Bilateral Medial Temporal Lobe Damage Does Not Affect Lexical or Grammatical Processing: Evidence From Amnesic Patient H.M.

Elizabeth A. Kensinger,[1*] Michael T. Ullman,[2] and Suzanne Corkin[1,3]

[1]*Department of Brain and Cognitive Sciences and Clinical Research Center, Massachusetts Institute of Technology, Cambridge, Massachusetts*

[2]*Departments of Neuroscience and Linguistics, Georgetown University, Washington, DC*

[3]*Nuclear Magnetic Resonance Center, Massachusetts General Hospital, Charlestown, Massachusetts*

ABSTRACT: In the most extensive investigation to date of language in global amnesia, we acquired data from experimental measures and examined longitudinal data from standardized tests, to determine whether language function was preserved in the amnesic patient H.M. The experimental measures indicated that H.M. performed normally on tests of lexical memory and grammatical function, relative to age- and education-matched control participants. Longitudinal data from four Wechsler subtests (Information, Comprehension, Similarities, and Vocabulary), that H.M. had taken 20 times between 1953 (preoperatively) and 2000, indicated consistent performance across time, and provided no evidence of a lexical memory decrement. We conclude that medial temporal lobe structures are not critical for retention and use of already acquired lexical information or for grammatical processing. They are, however, required for acquisition of lexical information, as evidenced in previous studies revealing H.M.'s profound impairment at learning new words. *Hippocampus 2001;11:347–360.* © 2001 Wiley-Liss, Inc.

KEY WORDS: lexicon; grammar; language; global amnesia; longitudinal; declarative memory

INTRODUCTION

The hippocampus and medial temporal lobes are implicated in the formation of new memories, both episodic and semantic (Scoville and Milner, 1957; Squire and Zola, 1998; Postle and Corkin, 1998; Gabrieli et al., 1988). It is less clear, however, whether these structures are also required for accessing established, long-term episodic or semantic memories (Nadel and Moscovitch, 1997; Squire and Zola, 1998; Tulving and Markowitsch, 1998; Vargha-Khadem et al., 1997). A key component of semantic memory is lexical memory: the stored information about words, including their meanings and forms (Tulving, 1972; Ullman et al., 1997; Ullman, 2001). It is currently unclear whether established lexical memories are preserved in global amnesia. Although numerous studies have reported cognitive impairments in amnesic patients (Ostergaard, 1987; Gabrieli et al., 1988; Shapiro et al., 1992; MacKay et al., 1998a,b; Postle and Corkin, 1998; Schmolck et al., 2000b), few have focused on language processing (MacKay et al., 1998a,b; Schmolck et al., 2000b).

In the present extensive study of language function in a patient with profound global amnesia, we address three main questions: 1) Is the capacity to use already-learned (preoperative) lexical information compromised by damage limited mainly to medial temporal lobe structures? 2) Is grammatical processing affected by medial temporal lesions? and 3) Does lexical memory degrade with time following medial temporal lobe damage? By comparing the results of this experiment to prior investigations (Gabrieli et al., 1988; Postle and Corkin, 1998), we were also able to address an additional question: Can the ability to retrieve previously learned lexical information be dissociated from the ability to learn new lexical information?

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*Correspondence to: Elizabeth A. Kensinger, Department of Brain and Cognitive Sciences and Clinical Research Center, Massachusetts Institute of Technology, E18-470, 77 Massachusetts Ave., Cambridge, MA 02139. E-mail: ekensing@mit.edu
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A DISSOCIATION WITHIN LANGUAGE: THE MENTAL LEXICON AND THE MENTAL GRAMMAR

Language is comprised of a mental lexicon and a mental grammar. The lexicon is a store of word knowledge, underlying memorization, retrieval, and recognition of words. The grammar underlies our ability to learn and use rules that specify the structure of language; such rules allow the combination of lexical forms into complex linguistic structures, including morphologically complex forms (e.g., walked, happiness), phrases, and sentences. It is unsettled whether these two capacities are subserved by distinct computational and neural systems (Pinker, 1994, 1999; Ullman, 2001; Ullman et al., 1997), or by a single computational system (Elman et al., 1996; Seidenberg, 1997).

Neuropsychology, electrophysiology, and neuroimaging have provided converging evidence to support a dissociation between the mental lexicon (memorized words) and the mental grammar (grammatical rules) (Neville et al., 1991; Damasio, 1992; Stromswold et al., 1996; Ullman et al., 1997; Caplan et al., 1998). Ullman et al. (1997) proposed that the mental lexicon depends upon a declarative memory system, including medial temporal lobe structures (for learning new information), and neocortical temporal and temporo-parietal regions (for storing already established knowledge of word meanings and forms). In contrast, the mental grammar is posited to be subserved by a frontal/basal-ganglia procedural (nondeclarative) memory system, implicated in motor, habit, and skill learning (Ullman et al., 1997; Ullman, 2001). Converging evidence for these distinct neural circuits comes from a number of different types of studies (reviewed in Ullman, 2001), including neuropsychological (Damasio and Damasio, 1992; Goodglass, 1993; Ullman et al., 1997, 2001), electrophysiological (Friederici et al., 1998; Kutas and Hillyard, 1980; Neville et al., 1991; Newman et al., 1999; Rosler et al., 1993), magnetophysiological (Rhee et al., 1999; Simos et al., 1997), and hemodynamic (Caplan et al., 1998; Newman et al., in press; Ni et al., 2000; Stromswold et al., 1996). Here we will summarize some neuropsychological results which pertain to the present study.

