Evidence for Semantic Learning in Profound Amnesia: An Investigation With Patient H.M.

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ABSTRACT: Until recently, it seemed unlikely that any semantic knowledge could be acquired following extensive bilateral damage to the medial temporal lobes (MTL). Although recent studies have demonstrated some semantic learning in amnesic patients, questions remain regarding the limits of this capacity and the extent to which it relies on those patients' residual MTL function. The present study examined whether detailed, semantic memory could be acquired by a patient with no functioning hippocampus. We used cued recall and forced-choice recognition tasks to investigate whether the patient H.M. had acquired knowledge of people who became famous after the onset of his amnesia. Results revealed that, with first names provided as cues, he was able to recall the corresponding famous last name for 12 of 35 postoperatively famous personalities. This number nearly doubled when semantic cues were added, suggesting that his knowledge of the names was not limited to perceptual information, but was incorporated in a semantic network capable of supporting explicit recall. In forced-choice recognition, H.M. discriminated 87% of postmorbid famous names from foils. Critically, he was able to provide uniquely identifying semantic facts for one-third of these recognized names, describing John Glenn, for example, as "the first rocketeer" and Lee Harvey Oswald as a man who "assassinated the president." Although H.M.'s semantic learning was clearly impaired, the results provide robust, unambiguous evidence that some new semantic learning can be supported by structures beyond the hippocampus proper. © 2004 Wiley-Liss, Inc.

KEY WORDS: memory; hippocampus; medial temporal lobe; declarative; parahippocampal gyrus; encoding

INTRODUCTION

The ability to acquire factual knowledge about the world (semantic memory) is a critical component of cognition. Studies with amnesic patients have provided key insights into the neural substrates supporting this ability (e.g., Corkin, 1984; Kapur, 1994; Vargha-Khadem et al., 1997; Kitchener et al., 1998; Verfaellie et al., 2000; Bayley and Squire, 2002). Observations of amnesic patients' profound deficits in acquiring factual information provided the first evidence that medial temporal lobe (MTL) structures play a critical role in semantic learning (Milner, 1959). Because of the heterogeneity of MTL lesions among patients, the contribution of distinct MTL structures to semantic learning remains an open question. Specifically, whether the hippocampus proper is necessary for all semantic learning, or whether some degree of semantic learning can occur in the absence of a functioning hippocampus, remains controversial (Vargha-Khadem et al., 1997; Squire and Zola, 1998; Tulving and Markowitsch, 1998). The present study examined whether any new semantic learning could be observed in a densely amnesic patient (H.M.) with a well-localized, bilaterally symmetrical MTL lesion that has left him with no hippocampal function. An extensive magnetic resonance imaging (MRI) investigation of H.M.'s lesion (Corkin et al., 1997) showed that the rostral 50% of H.M.'s hippocampal formation (i.e., the dentate gyrus, hippocampus, and subicular complex) had been resected during his 1953 operation. The remaining 2 cm of hippocampal tissue appeared atrophic. Moreover, because the entorhinal cortex, which provides the major sensory input to the hippocampal formation, was entirely resected, it is likely that the remaining 2 cm of hippocampal tissue is deafferented, and thus nonfunctional.

H.M. has provided a benchmark case for many questions regarding the role of the MTL in learning and memory (Corkin, 1984, 2002). Early investigations of H.M. revealed the importance of the hippocampus and surrounding cortex for a range of memory functions, including declarative semantic and episodic learning: the acquisition of episodic information about events (specific in time and place) as well as semantic (factual) knowledge. In 1953, he underwent an experimental operation in which his MTL structures were removed bilaterally to control his intractable epilepsy (Scoville and Milner, 1957). As a result, he has a dense anterograde amnesia (Scoville and Milner, 1957; Corkin, 1984, 2002). In innumerable tests administered over the past 50 years, H.M. has demonstrated severe deficits in semantic learning. For example, he is unable to learn new vocabulary in or out of the laboratory (Gabrieli et al., 1988; Postle and Corkin, 1998), and fails to recognize individuals who became famous after the onset of his amnesia (Marslen-Wilson and Teuber, 1975; Gabrieli et al., 1988). An intriguing, but less well-investigated, issue surrounds the degree to which some residual semantic learning has occurred (e.g., Milner et al., 1968; Corkin, 1984) despite the complete absence of hippocampal function. For example, H.M. is above chance at distinguishing recently adopted English words from nonword foils and at selecting postmorbid famous names from nonfamous lures (Gabrieli et al., 1988). Past studies, however, did not probe the depth of the knowledge he was able to acquire postoperatively. The knowledge he has demonstrated to

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date has been sufficiently inflexible and sparse that it could have been supported by declarative or nondeclarative learning (for an example of nondeclarative acquisition of factual knowledge in amnesia, see Bayley and Squire, 2002).

