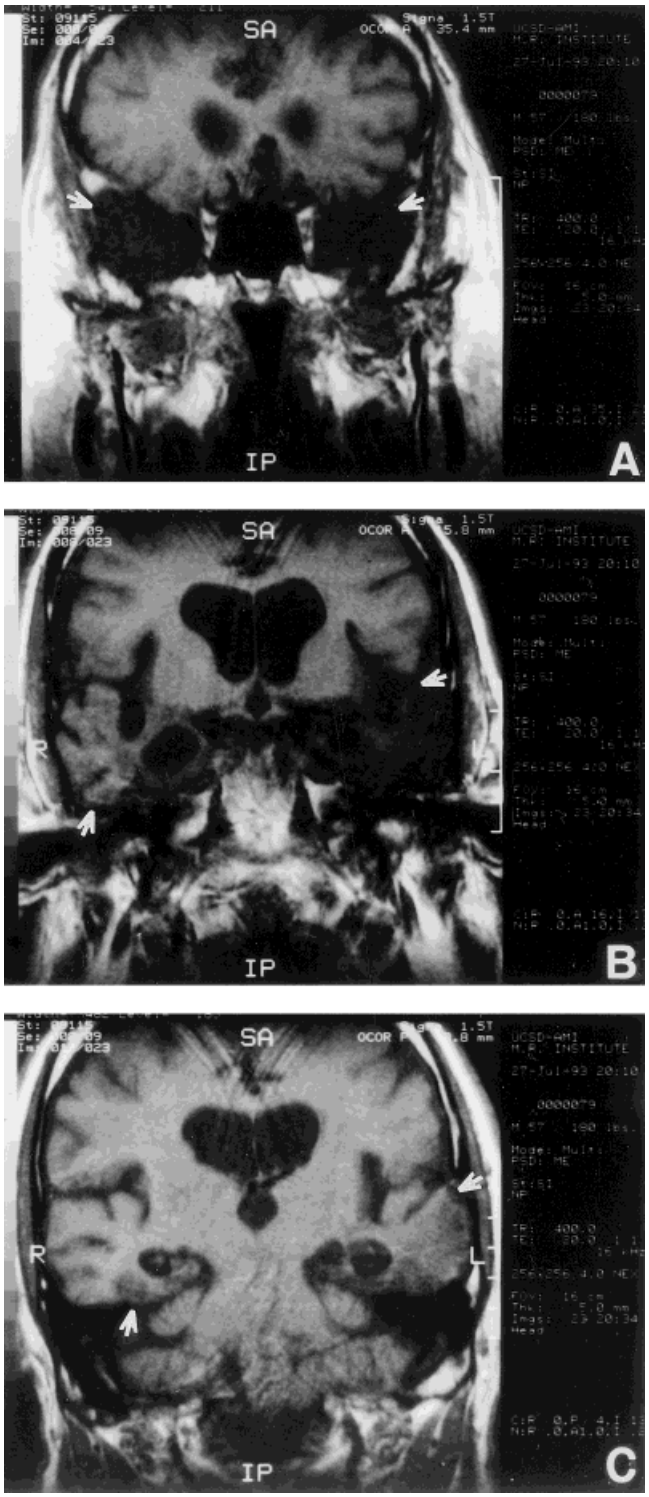
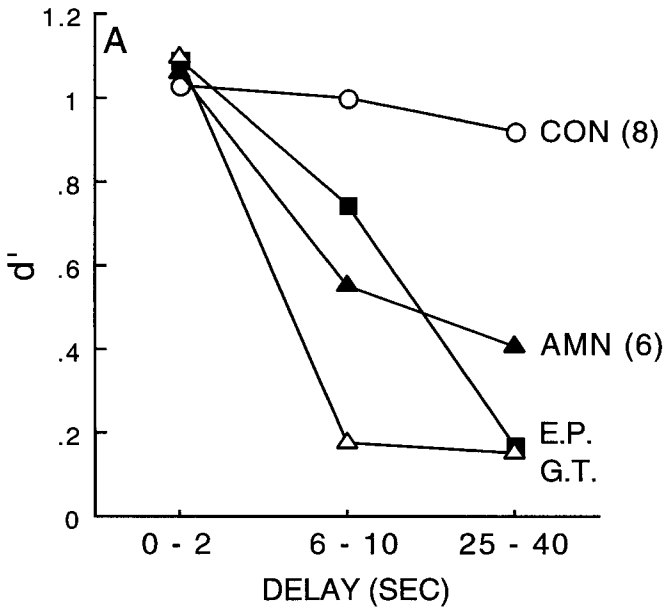