Neuropsychological studies of aphasic patients have dissociated lexicon from grammar, linking the former to temporal lobe regions and the latter to frontal/basal-ganglia regions. Anterior aphasia is associated with left frontal and basal-ganglia lesions and "agrammatic" speech (Damasio, 1992; Damasio and Damasio, 1992; Goodglass, 1993). These patients also have more difficulty producing, judging, and reading regular morphologically complex forms such as English regular past-tense forms, posited to be computed by grammatical affixation rules (e.g., walk + -ed → walked), than irregular morphological forms (e.g., went or sang), posited to be retrieved from lexical memory (Badecker and Caramazza, 1987, 1991; Hagiwara et al., 1999; Ullman et al., 1997, 2001).

In contrast, posterior aphasia is associated with temporal/temporo-parietal lesions and lexical-conceptual deficits (Damasio, 1992; Damasio and Damasio, 1992; Goodglass, 1993). On morphology tasks, they have greater difficulty producing, judging, and reading irregular than regular forms (Hagiwara et al., 1999; Ullman et al., 1997, 2001). Despite apparent exceptions in the literature to these distinctions (Dronkers et al., 1998), there does appear to be a grammatical/lexical dissociation between the language deficits that follow anterior lesions and those that stem from posterior lesions.

A dissociation between the mental lexicon and the mental grammar has also been found in comparisons between Parkinson's disease (PD) and Alzheimer's disease (AD). PD patients are more impaired at producing regular than irregular morphological forms, whereas AD patients show the opposite pattern (Ullman et al., 1997; Cappa and Ullman, 1998). The two diseases are known to affect different brain regions. Early PD affects the basal ganglia and pathways projecting to the frontal lobes, leaving the temporal lobes relatively unaffected (Alexander et al., 1990; Taylor et al., 1986). Early AD, in contrast, mainly affects medial temporal lobe structures, (Murphy et al., 1993; Arnold et al., 1991), including the hippocampus (Small et al., 1999), entorhinal cortex, and perirhinal cortex (Gomez-Isla et al., 1996; Arriagada et al., 1992), leaving frontal and basal ganglia structures relatively spared. The disparity in language deficits therefore supports the dissociation between a basal ganglia-frontal lobe system supporting grammatical processing, and a medial temporal lobe and temporal/temporo-parietal neocortical system underlying lexical memory (Ullman et al., 1997, in press).

A DISSOCIATION WITHIN LEXICAL MEMORY? LEARNING VS. RETRIEVAL

Lexical memory serves at least two distinct functions: the acquisition of new lexical knowledge, and the retrieval and processing of previously acquired information. It is unclear whether these two capacities are subserved by distinct computational and neural systems (Chomsky, 1995; Pinker, 1994, 1999; Ullman, 2001; Ullman et al., 1997), or by a single system (Elman et al., 1996; Joanisse and Seidenberg, 1999; Seidenberg, 1997).

We previously presented evidence supporting a dissociable lexical memory system. An investigation with amnesic patient H.M. (Gabrieli et al., 1988) found that he could not learn new word definitions, but was able to access word definitions learned before his operation. Similarly, Postle and Corkin (1998) indicated that H.M. did not show word-stem completion priming for words that came into use after his operation, but showed normal priming for words in use before the time of his surgery. The contrast in priming for pre- and postoperative words likely results from the fact that word-stem completion requires lexical representations of the stimuli. H.M.'s lack of priming for more recent words therefore suggests a lack of lexical representations for those words. These results support the view that medial temporal lobe structures are required for the acquisition of new words, including phonological word forms, while neocortical structures are sufficient for the processing of already memorized words.

Studies from MacKay et al. (1998a,b) have challenged this view, suggesting that H.M. is impaired in language comprehension. Using transcripts of interviews and tests conducted in the 1960s, they studied H.M.'s ability to detect sentence ambiguity (e.g., "We are confident that you can make it." where "make it" can mean to make a physical object, or to achieve a goal, or to arrive on time). Compared to healthy volunteers, H.M. detected significantly fewer sentence ambiguities (MacKay et al., 1998a,b); his descriptions of the ambiguous sentences were rated as less clear, concise, and coherent (MacKay et al., 1998a); and his conversations about his early childhood were rated by blind judges as less coherent and comprehensible (MacKay et al., 1998a).

Whether these findings do not indicate exclusively that medial temporal lobe structures are necessary for normal language comprehension. The ambiguity judgment task clearly has memory demands, in that the participant must remember the sentence in its entirety in order to detect its ambiguity. Some sentences may be longer than what can be stored in working memory, thus requiring long-term memory. Memory is also critical for remembering what explanations have already been stated. It is more difficult to give multiple meanings for a sentence if a person does not remember what explanation has already been given.

It is also possible that H.M. has difficulties with this task for a reason unrelated to his lesion and amnesia (Schmolck et al., 2000b). Schmolck et al. (2000b) reported that amnesic patients with medial temporal-lobe damage were better able to perform some aspects of ambiguity detection (deciding whether a nonambiguous sentence was ambiguous) than H.M. Therefore, H.M.'s impaired performance at ambiguity detection may stem from factors unrelated to his medial temporal-lobe lesion and amnesia.

While evidence suggests that H.M. is impaired at processing ambiguous sentences, we wanted to determine whether his poor performance on that task was related to a more general lexical or grammatical processing deficit. Ambiguity detection relies on the understanding of syntax and on the processing of word meaning. It is therefore possible that H.M.'s deficit in ambiguity detection results from a deficit in either area. Conversely, it is possible that his deficit is unrelated to any specific loss of lexical or grammatical processing. This investigation allowed us to distinguish between these possibilities.