The present investigation characterized the depth of H.M.'s semantic learning by probing his knowledge of individuals who became famous after his 1953 operation. We expected that, due to his profound amnesia, H.M. would be impaired at identifying these famous individuals. The critical question was whether he had acquired any declarative, semantic knowledge postoperatively, or whether all his new learning was supported by nondeclarative learning mechanisms, e.g., habit memory. Our strategy was two-pronged. One task determined whether semantic cuing enhanced H.M.'s previously established ability to retrieve names for postoperatively famous individuals, suggesting that this knowledge was supported by a semantic network rather than just perceptual fluency. A second task determined whether he could freely recall specific semantic details associated with the people whose names he recognized as famous.

TABLE 1.

*Implicit Name-Stem Completion Task**

First name given as cue	Last name generated by H.M.	Decade became famous
Billie	Graham	1950
Elvis	Presley	1950
Fidel	Castro	1950
James	Dean	1950
J.F.	Kennedy	1960
Lyndon	Johnson	1960
Martin Luther	King	1960
Ray	Charles	1960
Woody	Allen	1960
Billie Jean	King	1970
Sophia	Loren	1970
Ronald	Reagan	1980

*When given the first name as a cue, H.M. generated the last name for these individuals who became famous after the onset of his amnesia.

TASK 1: NAME-STEM COMPLETION

This task examined H.M.'s ability to retrieve preoperatively and postoperatively famous names. He performed two versions of a name-stem completion task. On day 1, he heard first names of famous people and was asked to complete the name with the first last-name that came to mind. Because this task did not require completion with a famous name, implicit memory could support performance on the task (i.e., H.M. could complete "Henry" with "Ford" not because he knew Henry Ford to be a famous individual, but simply because there was an associative link between Henry and Ford due to prior pairings of those names).

On day 2, H.M. again heard people's first names, this time preceded by semantic cues, e.g., "invented the first automobile." He was then explicitly asked to provide the last name of the famous person who matched the semantic and first-name cues. This manipulation allowed us to assess whether semantic cuing would boost his ability to generate famous names. Prior studies of H.M. have found mixed results with regard to benefits from semantic cuing on famous face identification (Marslen-Wilson and Teuber, 1975; Gabrieli et al., 1988). We asked whether he showed any benefit from semantic cues when knowledge of famous names, rather than faces, was assessed. Because first-name, last-name pairs occur in the media more frequently than do face-name pairs, it seemed plausible that H.M. could show a benefit from semantic cuing when his knowledge of famous names was assessed.

Methods

Participants

Only H.M. performed this task. This experiment was conducted in 2002 when he was 76 years old.

Task design

Day 1 (no cuing). The experimenter read aloud a first name, and H.M. was asked to give whatever last name first came to mind. No mention was made that some of these name stems could be completed with famous individuals. In some instances, he completed the names with individuals whom he had known personally (e.g., childhood friends, teachers). For many first names, however, he generated the last name of a famous person (e.g., when asked "When I say 'Ray,' what is the last name that comes to mind?" he said "Ray Charles"). Test materials comprised 70 names corresponding to faces that H.M. had identified as "famous" in previous administrations of the Famous Faces Test (Kensinger and Corkin, 2000). Of the first names presented as cues, 35 could be completed with last names of individuals who were famous premorbidly, and 35 with last names of individuals who became famous postmorbidly. We gave one point for each first name for which he generated a famous last name.

Day 2 (semantic cuing). On day 2, we first presented semantic cues for each individual (e.g., "famous artist, born in Spain in 1881, formulated 'Cubism,' works include 'Guernica'") and then asked H.M. to generate a last name once given the first name (e.g., "When I say 'Pablo,' what is the last name that comes to mind?") By comparing his performance in this session with that on day 1, we could examine whether his scores for post-1950s individuals improved with semantic cuing (suggesting that he had a link between the name and the semantic information). If no such link existed, his performance should have been relatively similar with cuing (day 2) or without cuing (day 1).

Results

Day 1 (no cuing). Following presentation of only a first name, H.M. completed 18 of 35 first names (51%) with the last names of preoperatively famous individuals. He completed 12 of 35 first names (34%) with the last names of postoperatively famous individuals (Table 1). He was more likely to generate names of individuals who became famous in an earlier time period (the late 1950s or 1960s) than at a later time period (the 1970s and 1980s; $\chi^2 = 5.91$, $P < 0.05$). Clearly his ability to acquire new semantic knowledge was impaired; however, the results from the no cuing condition suggest that he had at least sparse knowledge of famous individuals, sufficient to support a link between their first and last names.

