Published in final edited form as:
Hippocampus. 2008 ; 18(6): 575–583.

New Semantic Learning in Patients With Large Medial Temporal Lobe Lesions

P.J. Bayley[1], **R.C. O'Reilly**[2], **T. Curran**[2], and **L.R. Squire**[1,3,4,5,*]

1 *Department of Psychiatry, University of California, San Diego, La Jolla, California*

2 *Department of Psychology, University of Colorado, Boulder, Colorado*

3 *Veterans Affairs Healthcare System, San Diego, California*

4 *Department of Neurosciences, University of California, San Diego, La Jolla, California*

5 *Department of Psychology, University of California, San Diego, La Jolla, California*

Abstract

Two patients with large lesions of the medial temporal lobe were given four tests of semantic knowledge that could only have been acquired after the onset of their amnesia. In contrast to previous studies of postmorbid semantic learning, correct answers could be based on a simple, nonspecific sense of familiarity about single words, faces, or objects. According to recent computational models (for example, Norman and O'Reilly (2003) Psychol Rev 110:611–646), this characteristic should be optimal for detecting the kind of semantic learning that might be supported directly by the neocortex. Both patients exhibited some capacity for new learning, albeit at a level substantially below control performances. Notably, the correct answers appeared to reflect declarative memory. It was not the case that the correct answers simply popped out in some automatic way in the absence of any additional knowledge about the items. Rather, the few correct choices made by the patients tended to be accompanied by additional information about the chosen items, and the available knowledge appeared to be similar qualitatively to the kind of factual knowledge that healthy individuals gradually acquire over the years. The results are consistent with the idea that neocortical structures outside the medial temporal lobe are able to support some semantic learning, albeit to a very limited extent. Alternatively, the small amount of learning detected in the present study could depend on tissue within the posterior medial temporal lobe that remains intact in both patients.

Keywords

amnesia; memory; patient E.P.; patient G.P.; fact learning

INTRODUCTION

Semantic memory refers to general knowledge about the world, including knowledge of facts, objects, concepts, and vocabulary (Tulving, 1983; Squire, 1992; Hodges and Patterson, 1997; Eichenbaum and Cohen, 2001). The ability to acquire new semantic knowledge is impaired following medial temporal lobe (MTL) damage, and the severity of the impairment is related to the extent of damage. Patients with damage limited to the hippocampus (CA fields, dentate gyrus (DG), and subicular complex) have moderate difficulty in acquiring semantic

*Correspondence to: Larry Squire, Ph.D., VA Medical Center (116A), 3350 La Jolla Village Drive, San Diego, CA 92161. E-mail: lsquire@ucsd.edu

knowledge (Reed and Squire, 1998; Verfaellie et al., 2000; Manns et al., 2003; Bayley et al., 2006), whereas patients with damage that extends beyond the hippocampus to involve MTL cortex (entorhinal, perirhinal, and parahippocampal cortices) are profoundly impaired (Kitchener et al., 1998; Verfaellie et al., 2000; Westmacott and Moscovitch, 2001; O'Kane et al., 2004; Bayley and Squire, 2005; Stark et al., 2005; Bayley et al., 2006).

An important question has been whether the ability to acquire new semantic knowledge depends entirely on the MTL. There seem to be two possibilities. One possibility is that semantic learning cannot proceed independently of the MTL. By this view, sufficiently large lesions of the MTL should disable semantic learning quite completely. Some support for this view was obtained in a recent study (Bayley and Squire, 2005) of two profoundly amnesic patients (E.P. and G.P.) with large, well-characterized lesions of the MTL. E.P. and G.P. failed to demonstrate knowledge about facts and people for the period after they became amnesic, even on tests that were so easy that controls achieved near-perfect performance. They also failed a test where there would have been thousands of learning opportunities (draw a home floor plan).

An alternative possibility is that some semantic memory might be acquired directly in the neocortex, even after extensive MTL damage. This idea has its foundations in computational modeling (McClelland et al., 1995; O'Reilly and Rudy, 2000, 2001). The proposal is that new learning involves two distinct memory systems, one involving the hippocampus and one involving neocortex. The role of the hippocampus is to encode the details of specific events rapidly and with a minimum of interference. The role of the neocortex is to encode general features of the environment using overlapping and distributed representations. In formulations of this kind the neocortex has sometimes been identified as the MTL cortex that lies adjacent to the hippocampus (Norman and O'Reilly, 2003). This form of learning is slow, and information is integrated only gradually into existing memory stores. Even with relatively few exposures, these gradual changes are thought to provide the basis for a sense of familiarity about previously encountered items. Thus, even when an item cannot be recalled, or associated with its original context, information represented in neocortex might still allow the item to be identified.

Despite interest in the possibility that direct neocortical learning can occur in the absence of the MTL, there is limited experimental support for the idea. The difficulty is that most patients available for study have incomplete MTL lesions that make them unsuitable for addressing the question. As pointed out by O'Kane et al. (2004), the severely amnesic patient H.M. has a robust (albeit impaired) capacity for new semantic learning. Yet because H.M.'s MTL damage is incomplete, one cannot know whether his capacity for new learning is supported by residual MTL tissue (i.e., parahippocampal cortex and caudal perirhinal cortex) or by neocortex beyond the MTL.

The aim of the present study was to ask whether new semantic learning can be supported by neocortex beyond the MTL in the circumstance when damage to the MTL is virtually complete. Four tests of new learning were given: new vocabulary, famous names, famous faces, and new objects acquired at the patients' homes. The test items all involved information that would have been acquired gradually across multiple encounters. Further, memory was assessed using forced-choice tests of recognition memory with the idea that patients might have a notion that an item has been encountered even if there is little or no additional information available about the item (O'Reilly and Rudy, 2000; Norman and O'Reilly, 2003).

We tested two severely amnesic patients with large bilateral MTL lesions and six healthy controls using tests of semantic information that could only have been acquired after the onset of amnesia. An additional test (remote memory for famous faces) was given to insure that patients had the ability to perceive facial information. If the capacity for new semantic learning is fully dependent on MTL structures, the patients should not demonstrate knowledge of factual information that became available after the onset of their amnesia (i.e., postmorbidly). However, if gradual acquisition of new semantic knowledge can be supported by neocortical structures outside the MTL, the patients should demonstrate substantial postmorbid semantic learning.

MATERIALS AND METHODS

Participants

Two male amnesic patients participated (E.P. and G.P.). They became profoundly amnesic in 1992 (E.P.) and 1987 (G.P.) after contracting viral encephalitis. E.P. has 12 yr of education and was 83-yr-old at the time of testing. G.P. has 16 yr of education and was 60-yr-old at the time of testing. Both patients exhibit severe anterograde memory impairment on standard tests. For example, neither patient could recall any of a short prose passage after a 12-min delay (0 segments correct), and paired-associate learning scores across three trials were 0, 0, and 0 (maximum score, 10 per trial). In a previous study (Bayley and Squire, 2005), they demonstrated little new fact learning since becoming amnesic. Indeed, during repeated testing over many weeks they did not recognize that they had been tested before (Bayley et al., 2005).

Estimates of MTL damage were based on quantitative analysis of magnetic resonance images compared with data for four controls each (see Gold and Squire, 2005). Nine coronal MR images from the patients are available at www.jneurosci.org as supplemental material to Shrager et al. (2006). The volumes of the full anterior–posterior length of the hippocampus and the parahippocampal gyrus were measured following published procedures (Amaral and Insausti, 1990; Insausti et al., 1998). For each patient, the hippocampal and parahippocampal gyrus volumes were divided by the intracranial volume to correct for brain size (Gold and Squire, 2005).