LEXICAL MEMORY OVER TIME

To our knowledge, no studies have examined the stability of lexical memory over time in global amnesia. We were interested in determining whether the ease of lexical retrieval would remain constant following bilateral damage to medial temporal lobe structures, or whether retrieval would become more difficult over time. Studies have shown that aspects of lexical memory, such as vocabulary and semantic fluency, remain relatively stable with normal aging (Mayr and Kliegl, 2000; Horn and Cattell, 1967). It is unclear, however, whether this maintenance is related to explicit reinforcement of the lexical memories. We therefore wanted to investigate whether H.M. would show consistent performance in retrieving lexical information despite the absence of explicit reinforcement.

PRESENT EXPERIMENT

The goal of our study was threefold. First, we wanted to clarify whether H.M.'s lexical memory deficit is limited to the acquisition of new information, i.e., post-1950s (Gabrieli et al., 1988; Postle and Corkin, 1998), or whether he is also impaired in the use of already acquired information, i.e., pre-1950s (H.M.'s surgery was in 1953). To determine the extent of his lexical deficit, we administered a comprehensive series of tasks probing the use of established lexical knowledge. Second, we wanted to establish whether grammatical processing was impaired with medial temporal-lobe damage. To our knowledge, this study is one of the first examinations of grammar in medial temporal-lobe global amnesia. Third, we wanted to determine whether H.M.'s lexical memory had shown any decline since the time of his operation. To this end, we analyzed his longitudinal performance on subtests of the Wechsler Adult Intelligence Scale (Information, Vocabulary, Similarities, and Comprehension subtests).

MATERIALS AND METHODS

Participants

Patient H.M

In 1953, at age 27, H.M. underwent a bilateral medial temporal lobe resection as an experimental treatment for intractable epilepsy (Scoville and Milner, 1957). The operation partially alleviated H.M.'s epilepsy, but resulted in a profound global amnesia (Scoville and Milner, 1957; Corkin, 1994; Milner et al., 1968). The location of his lesion has been well-documented using magnetic resonance imaging (Corkin et al., 1997). Corkin et al. (1997) reported that the following structures were resected bilaterally: the medial temporal pole, amygdaloid complex (except for a small, dorsal remnant), entorhinal cortex, hippocampus proper, and rostral perirhinal cortex. The rostrocaudal extent of ablation was 5.4 cm on the left and 5.1 cm on the right. His lesion also extends laterally to include the rostral middle and superior temporal gyri. The following structures were spared: the caudal perirhinal cortex on both banks of the collateral sulcus, the posterior 2 cm of the dentate gyrus, hippocampus, and subicular complex, and the posterior parahippocampal gyrus (Fig. 1).