FIGURE 3. For G.T., three coronal T_1-weighted images, 2.0 cm apart, through the temporal lobe are arranged from rostral (A) to caudal (C). Damaged tissue is indicated by darker signal and includes all tissue medial to the arrowheads. Slice thickness = 5.0 mm. A: At the level of the temporal polar region, the entire temporal lobe is damaged bilaterally. B: At the level of the amygdala, the damage includes the amygdala, entorhinal cortex, perirhinal cortex, and fusiform gyrus bilaterally. On the right, the damage extends laterally to include part of the inferotemporal gyrus. On the left, the damage extends through all of the temporal lobe, including the inferior, middle and superior temporal gyri. C: More caudally, at the level of the hippocampus, the damage includes the hippocampal region and the parahippocampal gyrus bilaterally (at this level, parahippocampal cortex). On the right, the damage includes the fusiform gyrus; on the left, the damage extends laterally to include the fusiform gyrus as well as the inferior, middle, and superior temporal gyri.



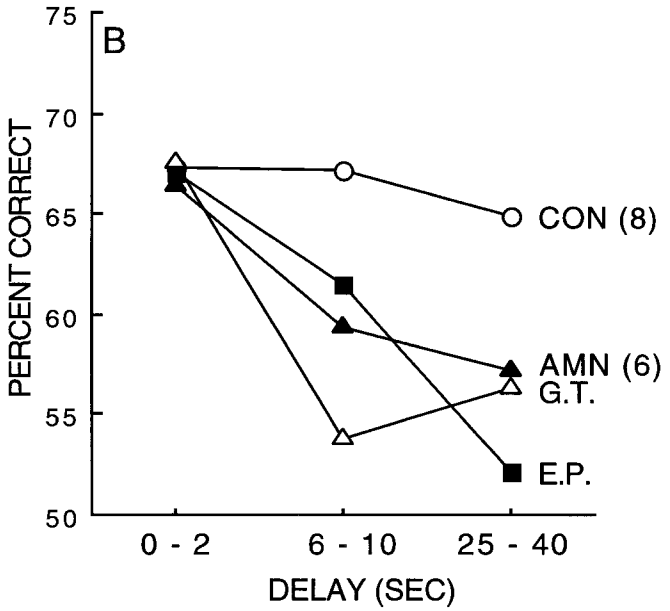


FIGURE 5. A: Discrimination accuracy (d') for the six delays (0–2 s, 6–10 s, and 25–40 s) for normal controls (CON), amnesic patients (AMN), and patients E.P. and G.T. For the CON subjects and AMN patients, standard errors of the mean ranged from 0.07 to 0.15. B: Percent correct scores for the six delays (0–2 s, 6–10 s, and 25–40 s) for normal controls (CON), amnesic patients (AMN), and patients E.P. and G.T.

correct scores as when the data were analyzed using d' scores. The percent correct scores show that intact performance by the amnesic patients at the short delays (0 and 2 s) was not an artifact of a ceiling effect.