Patients E.P. and G.P. have an average bilateral reduction in hippocampal volume of 97 and 96%, respectively (all values >9 standard deviation (SD)'s below the control mean). In addition, the volume of the parahippocampal gyrus is reduced by 94 and 93%, respectively (all values >10 SDs below the control mean). In both patients, there was complete loss of perirhinal and entorhinal cortex and significant damage to parahippocampal cortex (73% bilaterally for E.P. and 71% bilaterally for G.P.). Additional measurements were carried out for the frontal lobes, lateral temporal lobes, parietal lobes, occipital lobes, insular cortex, and fusiform gyrus (Bayley et al., 2005). For E.P. and G.P., the volumes of each of the major lobes are all within 9 and 13% of control volumes, respectively. E.P.'s lesion also includes the rostral portion of the fusiform gyrus (39% reduction on the left and 68% reduction on the right) and the insula, which is reduced in size (32% reduction on the left and 30% reduction on the right). Similarly, G.P.'s lesion includes the fusiform gyrus (41% reduction on the left and 56% reduction on the right) and the insula (80% reduction on the left and 49% reduction on the right).

Two groups of controls participated. One group was matched to patient E.P. and averaged 83.3 yr of age and 12.0 yr of education. The other group was matched to patient G.P. and averaged 57.6 yr of age and 14.0 yr of education. Each group consisted of three males who were given the tests of new vocabulary, famous names, famous faces, and remote famous faces. Informed written consent was obtained from all participants prior to their participation.

Memory Tests

Four tests were used to assess new learning since the onset of amnesia (new vocabulary, famous names, famous faces, and new objects at home). The two patients were tested in six sessions each (one to two tests per session), across an interval of 7 to 10 months. The controls were tested in two or three sessions (one to three tests per session) across 2 months. The tests were given in a forced-choice format. All test items were taken from the period 1992 onwards; i.e., from the period after they became amnesic.

A fifth test (the remote famous faces test) was given in a yes/ no format and assessed recognition for faces from the period well before the onset of amnesia. This test was included to determine whether the patients had the ability to perceive facial information.

At the end of each test session, participants were asked follow-up questions to assess their knowledge about the answers they had given. If the information was part of an integrated fund of knowledge, which is a hallmark of semantic memory (Tulving and Markowitsch, 1998), they might be expected to be able to provide additional information about their correct answers. In contrast, if the answers were achieved by simply guessing, or because correct answers tended to appear familiar, then additional information should be unavailable. All responses were tape recorded and transcribed for later scoring.

New vocabulary test—Participants were presented with 25 test items. Each test item contained one target word or phrase (a vocabulary term that had entered popular usage since 1992) and eight corresponding foil words or phrases. To create plausible foils for the targets, the foils were formed by recombining elements of the target item. For example, some target items referred to new products (e.g., “Prozac”; foils: “Flozac,” “Flozam,” “Prozam,” “Grozam,” “Grozac,” “Grodaz,” “Prodaz,” “Flodaz”). Other items referred to new sports (e.g., “Snowboarding”; foils: “Snowgliding,” “Waterboarding,” “Watergliding,” “Iceboarding,” “Snowblading,” “Icegliding,” “Waterblading,” “Iceblading”), or to new commercial companies (e.g., Google; foils: “Fooble,” “Foozle,” “Tooble,” “Toozle,” “Foogle,” “Goozle,” “Toogle,” “Gooble”). Participants were told that only one of the items was “real,” that the other items were fabricated, and that they should select the “real” item. Follow-up questions included; “What do you know about this item?,” “What kind of thing is it?,” “What is it used for?,” and “What does it do?”

Famous names test—Participants were presented with 24 test items. Each test item contained one target name (a person who had become famous since 1992) and eight foil names (e.g., “Ross Perot”; foils: “John Barwood,” “Henry Vidmar,” “Willie Minner,” “Daniel McAllister,” “Gregory Wallace,” “Tim Rushmore,” “Everett Conklin,” “Troy Simmons”). Participants were told that only one of the names was famous, that the other names were fabricated, and that they should select the famous name. Follow-up questions included; “What do you know about this person?,” “What are they famous for?,” “What do they do?”

Famous faces test—Participants were presented with 25 test items. Each test item contained a target photograph (a face of an individual who had become well-known after 1992, e.g., Brad Pitt) and eight nonfamous faces matched to the target face with respect to age, gender, and style of photograph. All the photographs were in color. Participants were told that only one of the faces was of a famous person, that the other faces were of nonfamous people, and that they should select the famous person. Follow-up questions included; “What do you know about this person?,” “What are they famous for?,” “What do they do?”

New objects at home test—This test was administered only to two patients and their spouses. Prior to testing, the spouse of each patient was asked to identify objects that had been acquired by their household after the onset of amnesia (e.g., car, lamp, table). The test contained eight items for each patient. Each item consisted of a photograph of the target object (e.g., a lamp) and five foil photographs of exemplars of the same object (e.g., different lamps). Before administering the test to the patients, their spouses were given the test to insure that someone familiar with the target objects could readily distinguish them from the foils. Because of the small number of test items, each patient was tested three times, each time with the items in a different order.

Remote famous faces test—Participants were given a 16-item yes/no test for famous faces (e.g., Winston Churchill, George Washington, Charlie Chaplin). The test consisted of eight photographs of people who were already famous by 1940 (i.e., long before the onset of amnesia) and eight foil photographs of nonfamous people who matched the famous faces with respect to age, gender, and the style of the photograph. Participants were presented with one photograph at a time and asked to respond “yes” to the targets and “no” to the foils. All the photographs were black and white. Follow-up questions included; “What do you know about this person?,” “What are they famous for?,” “What do they do?”

RESULTS

New Vocabulary

Both control groups performed better than 90% correct (Fig. 1). In contrast, patient E.P. chose only five correct items (20%), which was not reliably above the chance score of 11.1% (binomial test, $P = 0.08$). E.P. was unable to provide additional information about any of his correct answers. For example, he correctly identified “WorldCom” as a real word. When later asked to explain his answer, he replied “Everything around is common, similar. An average of the world. Not a particular item.” He also correctly identified “Bungee jumping” as a real phrase. He later explained this answer as “An insect or something jumping.”

Patient G.P. performed somewhat better and chose seven correct items (28.0%), which was an above-chance score (binomial test, $P < 0.05$). He was able to provide some additional information about his correct answers. For example, he correctly chose “Starbucks” to be a real word, and later described it as “coffee. It's a coffee. I used to get it.” In addition, he correctly chose “website” as a real word and later said that it was “…related to a computer. An existing computer program. Go to the website.”

Famous Names

The control groups performed better than 90% correct (Fig. 2). In contrast, patient E.P. chose only one name correctly out of 24 (4.2% correct). The single name he chose was “Timothy McVeigh.” When asked later to explain why he chose this name his reply suggested that he was guessing. “I'm probably wrong but the name seems to hit me. It seems to be in there for some reason. This could be another one” (pointing to another name). When E.P. was asked if he knew anything about him, he replied “no.” Patient G.P. performed somewhat better and chose eight correct names (33.3%) which was above the chance level of 11.1% (binomial test, $P < 0.05$). His answers to the follow-up questions suggested that he had some limited declarative knowledge about his correct answers. For example, he correctly chose the name “Tiger Woods” (a golfer) and described him as “a famous sporting person, athletic.” When asked about which sport he was famous for, he replied “bicycle.” His declarative knowledge did not extend to all his correct answers. For example, he correctly identified the name “Nancy Kerrigan” (an ice skater) as being famous but described her as “somebody in entertainment, an actress.”