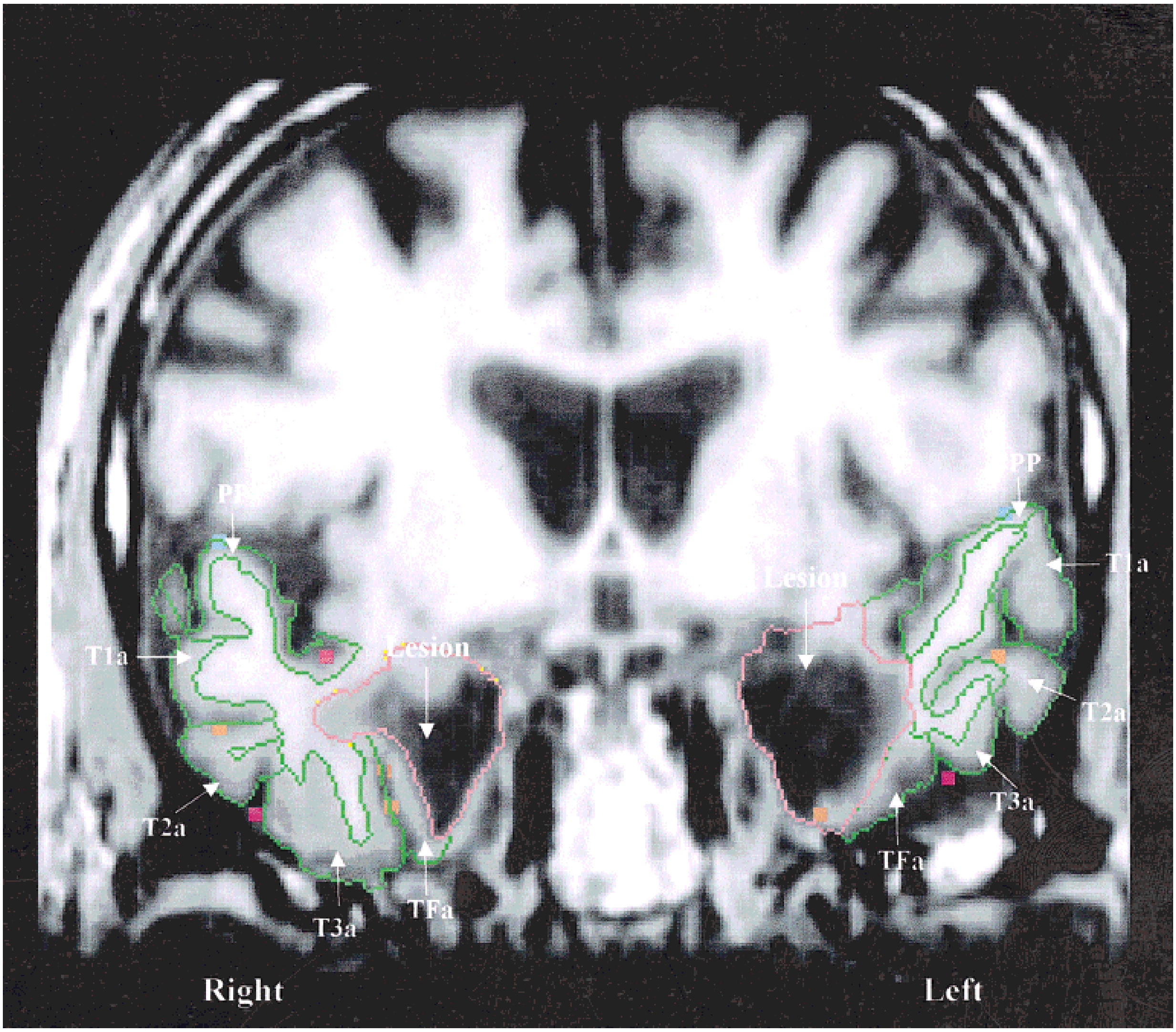

FIGURE 1. Locus of H.M.'s bilateral medial temporal lobe lesion. Area labeled "lesion" includes white matter, cortical, and cavitation portions of the lesion. Temporal-lobe white matter is more compromised at left than at right. Colored squares identify sulci that support gyral assignments. (The Cardviews software we used to view the image reconstructs dynamic orthogonal images into the cardinal viewing planes, and requires the tracing of sulci to ensure an accurate reconstruction; Caviness et al., 1996). PP, planum polare; T1a, superior temporal gyrus, anterior; T2a, middle temporal gyrus, anterior; T3a, inferior temporal gyrus, anterior; Tfa, temporal fusiform, anterior.

H.M. performed the experimental measures of lexical memory and grammatical processing on two occasions, the first in 1998 and the second in 1999, when he was 72 and 73 years old, respectively. Longitudinal data on standardized tests were collected between 1953–2000, when H.M.'s age ranged from 27–74 years. He had 12 years of education and was right-handed.

Healthy control participants

Healthy control participants (CON) comprised 7 men and 12 women matched in age and education to patient H.M. Mean age (in years) and education (in years) were 74 (SD = 2.1) and 12 (SD = 0.4), respectively. The participants were recruited through fliers posted throughout the Boston/Cambridge area and through the Harvard Cooperative on Aging. Participants were screened to eliminate those with a history of alcoholism, major heart disease, cancer, and neurological or psychiatric disorders; all were native English speakers and right-handed. All participants gave written consent, were tested individually, and were remunerated at $10/h for their participation.

Tasks

Completion of the tasks required 4–5 h of testing, spread over 1 or 2 days. Participants were given breaks approximately every hour, including an hour for lunch.

Lexical memory tasks

The lexical memory evaluation included measures of spelling, picture naming, name recognition, and fluency. Lexical memory was also probed with morphological processing tasks (see below). To avoid confounds based on when words entered the lexicon (e.g., pre- or postoperatively for H.M.), only words already in the lexicon in 1953 were included on these tests.

Spelling. Participants were asked to write out 50 words that were dictated to them (Appendix). We scored this task for number correct.

Picture naming, name recognition, and information retrieval. This series of tasks measured participants' lexical abilities by determining how well they were able to retrieve or recognize object names and memorized information.

Boston naming test (Kaplan et al., 1978; Huff et al., 1986). Participants were given two forms of this test, each with 42 black-and-white line drawings of objects that they were asked to name. Items were ordered by word frequency, from high to low frequency. The two forms of the test are of comparable difficulty, and have high intertest reliability (Huff et al., 1986).

Picture naming I (developed in the laboratory of M.T.U.). Participants named aloud 96 color pictures of objects (e.g., animals, musical instruments, tools), presented on a Macintosh computer screen one at a time. Responses were scored for number correct.

Picture judgment (developed in the laboratory of M.T.U.). Participants viewed 96 color pictures of objects (objects were different from those used in Picture Naming I) presented on a Macintosh computer screen one at a time, with a word written below each. Half of the items were correctly labeled, and half were incorrectly labeled. The experimenter read each word aloud. Participants decided whether the word correctly named the picture, by pressing a button labeled "yes" or one labeled "no." Responses were scored for number correct.

Picture naming II and category identification (Siri et al., 1999). Participants were asked to name aloud 105 black-and-white line drawings (Snodgrass and Vanderwart, 1980) presented on a Macintosh computer screen one at a time. Once they named an item, four category choices appeared, and they were asked to say aloud the appropriate category for that item. After selecting a category, the next item was presented. Categories included birds, clothing, four-footed animals, fruits, furniture, insects, items in a kitchen, musical instruments, parts of the human body, tools, toys, and vegetables. Responses were scored for number correct. Neither H.M. nor other participants made errors on category identification; therefore, scores are only reported for the picture naming task.

Landmark identification (Siri et al., 1999). Participants were read the names of 24 landmarks (e.g., Eiffel Tower, Alamo), and were asked to say where the landmark is located. Responses were scored for number correct.

Fluency

These tasks required participants to generate words fitting a given criterion (member of a specific semantic category or beginning with a specific letter).

Category fluency (Stones, 1978). In this task, participants were asked to orally generate as many exemplars of a category as possible in 60 s (e.g., "fruits"). Categories were given one at a time, for a total of 13 categories. Participants were instructed not to repeat any item names. For each category, we took the total number of items generated (not including perseverations). We then averaged across the 13 categories to produce the overall fluency score. H.M. was given a note card, with the category word written on it. This note card remained in front of him during the 60-s trial.