Primacy and Recency Effects

Figure 6 shows d' accuracy scores across the four presentation positions for the CON subjects for the short, middle, and long delays (0–2-s delays, 6–10-s delays, and 25–40-s delays). A two-way repeated measures ANOVA revealed no significant effect of delay ($P > 0.30$), a significant effect of position [$F(3, 21) = 3.93$; $P < 0.03$], and a significant delay × position interaction [$F(6, 21) = 2.87$; $P < 0.02$]. The interaction indicates that, as the length of the delay increased, performance improved at the first position (primacy) and decreased at the fourth position (recency). The improvement at the first position was not significant ($P > 0.20$); the decrease in performance at the fourth position was highly significant ($P < 0.01$). This pattern of performance is consistent with that reported previously for younger control subjects (Wright et al., 1985). One difference between the findings for the two studies is that Wright et al. (1985) observed a significant increase in performance at the first presentation position as the retention interval increased. Our older subjects exhibited a numerical increase in performance at the first presentation position with increasing retention interval, but the improvement was not significant.

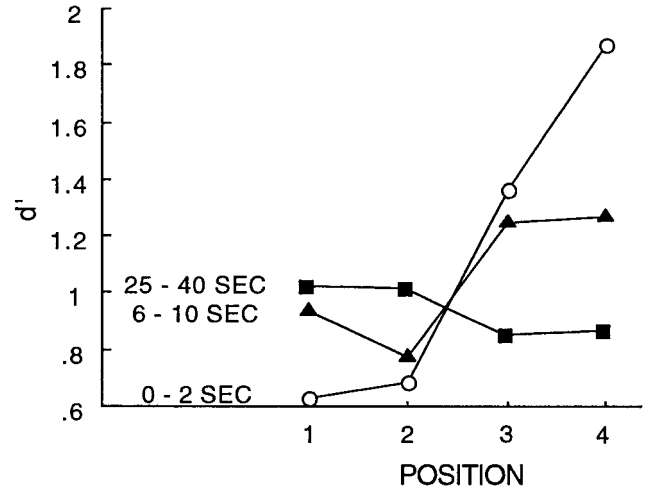


FIGURE 6. Discrimination accuracy (d') for the eight normal controls (CON) across the four presentation positions and the short, middle, and long delays (0–2 s, 6–10 s, and 25–40 s). Standard errors of the mean ranged from 0.14 to 0.29.

Discrimination Accuracy: Position Effects

Figure 7 shows d' scores for the six delays at each presentation position. Scores are averaged for the short (0–2-s), middle (6–10-s), and long (25–40-s) delays. A two-way repeated measures ANOVA comparing the performance of the control group and the amnesic group across the three delay intervals (short, middle, and long) revealed a marginally significant effect of group [$F(1, 12) = 3.59$; $P < 0.09$], a significant effect of delay [$F(2, 24) = 10.47$; $P < 0.01$], and a significant group × delay interaction [$F(2, 24) = 3.73$; $P < 0.04$]. Additionally, this analysis revealed a significant effect of position [$F(2, 24) = 9.09$; $P < 0.01$] and a significant delay × position interaction [$F(2, 24) = 7.28$;