Famous Faces

E.P.'s controls scored 81.0% correct, and G.P.'s controls scored 99.0% correct (Fig. 3). E.P. chose six faces correctly (24% correct), which was marginally better than the chance score of 11.1% (binomial test, $P = 0.052$). G.P. chose 16 faces correctly (64% correct), which was reliably about the chance score (binomial test, $P < 0.05$). The explanations given by the patients for their correct answers suggested that they had acquired some new declarative knowledge about famous people. For example, when asked to explain why he chose the photograph of Bill Clinton, E.P. replied “I'm 100% sure. He used to be a former president of the United States. Can't recall his name.” When asked to estimate when he was president, he replied “maybe 10 yr ago.” When asked to explain why he had correctly chosen the photograph of Jim Carey (a movie actor), E.P. replied “He appears to be a possibility.” When asked why he was famous, he replied “movies possibly.” Similarly, patient G.P. explained why he chose the photograph of Bill Clinton by saying “A president, Bush, or is that governor Bush? Current president of US. Has been re-elected. It's his last 4 yr. New election this year. He is a Republican.” He also described Jay Leno (TV talk-show host) as “An entertainment figure. Has a show at night. Has politicians and leaders.”

New Objects At Home

As would be expected, the spouses of the patients scored 100% correct (Fig. 4). E.P.'s score was 33.3% correct (3, 2, and 3 items correct on each test session, out of 8). His performance was marginally better than the chance score of 16.6% correct [$t(2) = 4.00$, $P = 0.057$], and his answers across the three test sessions were consistent. He always correctly chose the photographs of his new car and his new front door. However, his answers to the follow-up questions revealed little if any declarative knowledge about his correct choices. Instead, he responded to most items by simply pointing to them and saying “it's this one here.”

It is of interest that E.P. was also presented with another photograph outside regular testing, illustrating a table he had made at high school in 1931 (and that was still in his household). He was also shown photographs of five other tables. He chose the photograph of the correct table on all three occasions. He also reported considerable information about the table. When asked about his choice, he replied “Obvious. Made in 1931. Hayward High school. I got an A for it. I had to make all that. Had to draw it all out and cut it. Then you drill it there. Took me a couple of weeks. I used doweling to glue these together.”

Patient G.P achieved a score of 54.2% correct (5, 4, and 4 items correct on each test session, out of 8), which was well above the chance score of 16.6% correct [$t(2) = 9.00$, $P = 0.01$]. Like patient E.P., his answers were consistent across test sessions. He correctly identified four items on each of the three test sessions (patio chairs, dining table, chair, car). Further, his answers to the follow-up questions also revealed declarative knowledge about his correct answers. For example, when asked why he had chosen the patio chairs he said “They're in our dining room. We do use them outside, but we also use them in the dining room. I remember sanding them and staining them. We got them about 2-yr ago. They were bleached in the sun, so I sanded them and stained them.” In response to the follow-up question about “door” he stated “This is a challenge. I think it's this one. The reason I know about this is because we had problems with the door and the screen. The dog wants to go out. I put the screen on so many times.” These statements were later verified as accurate by his wife.

It is interesting that G.P.'s responses in some cases had the appearance of episodic rather than semantic memories. Having noted this, we reviewed all the responses made by both patients and all the controls and found that episodic information was in fact provided on only three occasions, each time by patient G.P. on the new objects at home test.

Combined New Vocabulary, Famous Names, and Famous Faces Tests

We next combined the 74 test items from the new vocabulary, famous names, and famous faces tests (Fig. 5A). Chance performance was 11.1%. E.P.'s controls scored 89.6% correct, and G.P.'s controls scored 94.1% correct. Both patients were severely impaired. Overall, E.P. scored 16.2% correct, which was not reliably above the chance score of 11.1% (binomial test, $P = 0.11$). Patient G.P. scored 41.9% correct, which was above chance (binomial test, $P < 0.001$).

We then asked about the nature of the correct answers given by the patients. On the one hand, the correct answers might have popped out in some automatic way in the absence of any additional knowledge about the items. On the other hand, the correct choices might have been accompanied by additional reportable information about the items. To choose between these possibilities, the transcripts for all participants and the corresponding test materials were given to two independent raters, who remained unaware of the identity of the participant and of the choice made for each test item. The raters scored each transcript, assigning a 0 or 1 to each test item. A score of 0 indicated that the respondent expressed no information about the correct answer beyond what could have reasonably been inferred from the test items. In contrast, a score of 1 indicated that the respondent had some reportable knowledge about the correct answer beyond what could be inferred from the test items themselves. The scores of the two raters were then averaged for each item, and the mean rating score across all correct items was calculated for each participant (Fig. 5B).

We next calculated an “expected” rating score for each participant, which estimated what the score would be if the participant had some reportable declarative knowledge about every test item that was answered correctly. For example, patient G.P. chose the correct answer for 31 items out of a total of 74 test items (i.e., he obtained a score of 41.9% correct; chance performance = 11.1%). He could have answered 8.2 of the 74 items correctly due to chance alone (i.e., 11.1% of 74 = 8.2 items). On the assumption that he would be expected to have no declarative knowledge about his correct guesses, these 8.2 items were given a rating score of 0. We then calculated what G.P.'s rating score would have been if he had had some declarative knowledge about all the remaining 22.8 items (31–8.2). Accordingly, we assigned a rating score of 1 to each of these 22.8 items. The “expected” rating score for G.P., assuming he had declarative knowledge about his correct answers and no declarative knowledge about his correct guesses, was then calculated as a mean rating score across all 31 correct items [i.e., $(8.2 \times 0) + (22.8 \times 1)/31 = 0.74$]. Similar calculations were performed for each of the other participants to determine what rating score would have been expected if the participant had reportable declarative knowledge about each of their correct answers.

The expected rating scores for the correct answers are shown in Figure 5B. Note that the observed and expected rating scores for the patients and the controls were in close agreement. This finding suggests that patients and controls had some declarative knowledge about the items that they answered correctly. If participants had answered questions in some automatic, unaware way and in the absence of declarative knowledge, the observed rating scores would have been noticeably lower than the expected rating scores. Thus, it was not the case that the patients answered a few questions correctly and then stated that they knew nothing at all about the items they had selected.

By way of comparison we also calculated rating scores for the incorrect answers. Here, the raters were estimating whether information offered by participants about their incorrect choices could in fact be counted as providing accurate information about the correct choice. These rating scores would of course be expected to be quite low, and they served as a baseline against which to evaluate the rating scores obtained for correct items. The finding was that the rating scores obtained for the incorrect answers were 0.07, 0.20, and 0.22 for E.P., G.P., and the controls, respectively. Each of these scores was significantly lower than the rating scores obtained for the correct answers ($P < 0.05$).

Remote Famous Faces

Figure 6 shows the results of the remote famous faces test. Patients performed well on this test, thereby demonstrating that they were capable of perceiving facial information and recognizing faces (provided they belonged to the remote past). The controls were combined into one group for this analysis ($n = 6$). Their score of 78.1% correct was well above the chance level of 50% correct [$t(5) = 4.70$, $P < 0.005$]. E.P. scored 87.5%, which was also above chance (binomial, $P < 0.005$). He correctly endorsed seven of the famous faces and one of the nonfamous faces. G.P. scored 75.0% correct, which fell just short of significance (binomial, $P = 0.08$). He correctly endorsed seven of the famous faces and three of the nonfamous faces.