Day 2 (semantic cuing). Following presentation of semantic cues and a first name, H.M. generated the last names of 33 of 35 preoperatively famous individuals (94%), and 23 of 35 postoperatively famous individuals (66%). For postoperatively famous names, he generated all of the last names given on day 1, indicating consistency in performance, and an additional 11 last names (Table 2). Analysis of variance (ANOVA) conducted across items with name type (premorbid, postmorbid) and cuing type (no cues, semantic cues) as within-item factors indicated a significant effect of name type ($F(1,34) = 28.63$, $P < 0.0001$), and cuing type ($F(1,34) = 39.36$, $P < 0.0001$), but no interaction between these two variables. Thus, semantic cues boosted H.M.'s last-name generation equally for individuals encountered premorbidly and postmorbidly, suggesting that he has some declarative knowledge of those who became famous postmorbidly. Evidence of a recall benefit from semantic cueing suggests a link between the semantic information and the names of the famous individuals with whom he was familiar.

TABLE 2.

Explicit Name-Stem Completion Task*

First name given as cue	Last name generated by H.M.	Decade became famous	Correct with no semantic cue?
Elvis	Presley	1950	yes
James	Dean	1950	yes
Billie	Graham	1950	yes
Fidel	Castro	1950	yes
Marlon	Brando	1950	no
Yul	Brenner	1950	no
J.F.	Kennedy	1960	yes
Lyndon	Johnson	1960	yes
Mao	Tse-Tung	1960	no
Martin Luther	King	1960	yes
Pablo	Picasso	1960	no
Ray	Charles	1960	yes
Woody	Allen	1960	yes
Ayatollah	Khomeini	1970	no
Billie Jean	King	1970	yes
Jimmy	Carter	1970	no
Liza	Minelli	1970	no
Mother	Teresa	1970	no
Sophia	Loren	1970	yes
Dorothy	Hammil	1980	no
Margaret	Thatcher[a]	1980	no
Princess	Diane[b]	1980	no
Ronald	Reagan	1980	yes

*When given semantic information and first names as cues, H.M. generated all the last names that he had given under implicit instructions (indicated by yes). In addition, he was able to generate 11 last names of individuals who became famous after the onset of his amnesia, whom he did not generate under implicit instructions.
[a]H.M. first said "Thatchinger," then corrected to "Thatcher."
[b]We gave credit for "Diane," although the correct answer is "Diana."

TASK 2: FAMOUS NAME IDENTIFICATION

Although the results of the name-stem completion task suggest that H.M. has at least some declarative knowledge about famous individuals, the results do not address the depth of his knowledge. The second task assessed the amount of detail that he could provide about these famous people.

Methods

Participants

H.M. and 11 age- and education-matched control (CON) (6 women, 5 men; ages 74–81, with 12 years of education) performed the task.

Task design

On 76 trials, participants viewed two names, one famous and one foil. We selected 37 individuals who were famous before the onset of H.M.'s amnesia, and 39 who became famous afterward. Foils, chosen from a Boston-area telephone book, matched the famous names in length and nationality. Participants were asked, "Which name is that of a famous person?" (chance = 50%). For the individuals selected as famous, participants provided information on why the person was famous. No specific prompting was given, although occasionally H.M. was asked whether he could "give more information."

We scored responses in two ways. The first score reflected the quality of information that supported correct recognition (following Kitchener et al., 1998). A 1-point response indicated that an individual had been uniquely identified by the response (e.g., identifying Julie Andrews as the female lead in "Sound of Music"). A 0.5-point response indicated that correct information was provided about the individual, but that the information was true of many famous people, and thus insufficient to identify the person uniquely (e.g., identifying Oprah Winfrey as a TV personality). A 0-point response indicated that no correct information was generated about the individual (e.g., identifying Al Landon as an actor).

The second score reflected the amount of semantic information known about each figure. We assigned 1 point for each piece of pertinent information supplied about a famous person (e.g., if the response for John F. Kennedy was that he had been president of the United States. and assassinated, the score would be 2 points).