Letter fluency (Stones, 1978). Task administration and scoring were identical to Category Fluency, but instead of categories, participants were asked to orally generate as many words as possible in 60 s beginning with a specific letter of the alphabet (F, A, or S). H.M. was given a note card, with the letter written on it. The note card remained in front of him during the 60-s trial.

Morphology

These tasks assessed participants' abilities to produce and judge regular and irregular inflectional or derivational forms.

Plural production (developed in the laboratory of M.T.U.). Participants generated plural forms of 16 regular (-s suffixed stems) and 16 irregular plural forms of real nouns to complete sentences such as "There is one boy. There are several _____." Or "There is one mouse. There are several _____." Regular and irregular forms were matched pairwise for stem and plural form frequency. Sentences were read aloud to the participants as they viewed the sentence, to avoid effects caused by differences in reading ability.

Past-tense production (developed in the laboratory of M.T.U.). Participants generated past-tense forms of regular (-ed suffixed stems) and irregular (not -ed suffixed) real verbs to complete sentences, such as "Every day I dig a hole. Yesterday I _____a hole." Sentences were read aloud to the participants as they viewed the sentence, to avoid effects caused by differences in reading ability. Two versions of the test were administered. In the first version, only real words (64 regular and 64 irregular verbs, matched pairwise on stem and past-tense form frequency) were used. All of the regulars had stems which were phonologically dissimilar to the stems of irregular verbs. In the second version, participants were asked to generate regular and irregular past-tense forms of 80 real verbs and 32 pseudowords (novel verbs, e.g., "Every day I loy a blanket. Yesterday I _____a blanket." or "Every day I crive a book. Yesterday I _____a book."). Of the 80 real verbs, 32 were regulars (whose stems were dissimilar to the stems of irregulars), 32 were irregulars (matched pairwise on stem and past-tense frequency to the regulars), and 16 were "rhyming regulars," whose stems rhymed or were otherwise phonologically similar to the stems of irregulars (e.g., glide-glided, vs. ride-rode, hide-hid). Half of the pseudowords (novel regulars) had stems that were phonologically similar to the stems of real regular verbs and dissimilar to the stems of irregular verbs. These words were expected to be regularized (e.g., loy-loyed; cf. toy-toyed). The other pseudowords (novel irregulars) had stems that were phonologically similar to the stems of real irregular verbs, and therefore could be either regularized or irregularized (e.g., crive-crived/crove; cf. drive-drove). Novel regulars were counted as correct only with the response of stem +-ed, whereas novel irregulars were counted correct only if they were irregularized.

Past tense judgment (developed in the laboratory of M.T.U.). One hundred twenty-eight sentences were read to the participants, as they viewed the sentence. They were instructed to respond "good" if "the sentence sounds acceptable to you . . . something an English speaker could say" and "bad" if the sentence "sounds as if there is something wrong with it." The sentences differed in whether they included the proper past-tense (Yesterday I tied my shoe.) or the stem form (Yesterday I try it on.). Sentences contained verb forms of 64 real verbs and 64 pseudowords. The real verbs included 32 regulars and 32 irregulars, matched pairwise on stem and past-tense frequency. The pseudowords included 32 novel regulars and 32 novel irregulars, which were item-matched on stem and expected past-tense phonological structure to the 32 real regulars and irregulars. None of these verbs was presented in the mixed real-and-novel past-tense production task. Because H.M. responded "bad" to every sentence with a novel verb (using as his rationale that "It's not really a verb"), only sentences using real verbs were included in the analysis.

Derivational morphology production (developed in the laboratory of M.T.U.). Participants generated 64 "regular" (-ness suffixed) and 64 "irregular" (-ity suffixed) nouns from adjectives presented in sentence contexts (e.g., "The girl is pretty. In fact, her _____is very noticeable." or "The boy is stupid. In fact, his _____is very noticeable.").

Syntactic processing tasks

Syntax comprehension I. Participants viewed black-and-white line drawings with multiple components (e.g., a girl running toward a running girl and a running boy). The experimenter then instructed the participant to point to some aspect of the picture (e.g., "Point to the girl who is running away."). The participant then responded by pointing to the correct element in the picture. The task consisted of two versions, each with 23 pictures, and was scored for number correct. All participants completed both versions of the test. The order of the forms was counterbalanced across participants.

Syntax comprehension II (adapted from van der Lely, 1996). Six verbs were presented in each of four sentence contexts, yielding 48 sentences per participant: 1) active transitive sentence (e.g., The girl mends the teddy bear.); 2) full verbal passive (The teddy bear is mended by the girl.); 3) short progressive passive (The teddy bear is being mended.); and 4) an ambiguous (potentially adjectival) passive (The teddy bear is mended.). Each sentence was accompanied by a set of four pictures, presented on the four quadrants of each page. The four pictures corresponded to four different interpretations of the sentence: 1) a transitive response where the agent was shown performing the action on the patient (e.g., a girl mending a teddy bear); 2) an adjectival response (e.g., a mended teddy bear); 3) a reversed response (e.g., a teddy bear mending a girl); and 4) a semantic distractor response. The participants were asked to point to the picture that best matched the sentence. The task was scored for the number of correct responses.

Longitudinal study

We compared H.M.'s performance on four subtests included in the Wechsler-Bellevue tests (WB-I and WB-II) and the Wechsler Adult Intelligence Scale-Revised Edition (WAIS-R): Information, Similarities, Comprehension, and Vocabulary. Although the WB-I and -II are not usually administered as part of a present-day neuropsychological examination, we have continued to test H.M. on these forms of the Wechsler because 1) these test versions were administered to him preoperatively, and 2) due to his profound amnesia, a few of the questions on the more recent test version (WAIS-R) are not familiar to him (e.g., "Who was Martin Luther King, Jr?"). We analyzed data from 20 testing sessions between 1953 (preoperative test administration) and 2000.