E.P. was able to provide some information about all seven faces that he correctly identified as being famous. He correctly named five of the seven faces and provided some information for the other two faces that he could not name. For example, he described the photograph of Jean Harlow as “An actress. I would say famous but I don't know her name. Her face seems familiar.”

Likewise, G.P. was able to provide information about the seven faces that he correctly identified as being famous. He correctly named five of the faces, and gave correct information about the two other faces that he could not name. For example, he described Charlie Chaplin as “a comedian in Hollywood. Early in Hollywood days. A very famous comedian. I'm trying to recall his specific name.” Jean Harlow was described as “ A famous actress. Not too much Marilyn Monroe, but in that era.”

DISCUSSION

Two patients (E.P. and G.P.) with large MTL lesions were given four tests of semantic knowledge that could only have been acquired after the onset of their amnesia. The tests were given in a forced-choice, recognition format and assessed new vocabulary terms, famous names, famous faces, and new objects acquired at home. The question of interest was whether the patients had any sense of familiarity for the test items that was sufficiently strong to allow them to select the correct items when they were presented among several incorrect (fictitious) items.

The patients performed markedly below control levels on all four tests. Yet there was evidence of some new learning. E.P. performed the poorest. He answered an occasional question correctly, obtaining scores just short of significance on two of the four tests (famous faces and new objects at home, $P < 0.06$) and chance performance on the two other tests. G.P. displayed a greater capacity for new learning, and his scores were above chance (albeit quite impaired) on each test. The correct answers given by the two patients had the characteristics of declarative memory (i.e., the knowledge was consciously accessible and was related to at least some additional knowledge). Thus, it did not appear to be the case that the correct answers simply popped out from a background of unfamiliar items in some automatic way in the absence of any additional knowledge. A fifth test was also given to assess recognition ability for famous faces from periods remote to the onset of amnesia. Both patients performed well on this test, indicating that they had preserved ability to perceive facial information.

The results of the present study can be usefully compared with an earlier study in which semantic learning was examined in the same two patients (Bayley and Squire, 2005). In this earlier study, the patients did not perform above chance on any of four tests of new semantic learning. In contrast, the same two patients showed evidence of some new learning in the present study (if one takes E.P.'s marginally significant scores on two of the tests [$P < 0.06$]

as evidence of new learning). The important difference between the tests in the two studies is that the tests used in the earlier study were conventional tests of recall and recognition that depended on the patients having well-integrated semantic memory. For example, in the famous faces test patients were shown photographs of famous people and asked a yes–no question (e.g., “Is this person's name Tiger Woods?”). Similarly, in the “20 easy facts test” the patients were asked questions such as “What is the new European currency called?,” and they were asked to choose the correct answer from three plausible alternatives. In contrast, in the present study memory was cued using simple stimuli that required only a sense of familiarity about the test items. Whereas the earlier test material required that participants have some integrated, or associative, knowledge (e.g., a face and the name “Tiger Woods”), the present test material required only that participants find the correct item more familiar than the incorrect items. These kinds of questions make fewer demands on memory than the tests used earlier.

The new learning demonstrated by the patients could reflect direct neocortical learning or it might have been supported by residual MTL tissue. Both patients have some remaining parahippocampal cortex (~29% bilaterally for G.P. and 27% bilaterally for E.P.), and it is difficult to entirely rule out the possibility that this tissue supported some new learning. However, if the remaining parahippocampal cortex can support new learning, one could have expected that new learning would have been exhibited in our earlier study (Bayley and Squire, 2005). The results therefore raise the possibility that some gradual semantic learning can be supported by neocortex outside the MTL. If so, the amount of learning that can occur appears to be quite modest, even when methods are used that, on theoretical grounds, would be optimal for detecting such learning.

It is also worth noting that the damage in E.P. and G.P. was not entirely restricted to the MTL. Both E.P. and G.P. have damage to the rostral aspect of the fusiform gyrus and to the insular cortex. Although this damage did not impair face perception per se (see Fig. 6), one cannot rule out the possibility that damage beyond the MTL contributed to their impaired semantic knowledge and that performance would have been better if the damage had been entirely restricted to the MTL.

One can also ask whether the knowledge that was acquired by the two patients was unusual or qualitatively distinct in any discernible way, in comparison to knowledge about the world that is acquired over the years by healthy individuals. In a previous study, E.P. demonstrated gradual learning of fact-like knowledge (three-word sentences) across 24 study sessions distributed across 12 weeks (Bayley and Squire, 2002), and the knowledge had the characteristics of nondeclarative memory. Other studies have documented similar learning abilities in profoundly amnesic patients. For example, in one study, (Bayley et al., 2005), E.P. and G.P. reached high levels of performance in a two-choice discrimination task but at the same time were surprised at their success and could not explain how they made their choices. In these and other cases (Glisky et al., 1986; Stark et al., 2005), the new learning appeared to be non-declarative: it was unavailable to conscious awareness and was often rigidly organized.

In contrast to these findings of gradual, nondeclarative learning in the laboratory, the learning detected in the present study (which had occurred incidentally over many years) had the characteristics of declarative memory. First, the findings in Figure 5B show that the patients had some declarative knowledge about their answers. Second, the patients did not consistently suggest that they were guessing. Other patients with severe memory impairment have also been described as being capable of some new semantic learning, and in these cases the new knowledge was thought to be declarative (Kitchener et al., 1998; Westmacott and Moscovitch, 2001; O'Kane et al., 2004).

It is interesting that G.P. performed better than E.P. across all four tests of new learning. There appear to be three possibilities. First, patient E.P. may have had less exposure to the test items and hence fewer learning opportunities. However, in the case of the “new objects at home” test, both patients presumably had what amounted to thousands of learning opportunities for the target objects. Yet, E.P. performed more poorly than G.P. on this test. A second possibility is that G.P.'s better performance is related to the fact that he became amnesic at a much younger age than E.P. (at 41 vs. 70 yr of age). There have been suggestions that hippocampal damage can lead to greater functional sparing if the injury is sustained early in life, perhaps due to greater neuronal plasticity at a younger age (Isaacs et al., 2003; Vargha-Khadem et al., 2003). Yet, these suggestions relate to brain damage that occurs during childhood and there is little empirical basis for applying these ideas to patients with adult-onset amnesia. A third possibility is that G.P. has sparing of tissue or connections within the MTL that are damaged in E.P. While this remains a possibility, detailed, quantitative measurements of magnetic resonance imaging (MRI) scans have not revealed any significant differences in the extent of MTL damage in these two patients (see Methods). Perhaps neurohistological evidence would reveal differences that cannot be detected by MRI. In any case, it is worth mentioning that G.P. has always appeared to be somewhat less disabled than E.P. on the basis of both formal testing and informal observation.

In summary the results demonstrate that under appropriate test conditions, patients with large MTL lesions are capable of demonstrating some new factual learning. These conditions are found in recognition tests using simple stimuli that ask for familiarity judgments about single items such as faces, objects, and words. The findings can be viewed as consistent with complementary-learning systems models (O'Reilly and Rudy, 2000, 2001; Norman and O'Reilly, 2003), which predict that some new learning can occur directly in the neocortex and independently of the MTL. If so, the amount of learning that can occur appears to be quite modest (consistent with the slow learning rate hypothesized for neocortex in those models).

Acknowledgments

We thank Jennifer Frascino and Mark Starr for assistance.

Grant sponsors: Medical Research Service of the Department of Veterans Affairs, Metropolitan Life Foundation; National Institute of Mental Health (NIMH); Grant number: MH24600.