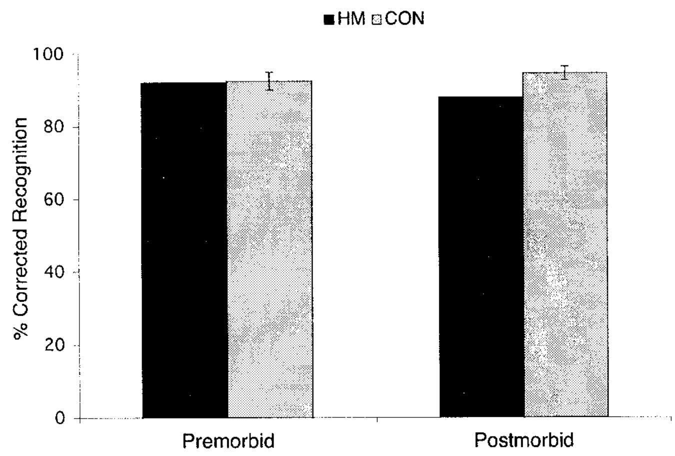

FIGURE 1. Corrected accuracy in two-alternative forced-choice recognition of names was calculated by subtracting false alarms from hits. In each trial, participants were presented with the name of a famous person and a foil name. The famous names included 37 names of people who became famous prior to the onset of H.M.'s amnesia in 1954 and 39 people who became famous after 1954.

Results

We describe the results for two-alternative forced-choice recognition of famous names and for recall of semantic information about recognized public figures.

Two-alternative forced-choice recognition

In distinguishing famous names from their foils, H.M. scored 87.8% for postmorbid individuals (Fig. 1). This value significantly exceeds that expected by chance (50%) and approximates his score for premorbid individuals (91.9%). A *t*-test conducted across items revealed no significant effect of name type (premorbid, postmorbid) on his recognition performance ($P > 0.50$). CON scored 94.3% (SD = 5.9%) for those who became famous after 1953, and 93.5% (SD = 8.0%) for individuals who became famous before 1953. An ANOVA conducted across items with name type (premorbid, postmorbid) as a between-item factor and group (H.M., CON) as a within-item factor indicated no effect of group ($F < 2$), no effect of name type ($F < 0.10$), and no interaction between group and name type ($F < 1$). Subsequent *t*-tests confirmed that the two groups did not differ in their ability to identify premorbidly ($t < 1$) and postmorbidly ($t < 1$) famous individuals. Despite the finding that H.M. performed no worse than control participants in identifying famous names of people who came to prominence after the onsite of his amnesia, it is possible that this learning was wholly attributable to nondeclarative memory, i.e., habit learning.

Recall of semantic information regarding public figures

Qualitative score. When we assigned scores of 0, 0.5, or 1, for premorbid public figures who were correctly recognized in the forced-choice recognition test, H.M. received 0.62 points per figure on average (Fig. 2). His performance compared favorably with CON, who scored, on average, 0.57 points (SD = 0.14). For postmorbid public figures, H.M. scored an average of 0.39 points, whereas CON scored, on average, 0.59 points (SD = 0.15). An ANOVA with name type (premorbid, postmorbid) as a within-items factor and group (HM, CON) as a between-items factor revealed a marginal effect of group ($F = 3.54$, $P < 0.07$), an effect of name type ($F(1,76) = 4.25$, $P < 0.05$), and an interaction between group and name type ($F(1,76) = 9.17$, $P < 0.01$). Subsequent *t*-tests demonstrated that H.M. performed similarly to CON for premorbid individuals ($t < 1$) but marginally worse than CON for postmorbid individuals ($t(40) = 3.14$, $P < 0.05$). These results indicate that the semantic information that H.M. provided for post-1953 individuals was impoverished as compared with CON, and as compared with the information he furnished for individuals who became famous prior to 1953. Nevertheless, he was capable of providing accurate, distinguishing information for a number of individuals who became famous after 1953.

Quantitative score. Scores of 1 in the qualitative scoring method could include a range of details. To assess the amount of knowledge that H.M. had ascertained about these individuals, we computed scores based on the quantity of information generated about each one. For premorbid individuals whom H.M. correctly identified as famous, he was able to provide, on average, 1.35 pieces of relevant information (Fig. 3). This performance compared favorably with that of CON, who provided 1.49 (SD = 0.38) pieces on average. For those who became famous postoperatively, H.M. generated an average of 0.76 pieces of information, while CON provided 1.54 (SD = 0.33) pieces of information on average. An ANOVA conducted across items with name type (premorbid, postmorbid) as a within-item factor and group (H.M., CON) as a between-item factor indicated a significant effect of group ($F(1,76) = 16.40$, $P < 0.0001$) and name type ($F(1,76) = 3.92$,