For all four subtests, scores were calculated following the Wechsler guidelines; raw scores were converted to age-adjusted "scaled scores" provided in the Wechsler testing manuals.

Information. Participants were asked to answer either 25 or 29 questions (on the WB-I/WB-II and WAIS-R, respectively) about people (e.g., Who wrote Hamlet?), places (e.g., On what continent is Brazil?), or general knowledge facts (e.g., How many weeks are there in a year?).

Similarities. Participants were given 12 or 14 sets of two words (on the WB-I /WB-II and WAIS-R, respectively), and were asked to determine what each set of words had in common (e.g., for eye and ear, the participant might respond that they are both sensory organs).

Comprehension. Participants were given 10 or 16 scenarios or statements (on the WB-I /WB-II and WAIS-R, respectively), and were asked either how they would respond in a given situation (e.g., What would you do if you were lost in the forest in the daytime?) or to explain a given phenomenon (e.g., Why does land in the city cost more than land in the country?).

Vocabulary. Participants were asked to orally define a set of 42 or 35 words (on the WB-I /WB-II and WAIS-R, respectively).

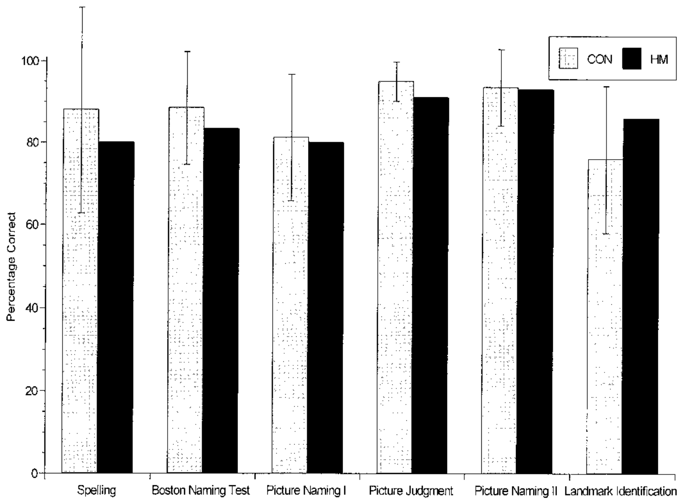

FIGURE 2. H.M. performed as well as CON on spelling, picture naming, and name recognition tasks. Bars indicate ±2 SD. H.M. scored within 1 SD of the CON mean on all tasks aside from Picture Judgment, on which he was within 2 SD of the CON mean.

Data Analysis

On the experimental tests of lexical and grammatical processing, we considered H.M. to be impaired when he was either 2 SD below the mean of CON or the worst performer compared to 19 CON. We initially tested 12 CON on all tests. On tests where H.M. performed below 1 SD of the mean of 12 CON, we then tested another 7 CON to determine whether H.M. would score 2 SD below the CON mean, or be the poorest performer. If H.M. demonstrated the lowest score (i.e., 20th out of 20), he would be significantly impaired at the $P < 0.05$ level, because the likelihood that an individual would be 20th out of 20 simply by chance is 1/20 or 0.05. This type of analysis is essentially a "permutation" or "randomization" test (Edgington, 1995; Good, 1994). We could not perform conventional parametric significance tests (*t*-tests or ANOVAs) across subjects, because these tests require within-group variances based on independent observations which are not obtainable with a one-subject design (as with patient H.M.). We did, however, perform paired *t*-tests, looking at the difference between the means of the two subject groups (H.M. and matched controls) across items. *T*-tests were performed individually for each task. All *P* are reported as two-tailed. We also performed repeated-measure ANOVAs across items, with item type (irregular vs. regular) as a between-item factor, and subject group (H.M. and CON) as a within-item factor.

For the longitudinal data, we performed a separate analysis for each of the dependent variables (Information, Comprehension, Similarity, and Vocabulary). In each case, we ran a general linear model (GLM) analysis testing for level effects (mean differences) of the form of the test (WB-I, WB-II, WAIS-R), linear effects of time, and any interaction between the two. Residuals from the model were tested for significant first-order autocorrelation, which would violate assumptions of significance tests for GLM.

RESULTS

Lexical Memory Tasks

H.M. performed within 1 SD of the CON on the spelling task, and on all tests of picture naming and name recognition, with the exception of Picture Judgment (Fig. 2). On the Picture Judgment task, he was within 2 SD of the CON mean, and was not the lowest performer (4 of 19 CON had scores lower than H.M.). Paired *t*-tests indicated no difference between H.M. and CON on any of these tests ($P > 0.15$).

In contrast, H.M. was the poorest performer on Category Fluency and Letter Fluency (performing worse than 19 CON), indicating a significant impairment ($P < 0.05$). He performed below 2 SD of the CON mean on Category Fluency, but within 2 SD of the CON mean on Letter Fluency (Fig. 3). H.M. generated words at a fairly uniform rate throughout the minute interval, and showed no evidence of exhausting category exemplars. Paired *t*-tests indicated a significant difference between H.M. and CON on both category and letter fluency ($P < 0.01$). A repeated-measures ANOVA with task (category vs. fluency) as a between-item factor, and subject (H.M. vs. CON) as a within-item factor, indicated an effect of subject ($P < 0.05$), no effect of fluency task, and no interaction of subject ζ task.