REFERENCES

Amaral, DG.; Insausti, R. Hippocampal formation. In: Paxinos, G., editor. The human nervous system. Academic Press; San Diego: 1990. p. 711-755.

Bayley PJ, Squire LR. Medial temporal lobe amnesia: gradual acquisition of factual information by nondeclarative memory. J Neurosci 2002;22:5741–5748. [PubMed: 12097527]

Bayley PJ, Squire LR. Failure to acquire new semantic knowledge in patients with large medial temporal lobe lesions. Hippocampus 2005;15:273–280. [PubMed: 15523609]

Bayley PJ, Frascino JC, Squire LR. Robust habit learning in the absence of awareness and independent of the medial temporal lobe. Nature 2005;436:550–553. [PubMed: 16049487]

Bayley PJ, Hopkins RO, Squire LR. The fate of old memories after medial temporal lobe damage. J Neurosci 2006;26:13311–13317. [PubMed: 17182781]

Eichenbaum, H.; Cohen, NJ. From conditioning to conscious recollection: Memory systems of the brain. Oxford UP; New York: 2001.

Glisky EL, Schacter DL, Tulving E. Computer learning by memory-impaired patients: Acquisition and retention of complex knowledge. Neuropsychologia 1986;24:313–328. [PubMed: 3755511]

Gold JJ, Squire LR. Quantifying medial temporal lobe damage in memory-impaired patients. Hippocampus 2005;15:79–85. [PubMed: 15390163]

Hodges J, Patterson K. Semantic memory disorders. Trends Cogn Sci 1997;1:68–72.

Isaacs EB, Vargha-Khadem F, Watkins KE, Lucas A, Mishkin M, Gadian DG. Developmental amnesia and its relationship to degree of hippocampal atrophy. Proc Natl Acad Sci USA 2003;100:13060–13063. [PubMed: 14555756]

Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkanen A. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. Am J Neuroradiol 1998;19:659–671. [PubMed: 9576651]

Kitchener EG, Hodges JR, McCarthy R. Acquisition of postmorbid vocabulary and semantic facts in the absence of episodic memory. Brain 1998;121:1313–1327. [PubMed: 9679783]

Manns JR, Hopkins RO, Squire LR. Semantic memory and the human hippocampus. Neuron 2003;37:127–133. [PubMed: 12691670]

McClelland JL, McNaughton BL, O'Reilly RC. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychol Rev 1995;3:419–457. [PubMed: 7624455]

Norman KA, O'Reilly RC. Modeling hippocampal and neocortical contributions to recognition memory: A complementary-learning-systems approach. Psychol Rev 2003;110:611–646. [PubMed: 14599236]

O'Kane G, Kensinger EA, Corkin S. Evidence for semantic learning in profound amnesia: an investigation with patient H.M. Hippocampus 2004;14:417–425. [PubMed: 15224979]

O'Reilly RC, Rudy JW. Computational principles of learning in the neocortex and hippocampus. Hippocampus 2000;10:389–397. [PubMed: 10985278]

O'Reilly RC, Rudy JW. Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. Psychol Rev 2001;108:311–345. [PubMed: 11381832]

Reed JM, Squire LR. Retrograde amnesia for facts and events: Findings from four new cases. J Neurosci 1998;18:3943–3954. [PubMed: 9570821]

Shrager Y, Gold JJ, Hopkins RO, Squire LR. Intact visual perception in memory-impaired patients with medial temporal lobe lesions. J Neurosci 2006;26:2235–2240. [PubMed: 16495450]

Squire LR. Declarative and nondeclarative memory: Multiple brain systems supporting learning and memory. J Cogn Neurosci 1992;4:232–243.

Stark C, Stark S, Gordon B. New semantic learning and generalization in a patient with amnesia. Neuropsychology 2005;19:139–151. [PubMed: 15769198]

Tulving, E. Elements of episodic memory. Oxford University Press; Cambridge: 1983.

Tulving E, Markowitsch HJ. Episodic and declarative memory: Role of the hippocampus. Hippocampus 1998;8:198–204. [PubMed: 9662134]

Vargha-Khadem F, Salmond CH, Watkins KE, Friston KJ, Gadian DG, Mishkin M. Developmental amnesia: Effect of age at injury. Proc Natl Acad Sci USA 2003;100:10055–10060. [PubMed: 12904585]

Verfaellie M, Koseff P, Alexander MP. Acquisition of novel semantic information in amnesia: Effects of lesion location. Neuropsychologia 2000;38:484–492. [PubMed: 10683398]

Westmacott R, Moscovitch M. Names and words without meaning: Incidental postmorbid semantic learning in a person with extensive bilateral medial temporal lobe damage. Neuropsychology 2001;15:586–596. [PubMed: 11761048]