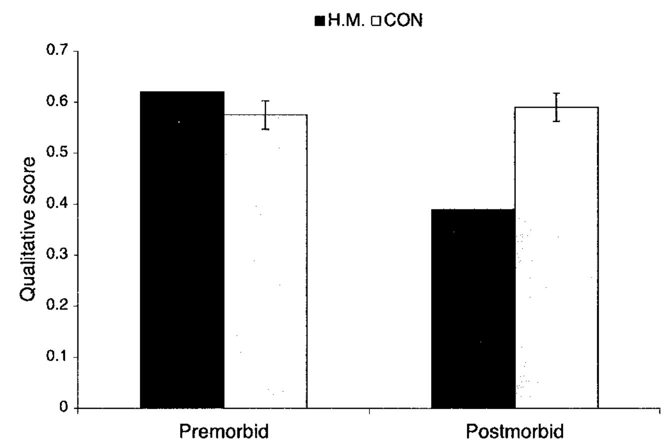

FIGURE 2. Qualitative scoring. Quality of semantic information participants generated about each correctly recognized public figure was measured by allotting 1 point for each figure when recognition was accompanied by uniquely identifying semantic information, 0.5 points if accurate but nonunique information was provided about the public figure, and 0 points if the participant could provide no accurate semantic information despite accurate recognition.

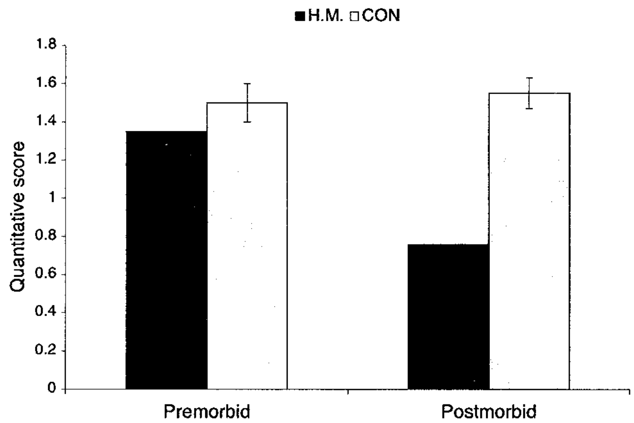

FIGURE 3. Quantitative scoring. The amount of semantic information participants generated about each correctly recognized public figures was measured by allotting 1 point for each accurate piece of relevant semantic information provided.

$P < 0.05$), and a significant interaction between these two variables ($F(1,76) = 7.73$, $P < 0.01$). Subsequent *t*-tests showed that H.M. and CON performed comparably on premorbid names ($P > 0.3$), but that H.M. performed more poorly than CON when providing details for postmorbid names ($t(40) = 5.07$, $P < 0.0001$). The conclusions remain the same if we consider 2 SD below the CON mean to represent an impairment: H.M. then showed normal performance for premorbid names, but impaired performance for postmorbid names. Critically, although the overall number of details given by H.M. was lower than CON (as expected, due to his dense amnesia), he was, nevertheless, capable of retrieving detailed information about a number of people who became famous following the onset of his amnesia (Table 3).

The results using the quantitative analyses confirmed and extended those using the qualitative analysis: H.M. was capable of providing numerous pieces of information for a select number of individuals who became famous after his operation. Although his performance was poorer than CON, and significantly worse than his performance for premorbidly famous individuals, he did show conscious access to semantic information learned after 1953. As with name-stem completion, he exhibited better memory (i.e., generated more details) for individuals who became famous in the 1960s than for those who became famous during the 1980s ($\chi^2 = 6.14$, $P < 0.05$).

DISCUSSION

A recent investigation of patients with small lesions circumscribed to the hippocampus demonstrated that semantic learning is impaired following hippocampal damage (Manns et al., 2003). This prior study, however, could not speak to whether semantic learning could proceed in the absence of hippocampal function because the patients' hippocampal damage was not complete. Thus, the present investigation is the first to demonstrate that some semantic knowledge can be acquired in the absence of any discernible hippocampal function. H.M., despite a lesioned and deafferented hippocampus, demonstrated that he is not wholly incapable of acquiring new semantic information. Specifically, he was not

TABLE 3.

H.M. Was Able to Generate Two or More Pieces of Information for 11 People* Who Became Famous Following the Onset of His Amnesia

Name	Decade became famous	Information generated
Cardinal Spellman[a]	1960	Gave speech in NYC at St. Patrick's cathedral; he stood on the steps going in there
John F. Kennedy[a]	1960	Became president, somebody shot him, and he didn't survive, he was Catholic
John Glenn[b]	1960	First rocketeer, the first to be in a rocket, he went to the moon, landed, and stayed up there a while, and returned safely
Julie Andrews	1960	Famous for her singing, on Broadway
Lee Harvey Oswald[c]	1960	He assassinated the president
Mohandas Ghandi	1960	From India, prime minister there
Ray Charles	1960	Tall, negro man, singer
Woody Allen	1960	Comic, in movie pictures
Liza Minelli	1970	Movie star and actress, dancer too
Sophia Loren	1970	Movie star, came from Europe
Michael Gorbachev	1980	Famous for making speeches, head of the Russian parliament

*Although he did not generate the information in this testing session, on the day in which the name-stem completion task was given, after generating Ronald Reagan, he indicated that he was "in movie pictures," and when asked whether he was famous for anything else, H.M. said "for politics, he was president."