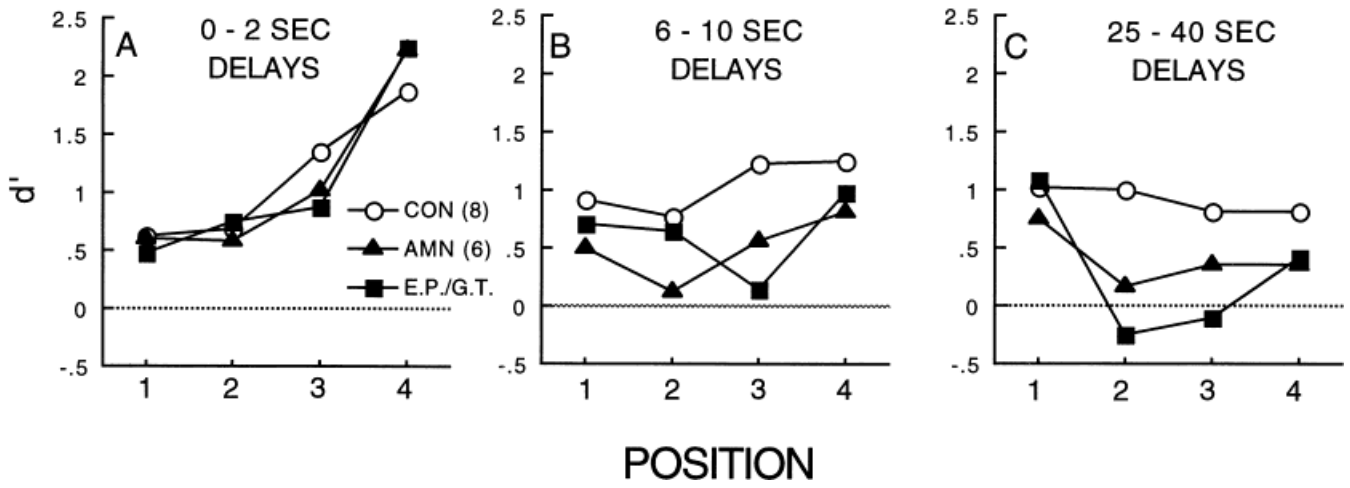


FIGURE 7. Discrimination accuracy (d') for (A) the 0–2-s delays, (B) the 6–10-s delays, and (C) the 25–40-s delays at each of the four presentation positions for normal controls (CON), amnesic patients (AMN), and patients E.P. and G.T. For the CON subjects and AMN patients, standard errors of the mean ranged from 0.11 to 0.29.

$P < 0.01$]. At the short delays, both the AMN group and patients E.P. and G.T. performed consistently across all positions at the same level as the control subjects and the other amnesic patients (Fig. 7A).

In contrast to their fully intact performance at the short (0–2-s) delays, at the other delays the AMN group and patients E.P. and G.T. performed more poorly than the CON group (Fig. 7B,C). At the middle delays (6–10 s), the AMN group was significantly impaired at the second and third presentation positions (both $P < 0.05$). At the longest delays (25–40 s), the AMN group was significantly impaired at the second position ($P < 0.01$). Similar to their performance when collapsed across presentation positions (Fig. 5), at both the middle and long delays, patients E.P. and G.T. performed more poorly than the CON group. In addition, at both the middle and long delays, the performance of patients E.P. and G.T. was not significantly above chance at any presentation position.

DISCUSSION

There has been uncertainty concerning the specific contribution of the perirhinal cortex to performance on tests of visual recognition memory. In particular, it has not been clear whether its contribution is mainly perceptual, or mainly mnemonic, or whether the perirhinal cortex contributes to both perception and memory. One way to distinguish these possibilities is to assess the effects of damage to the perirhinal cortex when the demands on memory are either very low or very high, i.e., when the delay between the presentation of sample stimuli and test varies from 0 s to many seconds. To ensure that the sample stimuli cannot be easily rehearsed, and thereby maintained in working memory for the duration of the retention interval, it is important to use complex stimuli that are difficult to label verbally. We found that two amnesic patients with medial temporal lobe damage, which includes complete damage to perirhinal cortex, performed normally on a visual recognition memory test involving complex visual stimuli with delays of 0 and 2 s; however, these patients were impaired at delays of 6 s and longer. Additionally, at the long delays of 25 and 40 s, these patients performed worse than all the other subjects. Thus, medial temporal lobe damage that includes the perirhinal cortex in humans produces a delay-dependent visual recognition memory deficit and does not affect perceptual processing of complex visual stimuli.

We also found that patients with damage limited to either the hippocampal formation or midline diencephalic structures demonstrated intact visual recognition memory with delays of 0 and 2 s and impaired performance at delays of 6 s and longer. It has been suggested that damage limited to the hippocampal region does not impair recognition memory performance (Aggleton and Shaw, 1996). However, in the present study the two patients with damage limited to the hippocampal formation performed worse than all but one control subject at delays of 6 s and longer (mean d' for A.B., 0.54; L.J., 0.40; Control, 0.98). Additionally, in other studies, amnesic patients with damage limited primarily to the hippocampus or the hippocampal formation demonstrated impaired performance on several tests of recognition memory (Reed and Squire, 1998). Thus, impaired recognition memory can be commonly observed after hippocampal damage in humans.