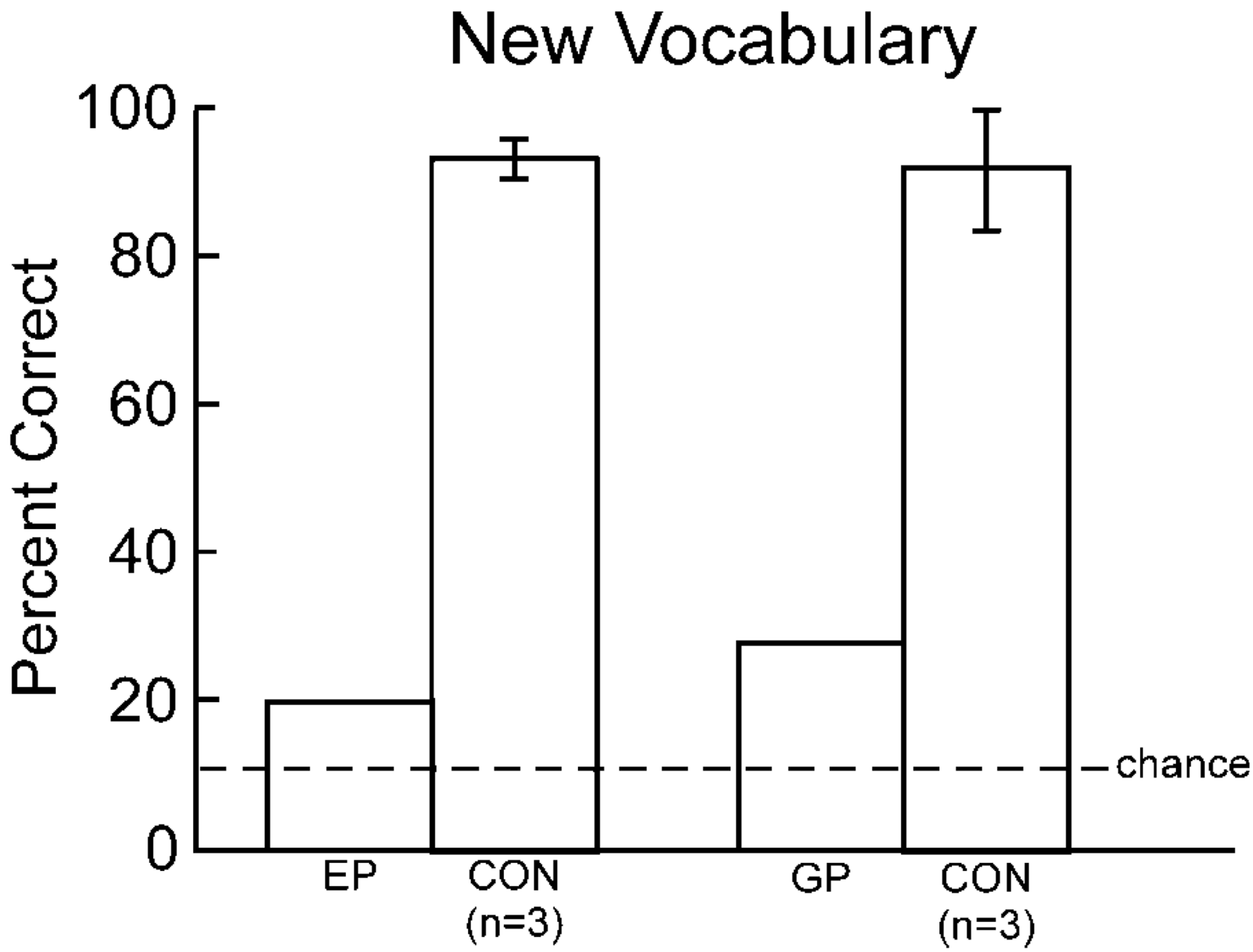

FIGURE 1.
New vocabulary. Performance of patients E.P., G.P., and controls (CON) on 25 multiple-choice questions about vocabulary words that could only have been learned after the onset of amnesia. Each test item contained one target word (e.g., Prozac) and eight foil words (e.g., Flozac, Prozam, Grodaz, etc). Brackets show standard error of the mean, and the dashed line indicates chance performance (11.1%).

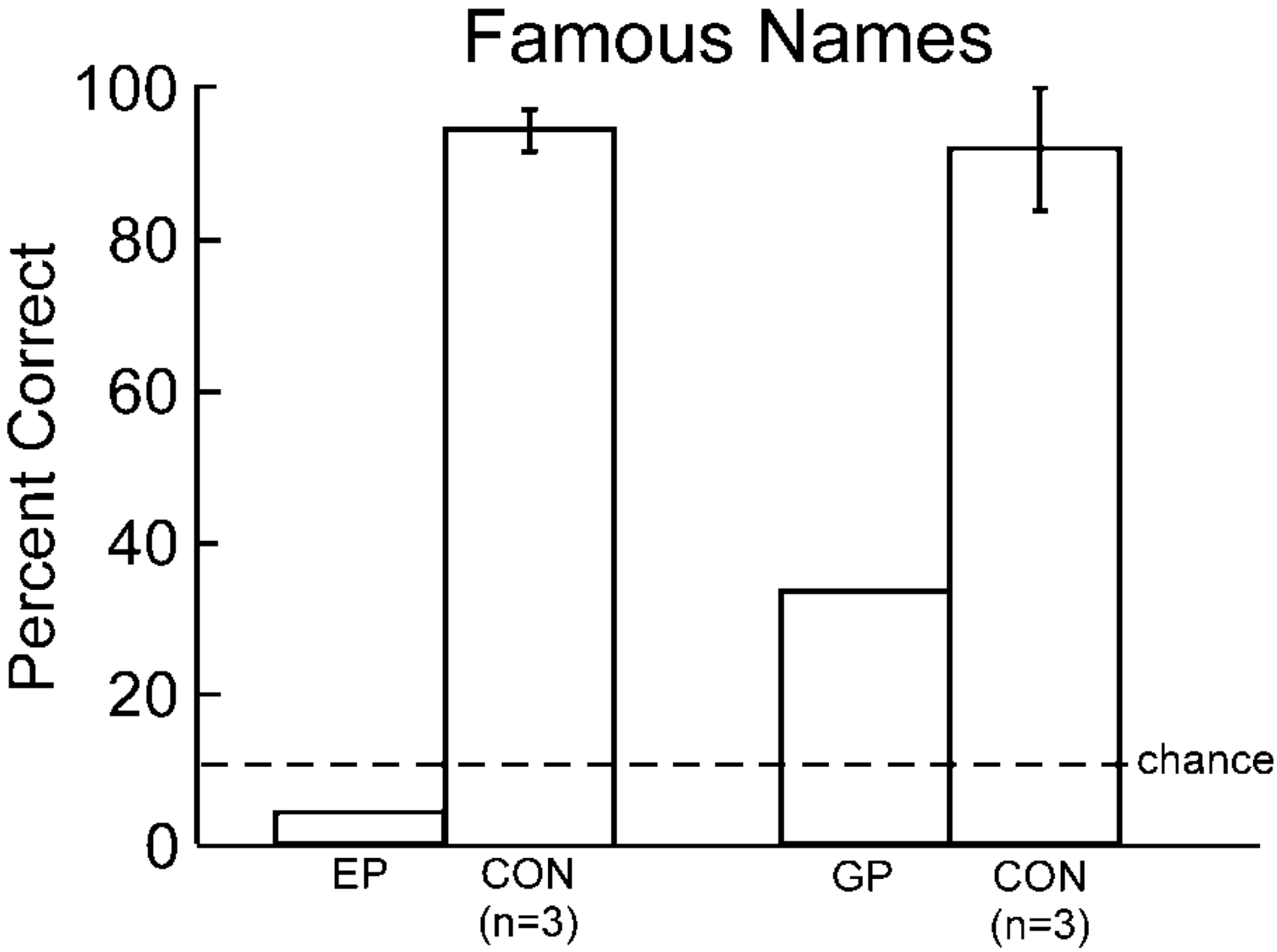

FIGURE 2.

Famous names. Performance of patients E.P., G.P., and controls (CON) on 24 multiple-choice questions about people who had become well-known after the onset of amnesia (e.g., Colin Powell). Each test item contained one target name and eight foil names (e.g., Ralph Penfield, Peter Bergey, John Musser, etc.). Brackets show standard error of the mean, and the dashed line indicates chance performance (11.1%).