[a]H.M. is Catholic; therefore, these individuals may have been of particular importance to him.

[b]John Glenn never landed on the moon. Nevertheless, H.M. was credited with providing uniquely identifying information in this instance because his response is clearly based on accurate knowledge, although imprecise in its detail.

[c]When asked which president Oswald assassinated, he said Roosevelt, but then indicated that was not the correct name. He stated that he thought Oswald was on a balcony and assassinated the president from there.

devoid of knowledge about people who became famous following the 1953 operation that rendered him profoundly amnesic. He generated the correct last names of more than one-third of postoperatively famous people whose first names were provided as recall cues. In a separate, forced-choice recognition task, he successfully distinguished 87% of postoperatively famous names from their foils. This semantic knowledge extended beyond low-level perceptual learning. For example, H.M.'s name-stem completion performance was significantly improved when he received semantic cues, suggesting that his knowledge of postoperatively famous people encompasses semantic as well as lexical/phonological information. Moreover, he could provide uniquely identifying information about 12 individuals who became prominent subsequent to his operation. These results provide robust, unambiguous evidence that at least some semantic learning can be supported by structures beyond the hippocampus.

While it is interesting to note the extent to which semantic learning can occur without hippocampal function, it is equally interesting to note the ways in which this learning was quantitatively and qualitatively different from that of CON. Quantitatively, H.M. was capable of generating semantic knowledge about only a fraction of the individuals who were well known to CON. Moreover, the information he generated about the postmorbid people familiar to him was relatively sparse as compared with CON, and as compared with the amount of information he was able to generate about premorbidly famous individuals. H.M., for example, was unable to provide even the sex of some of the names that he selected as famous (e.g., He responded that Yoko Ono was "an important man in Japan"). Further, while CON were better at generating knowledge about individuals who became famous recently as compared with remotely, consistent with the general pattern of forgetting typically observed in healthy individuals (e.g., Bahrick et al., 1975), H.M. showed the reverse pattern of performance (see also Verfaellie et al., 2000; Westmacott and Moscovitch, 2001). Further, his ability to produce information about postoperatively famous individuals was sporadic. For example, in prior attempts to assess his learning about famous individuals, he has successfully identified Ronald Reagan as a president and Margaret Thatcher as a British politician (Kensinger et al., unpublished observations), but was unable to generate their occupations during this investigation. And, during the current investigation he indicated that John F. Kennedy had been assassinated, whereas there had been prior occasions when he had said that Kennedy was still alive.

The restricted nature of the semantic knowledge H.M. was able to demonstrate makes it unlikely that the mechanisms he relied on for learning were identical to the mechanisms healthy adults use to acquire semantic knowledge so prolifically and spontaneously. Specifically, his ability to show any fast learning of semantic knowledge appears to have been eliminated, presumably due to his bilateral hippocampal lesion (Kapur, 1994; Holdstock et al., 2002). His only mechanism for learning appears to be via slow-learning, whereby following extended repetitions of information, he is capable of gleaning some information (McClelland et al., 1995; O'Reilly and Rudy, 2000). Given the impoverished nature of H.M.'s semantic learning, it is likely that the well-documented role of the hippocampus in one-trial learning serves to support not only episodic learning but the accumulation of rich semantic knowledge over time.

Two lines of evidence support the hypothesis that some semantic learning may occur in dense amnesia only following extensive repetition. First, previous studies have shown that when amnesic patients are able to learn new information, they do so much more slowly than CON (Kovner et al., 1983; Glisky et al., 1986a,b; Tulving et al., 1991; Hayman et al., 1993; Van der Linden et al., 1994) or with extra study time (Freed et al., 1987; Freed and Corkin, 1988). Second, in this and previous studies, amnesic patients were more likely to recognize as familiar, or to generate information about, individuals who became famous at an earlier postmorbid period than a later period, perhaps because of the additional exposure (e.g., Verfaellie et al., 2000; Westmacott and Moscovitch, 2001). This latter pattern may explain why H.M.'s new learning shows the reverse pattern of forgetting from that generally observed in healthy individuals.