The ability to remember the items that occur early in a long list of items has traditionally been taken to reflect long-term memory, whereas the ability to remember the final items reflects short-term (immediate) memory (Baddeley and Warrington, 1970; Wright et al., 1985). Baddeley and Warrington (1970) demonstrated that on a test of immediate recall, amnesic patients performed normally on the last items of a list (items 9 and 10), but were impaired on the early items in the list. In our study, the amnesic patients, as

well as patients E.P. and G.T., performed normally at all presentation positions when the delay was short (0–2 s). The number of items presented for learning (four items) was probably not large enough to detect differences between groups at the short delays, i.e., the four items did not result in a long enough delay between the first items in the list and the test.

In the report by Wright et al. (1985), normal subjects significantly improved their performance at the first presentation position as the delay interval increased. In the present study, although the performance of control subjects at the first position did improve numerically as the delay increased (Fig. 6), this effect was not significant, perhaps because our subjects were much older than those in the earlier study. Note also that the amnesic patients were not noticeably impaired at the first presentation position even at the longer delays. Impaired performance by amnesic patients for the first presentation position might be easiest to detect when control subjects demonstrate a significant advantage at the first presentation position. In addition, it is possible that the amnesic patients attempted to bridge the long retention intervals by focusing on the first item that was presented and trying to hold in mind some of its features.

The present results indicate that patients with complete damage to the perirhinal cortex demonstrate intact visual recognition performance with delays of 0 and 2 s. Whereas the damage in patient E.P. is largely confined to medial temporal lobe structures (Reed and Squire, 1998), the damage in patient G.T. extends laterally from the perirhinal cortex to include much of the temporal lobe. In monkeys, lesions of the temporal lobe cortex immediately lateral to the perirhinal cortex (area TE) profoundly impair visual recognition performance, even with delays of only 0.5 s (Zola et al., 1997). This impairment is consistent with the known role of monkey area TE in higher order visual perception (Gross, 1973). The question therefore arises as to why G.T. did not exhibit perceptual impairment (specifically, he performed well at the 0- and 2-s delays). Neuroimaging work suggests that in humans, the lateral temporal lobe area involved in processing complex visual objects is situated more posteriorly and ventrally than in the monkey (Sergent et al., 1992; Haxby et al., 1994; Ungerleider and Haxby, 1994). The damage in patient G.T. ends approximately 1 cm anterior to this area on the left side and 3 cm anterior to this area on the right side (Haxby et al., 1994). Accordingly, it appears that G.T. does not exhibit perceptual impairment because the areas important for processing complex visual stimuli are spared by his anterior lateral inferotemporal damage.

Other work suggests that damage to anterior lateral inferotemporal cortex produces semantic rather than perceptual deficits (Hodges et al., 1992; Gerrard et al., 1997). Patients with damage to anterior lateral inferotemporal cortex are impaired at naming objects, sorting pictures into conceptual categories, matching objects with their names, and naming objects in response to their descriptions, among other visual semantic deficits. However, these patients demonstrate intact perceptual abilities as indicated by their competence in copying complex objects and figures (Srinivas et al., 1997). The present findings are consistent with the idea that, in humans, damage to anterior lateral inferotemporal cortex does not produce a visual perceptual deficit. We are currently examining the performance of patient G.T. on a wide range of tests designed to assess his visual semantic ability.

In summary, the results demonstrate that amnesic patients with damage limited to the hippocampal region or diencephalic structures, as well as amnesic patients with complete damage to the perirhinal cortex, exhibit intact short-term visual recognition memory. Against this background of intact short-term memory, all patients demonstrate a delay-dependent memory impairment that is evident at delays of 6 s and longer. These data indicate that the perirhinal cortex is not involved in the perceptual processing of complex visual stimuli. Together with the available data from nonhuman primates, our findings suggest that the perirhinal cortex is involved in memory in a way similar to other structures of the medial temporal lobe memory system, i.e., it is involved selectively in the formation of long-term memory.

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