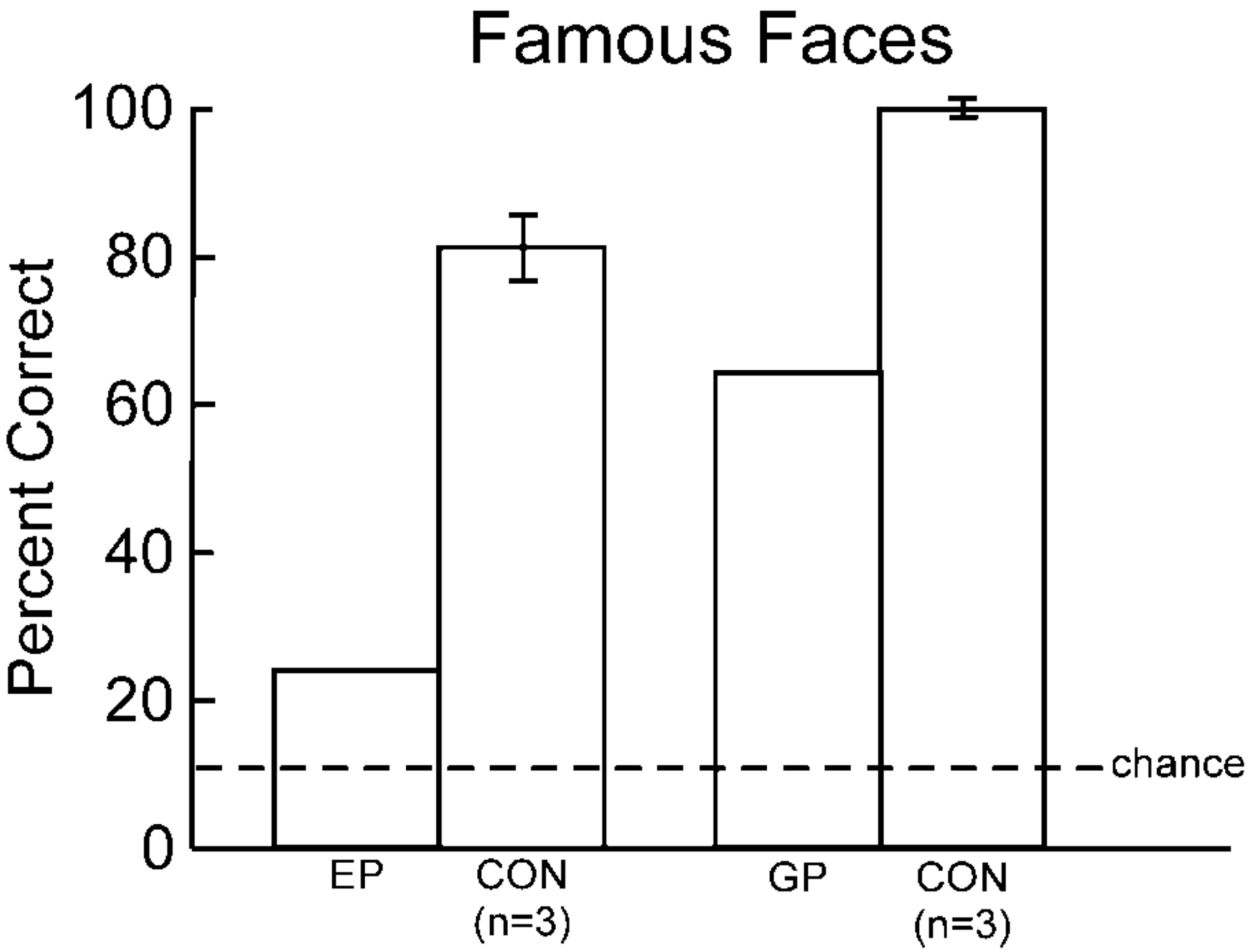

FIGURE 3.
Famous faces. Performance of patients E.P., G.P., and controls (CON) on 25 multiple-choice questions about people who had become famous after the onset of amnesia. Each test item contained a photograph of a famous person (e.g., President George W. Bush) and eight nonfamous persons who matched the target photograph with respect to age, gender and the style of the photograph. Brackets show standard error of the mean, and the dashed line indicates chance performance (11.1%).

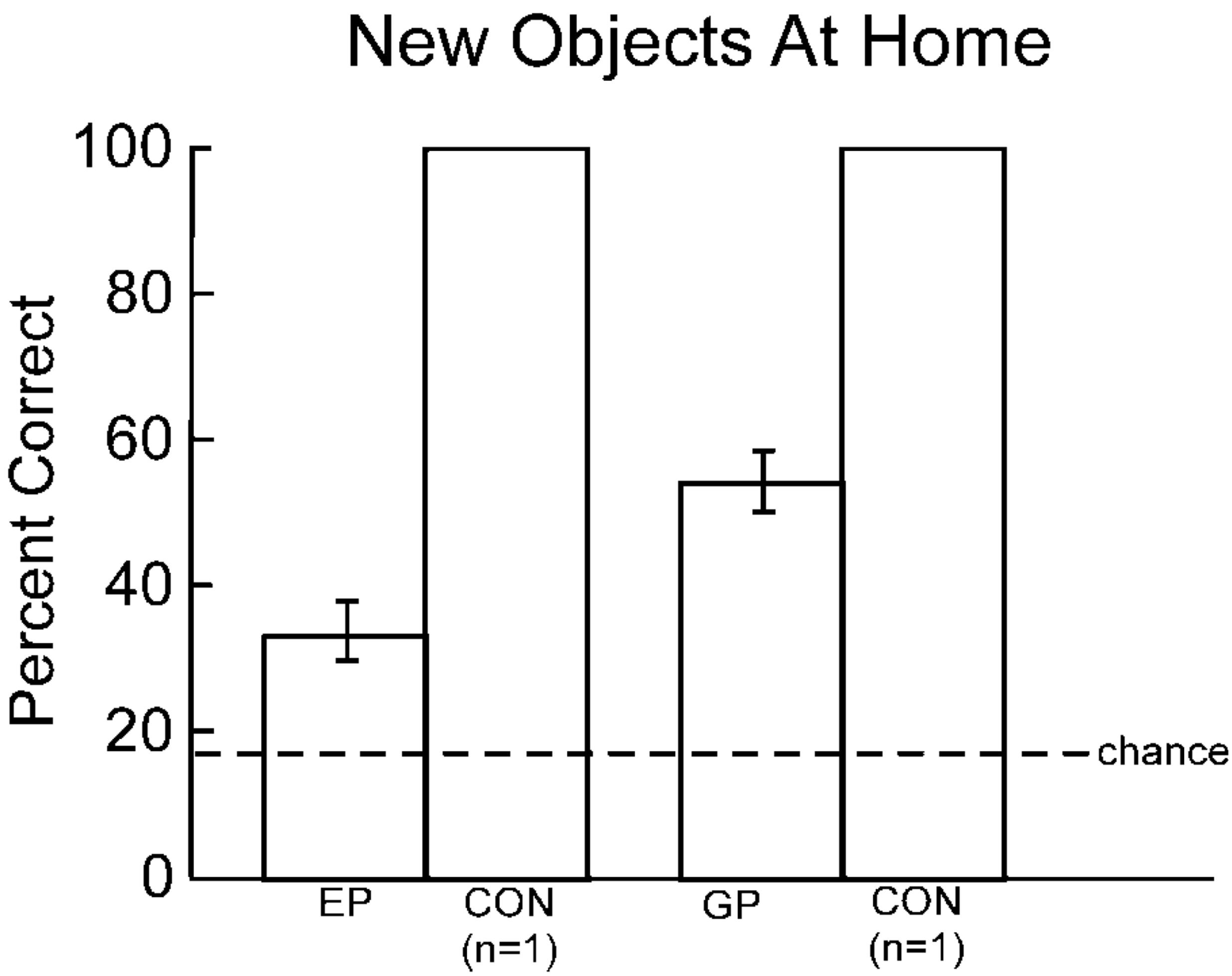

FIGURE 4.
New objects at home. Performance of patients E.P., G.P., and controls (CON) on eight multiple-choice questions about objects that were acquired by the patient's household after the onset of amnesia (e.g., car, lamp, table). Each test item consisted of a photograph of the target object and five photographs of different exemplars of the same object (e.g., a different lamp). The patients' spouses served as controls. Brackets show standard error of the mean, and the dashed line indicates chance performance (16.7%).