The results of the present experiment, with H.M., indicated that it is possible to acquire at least some new semantic information in the absence of a functioning hippocampus. It is important to consider, however, whether H.M.'s acquisition of limited semantic information does, in fact, represent declarative learning, or as has recently been demonstrated in another amnesic patient, reflects nondeclarative perceptual memory (Bayley and Squire, 2002). H.M.'s learning does share one important characteristic with habit or skill learning, namely that it likely was acquired gradually with repeated learning opportunities. In several important respects, however, H.M.'s learning differs from nondeclarative, or procedural, memory. First, as stated above, a hallmark of declarative memory is that it is accessible to conscious awareness and can be consciously brought to mind as a verbal proposition or nonverbally as an image, unlike procedural knowledge which is accessible only through reenacting the task in which the knowledge was learned (Squire, 1986). H.M. was able to freely recall specific details about a limited number of postoperatively famous people (e.g., John Glenn as "the first rocketeer") or events (e.g., the assassination of John F. Kennedy). Second, animal (e.g., Eichenbaum et al., 1989) and human (Bayley and Squire, 2002) lesion studies have shown that the expression of habit memory is rigidly determined by the manner in which it was acquired, whereas semantic knowledge can be recapitulated flexibly in response to a variety of relevant stimuli. H.M. has repeatedly retrieved information about a small number of famous figures regardless of the specific language used to frame the question, or the modality of the stimuli, e.g., pictures versus words (Kensinger et al., unpublished observations). Third, H.M.'s ability to generate familiar last names in response to first-name cues could be explained as a relatively automatic stimulus-response reaction supported by procedural memory. However, the fact that he benefited as much from semantic cueing about postmorbid names as about premorbid names demonstrates that this new knowledge, like his premorbid knowledge, has been incorporated into a semantic network capable of supporting conscious recall. Thus, we conclude that H.M. is capable of limited declarative, semantic learning.

Why is it that H.M. exhibited postmorbid semantic learning about famous personalities in this study, despite prior failures to demonstrate semantic learning (e.g., Gabrieli et al., 1988; Postle and Corkin, 1998)? One possibility is the difference in the number and type of exposures to the stimuli. The personalities that H.M. successfully identified, such as John F. Kennedy and John Glenn, would likely have been individuals he was exposed to on numerous occasions and in a variety of contexts and modalities. In contrast, past studies have either tested H.M. on material learned in the laboratory over a restricted period of time (Gabrieli et al., 1988) or probed his knowledge of infrequently encountered new vocabulary words (Postle and Corkin, 1998). The variability in encoding opportunities for the famous individuals assessed here may have given rise to a richer and more flexible memory trace, as has been demonstrated for normal participants in a vast psychological literature (Madigan, 1969; Melton, 1970; Glenberg, 1979; Dempster, 1990). Despite the relatively large number of encoding opportunities related to such notable personalities as John F. Kennedy, H.M., because of his amnesia, is less likely to engage in conversations about public personalities and events that could give rise to rich semantic encoding. This deprivation could contribute to the paucity of his new learning.

Another possibility is that the stimuli used with H.M. may have, at least in some instances, allowed him to capitalize on prior knowledge. H.M. has demonstrated an ability to learn the solutions to crossword puzzle cues that allow him to benefit from premorbid knowledge (e.g., correctly filling in "polio" following a cue mentioning the Salk vaccine; Skotko et al., in press), although this learning was not permanent. Further, Glisky et al. (1986a,b) described amnesic patients who were able to learn new computer terms that were based on common words (e.g., "loop" and "save"). For example, prior to his operation, H.M. may have been familiar with John F. Kennedy as a war hero and U.S. congressman. This knowledge may have made it easier for H.M. to learn additional information about him, including the fact that J.F.K. became president and was later assassinated. Similarly, H.M. has frequently reported that in addition to being an actor, Ronald Reagan later became president (Kensinger, unpublished observations). Such bootstrapping, however, could not account for his knowledge of John Glenn, who did not make history as the first man to orbit Earth until 1962, or his descriptions of several of the other celebrities he identified.

The relative depth and flexibility of semantic learning displayed by H.M. distinguish the current findings from those recently observed in an investigation of the densely amnesic patient E.P. (Bayley and Squire, 2002). Like H.M., E.P. failed to demonstrate declarative semantic learning when information was acquired in a laboratory, with repeated exposure to stimuli in invariant contexts. In cued recall and forced-choice recognition tests, E.P. showed significant learning of novel three-word sentences taught to him repeatedly in at least 32 experimental sessions. Nevertheless, his performance remained well below CON who received only two learning sessions (Bayley and Squire, 2002). For E.P., however, the learning appeared to depend entirely on nondeclarative memory. First, it lacked the flexibility that characterizes semantic learning: E.P.'s knowledge did not transfer to new test sentences formed by replacing a word in the studied sentence with a synonym. Second, based on response times and self-reports, he appeared to be no more confident about his correct responses than about his incorrect responses. Thus, he failed to exhibit the conscious awareness of his new knowledge that is a critical feature of declarative memory.