These results indicate preserved lexical memory performance on all tests except Category Fluency and Letter Fluency, and they provide no evidence of a disproportionate impairment on Category Fluency vs. Letter Fluency.

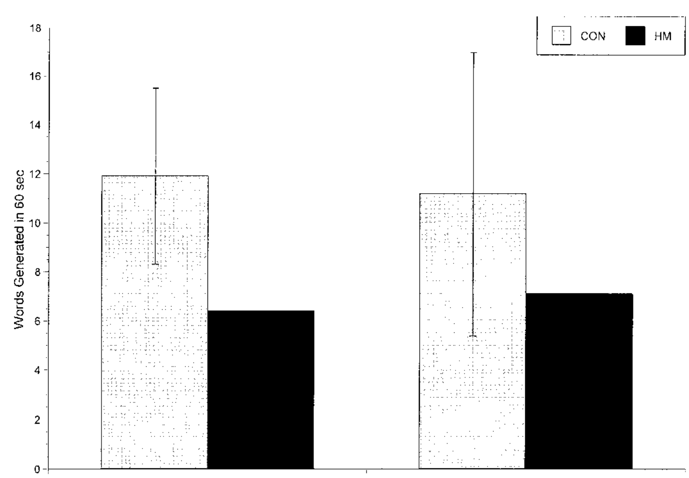

FIGURE 3. H.M. performed significantly worse than CON on fluency tasks. Bars indicate ±2 SD. H.M. was the worst performer (as compared to 19 CON) on both fluency tasks, indicating significant impairment ($P < 0.05$)

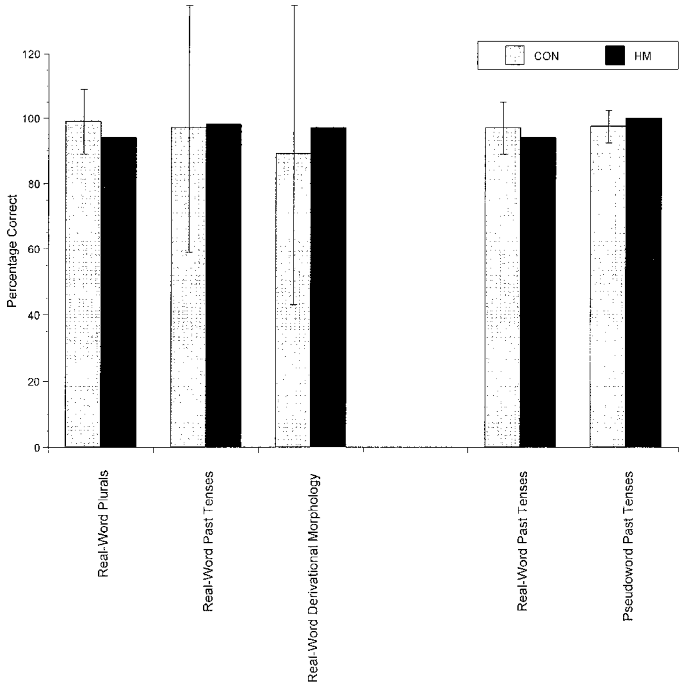

FIGURE 4. H.M. Performed within 1 SD of the CON mean when producing regular word forms on all morphology production tasks. Bars indicate ±2 SD. Graphs indicate percentage correct for (from left to right) 1) all regular, real-word plurals (e.g., dog-dogs) from the plural production; 2) all regular real-word past-tenses (e.g., walk-walked) from the real-word-only past-tense production task; 3) all regular derivational forms (e.g., bald-baldness) from the derivational morphology production task; 4) and 5) are taken from the past-tense production task with real and novel verbs: 4) percentage correct for all regular real-word past-tenses on the task; 5) percentage correct for all novel regular past-tenses from the task.

Morphology Tasks

Production of regular word forms

H.M. was within 1 SD of the CON mean on all production tasks for real and novel regular word forms on all tasks: the real word-only plural, past-tense and derivational morphology production tasks; and the past-tense production task combining real and pseudowords (Fig. 4). Similarly, paired *t*-tests indicated that H.M.'s production of regular forms did not differ from that of CON for production of either real or pseudowords in any of these tasks ($P > 0.15$). Analyses were conducted separately for 1) the real words in the real-word-only tasks; 2) real and pseudowords combined in the real-and-novel past-tense production task; 3) real words only from this combined task; and 4) pseudowords only from this task.

Production of irregular word forms

H.M. was within 1 SD of the CON mean on all production tasks for real and novel irregular word forms (Fig. 5). Paired *t*-tests indicated that his production of irregular word forms did not differ from CON on any task ($P > .15$).

Comparison of regular and irregular word form production

Repeated-measures ANOVAs, with item type as a between-item factor, and subject as a within-item factor, were conducted to look at the effect of regularity (irregular vs. regular) on each of the production tasks. On the real-word-only past-tense production task, the ANOVA indicated an effect of regularity (regular > irregular; $P < 0.05$), but no effect of subject or subject ζ regularity interaction. On the plural production task, the ANOVA indicated a marginally significant effect of regularity (regular > irregular; $P < 0.1$), but no effect of subject or subject ζ regularity interaction. On the derivational morphology task, the ANOVA indicated a strong effect of item type (regular > irregular; $P < 0.0001$), and a marginally significant effect of subject and subject ζ regularity interaction ($P < 0.1$).