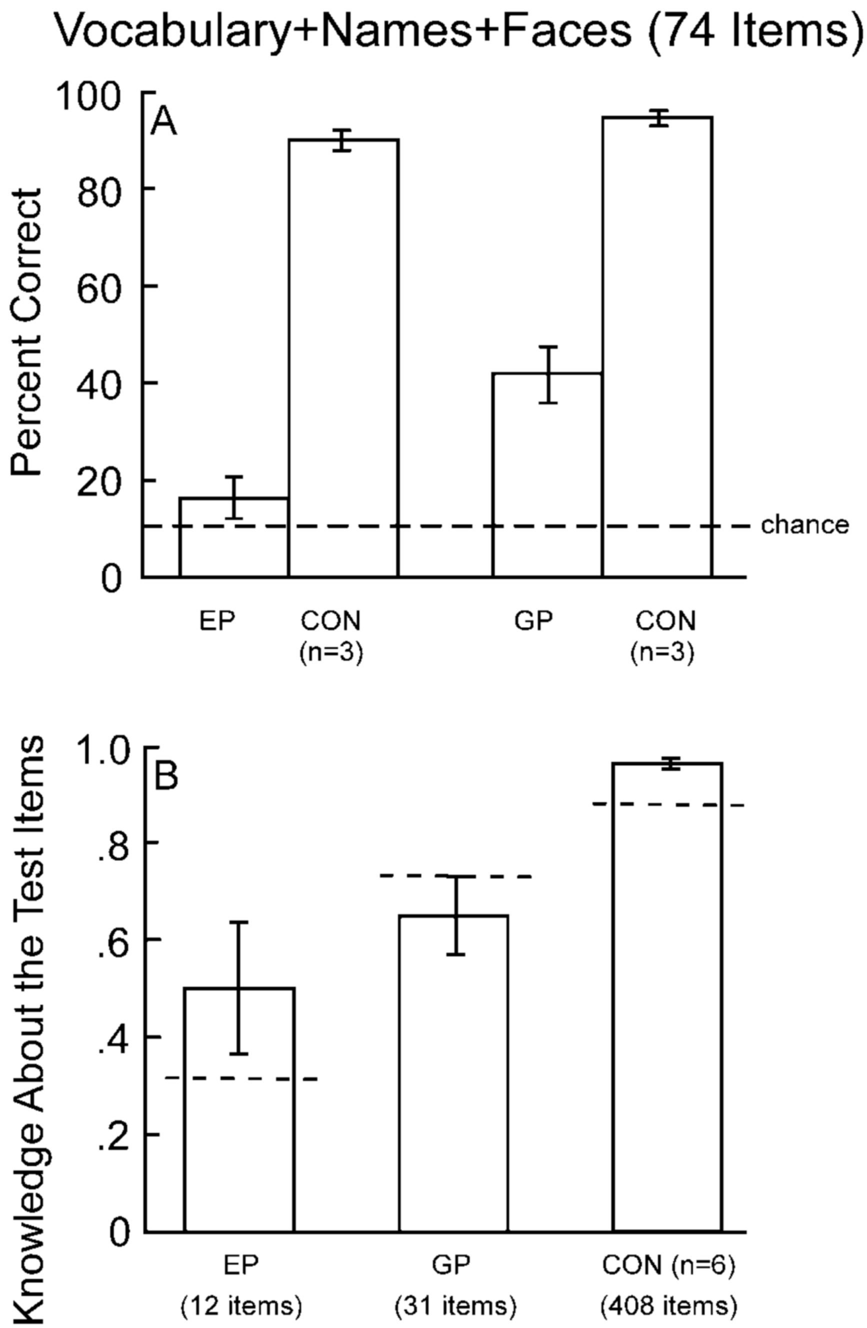

FIGURE 5.
Summary of performance on the tests of new vocabulary, famous names, and famous faces. (A) Mean percent correct. Brackets show standard error of the mean, and the dashed line indicates chance performance (11.1%). (B) Declarative knowledge available to participants about their correct answers. After each response, participants were asked to provide any information they could about the selected item. (0 = no knowledge, 1 = some knowledge about the item). An “expected” score was also calculated (dashed line). The expected score is the score that would have been obtained if participants had guessed the correct answer 11.1% of the time and had some declarative knowledge about their other correct answers.

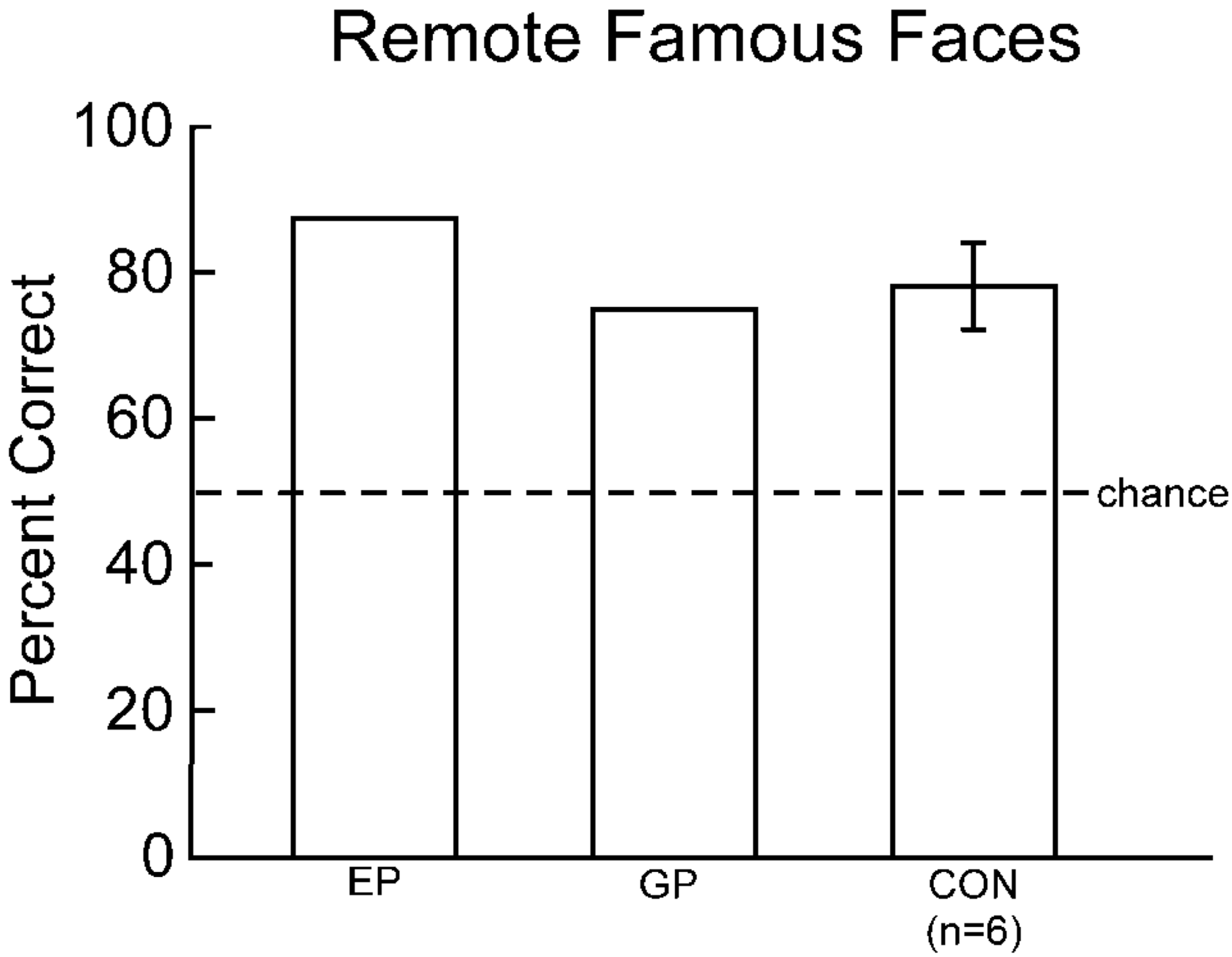

FIGURE 6.
Remote famous faces. Performance of patients E.P., G.P., and controls (CON) on 16 yes/no questions about persons who were well known by 1940. Participants saw 16 photographs one at a time (eight photographs of people famous during the patients early life, long before the onset of amnesia [e.g., Abraham Lincoln, Judy Garland, Adolf Hitler] and eight photographs of nonfamous persons). Brackets show standard error of the mean, and the dashed line indicates chance performance (50%).