While methodological differences may account for the divergent findings in the two amnesic patients, it is also possible that the null finding with E.P. (i.e., the lack of declarative, semantic learning) could be explained by differences in lesion extent. Like H.M., E.P. has complete hippocampal dysfunction (Stefanacci et al., 2000), but he has more extensive extrahippocampal medial temporal lobe damage than H.M. (Corkin et al., 1997). Specifically, H.M.'s parahippocampal cortex (i.e., the caudal portion of parahippocampal gyrus) and the caudal portion of his perirhinal cortex remain intact and, at least in the case of parahippocampal cortex, functional (Corkin, 2002). In contrast, E.P.'s lesion includes his entire perirhinal cortex bilaterally, as well as 18% of parahippocampal cortex on the left and 57% on the right (Stefanacci et al., 2000). Further, E.P.'s lateral cortex and insula are reduced in volume bilaterally, by19% and 13%, respectively (Bayley and Squire, 2002). In contrast, H.M.'s lateral temporal lobe and insula are spared, except for damage to the medial temporal pole (Corkin et al., 1997).

If the contrasting pattern of performance is due to differences in lesion location, as compared with task or stimulus-related variables, then it would follow that the regions spared in H.M. (parahippocampal cortex and the caudal portion of perirhinal cortex, and perhaps lateral temporal cortex) are sufficient to allow for some acquisition of declarative, semantic knowledge, at least following extensive repetitions spread over a lengthy period of time. This view is consistent with the hypothesis proposed by Kapur (1994), Vargha-Khadem et al. (1997), Tulving and Markowitsch (1998), and prior studies with amnesic patients (Verfaellie et al., 2000).

The present investigation speaks not only to the ability of regions beyond the hippocampus proper to support some new semantic learning, but also to a distinction between the neural substrates supporting episodic and semantic learning. An ongoing debate questions whether semantic learning can be supported in the absence of episodic learning (as allowed by the *episodic theory* espoused by Tulving colleagues (Tulving, 1972, 1985, 1987; Tulving and Markowitsch, 1998), or whether episodic learning is a prerequisite for semantic learning (as proposed in the *declarative theory* by Squire and Zola (1998). H.M. and E.P. are the only patients in the literature who could address this question because other amnesic patients do not meet the necessary criteria (i.e., an inability to acquire episodic knowledge, and amnesia resulting from relatively symmetrical, bilateral MTL lesions; Squire and Zola, 1998; Bayley and Squire, 2002). In half a century of testing, H.M. has never shown evidence of new episodic learning. He has consistently failed to learn verbal or nonverbal information (Corkin, 1984, 2002), he provides no anecdotal evidence of episodic learning (e.g., he is unaware of what he ate at his last meal), and the meager learning that he has shown (on tests of recognition; Freed et al., 1987; Freed and Corkin, 1988) can be accounted for by a "feeling of familiarity," which Jacoby and colleagues have argued may rely on processes distinct from declarative memory (Jacoby and Dallas, 1981; Kelley and Jacoby, 1990; Whittlesea et al., 1990; Jacoby, 1991). Thus, H.M.'s ability to show declarative, semantic learning underscores the possibility of a mechanism that supports declarative semantic knowledge acquisition, which can be instantiated by facts encoded over repeated exposures, but that is insufficient to support episodic learning, which depends on one-trial learning of discrete events. In fact, the behavioral pattern observed in H.M. suggests that the critical distinction between hippocampal-dependent and hippocampal-independent learning may best be characterized not only by the content of the information learned, i.e., generalized factual knowledge or event-based episodic information, but also by whether the learning is acquired in one or a few trials, or over extended repetitions (McClelland et al., 1995; O'Reilly and Rudy, 2000).

In conclusion, our results demonstrate that some declarative, semantic learning can be supported by regions beyond the hippocampus proper. Processes engaged by the posterior parahippocampal gyrus (i.e., parahippocampal and perirhinal cortices), and perhaps temporal neocortex, may support the slow acquisition of semantic knowledge following multiple exposures to factual information spread over an extended period of time. This slow, semantic learning appears to occur in the absence of episodic learning, and is sufficient to support a limited amount of consciously accessible (declarative) semantic knowledge.

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