On the combined pseudo- and real-word past-tense production task, ANOVAs indicated a significant effect of regularity (regular > irregular), word type (real > pseudoword), and interaction of regularity ζ word type ($P < 0.0001$); no effect of subject or of subject ζ regularity interaction; but a significant interaction of

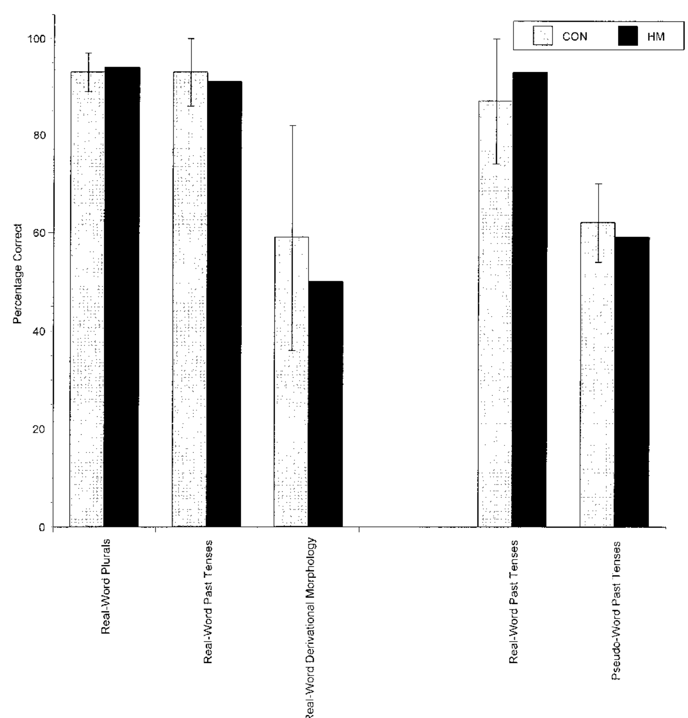

FIGURE 5. H.M. performed within 1 SD of the CON mean when producing irregular word forms on all morphology production tasks. Bars indicate ±2 SD. Graphs indicate percentage correct for (left to right) 1) all irregular, real-word plurals (e.g., ox-oxen) from the plural production task; 2) all irregular real-word past-tenses (e.g., sit-sat) from the real-word-only past tense production task; 3) all irregular derivational forms (e.g., stupid-stupidity) from the derivational morphology production task; 4) and 5) are both taken from the test with both real and novel words mixed together: 4) percentage correct for all irregular real-word past-tenses on the task; 5) percentage correct for all novel irregular past-tenses (e.g., crive-crove).

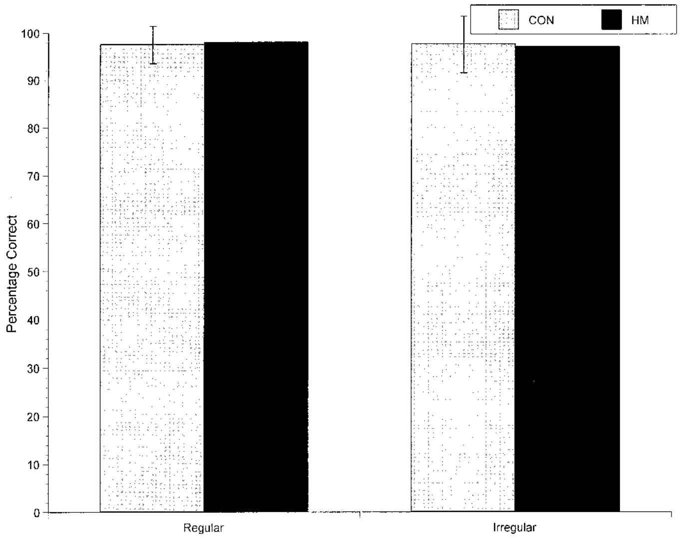

FIGURE 6. **H.M. performed within 1 SD of the CON mean when judging sentences with regular or irregular verb forms. Bars indicate ±2 SD.**

subject ζ word type ($P < 0.05$) and a marginally significant subject ζ word type ζ regularity interaction ($P < 0.1$). Paired *t*-tests showed that both H.M. and CON did worse on pseudowords than on real words ($P < 0.001$). When real words were analyzed separately, the ANOVA indicated an effect of regularity (regular > irregular; $P < 0.001$), no effect of subject, and no subject ζ regularity interaction. When pseudowords were analyzed separately, the ANOVA indicated an effect of regularity (regular > irregular; $P < 0.001$), no effect of subject, and no subject ζ regularity interaction.

These results suggest that H.M.'s morphological production is not affected. They also indicate that H.M. is not disproportionately impaired at producing irregular morphologic forms as compared to regular forms.

Past-tense judgment

H.M. performed as well as CON at determining whether a sentence was "good" or "bad." He performed within 1 SD of the CON mean for sentences with regular and irregular verb forms (Fig. 6). *T*-tests indicated that H.M. did not differ significantly from CON in sentence judgment for either of these sentence types $P > .15$. A repeated-measures ANOVA, with item type (irregular vs. regular) as a between-item factor, and subject as a within-item factor, showed no effect of regularity, subject, or regularity ζ subject interaction.

Syntactic Processing Tasks

H.M. was within 1 SD of the CON mean on both tasks of Syntax Comprehension (Fig. 7). *T*-tests indicated that he performed significantly better than CON on both Syntax tasks ($P < 0.05$). These results suggest that H.M. has preserved syntactic processing, at least on those aspects of syntax measured by these tasks.

Longitudinal Analysis

For all four analyses, the interaction of Wechsler test form and time (year the Wechsler was taken) was nonsignificant. Upon removing the interaction term, there was no significant effect of time, when collapsing across all four test forms. There were, however, significant ($P < 0.05$) level effects of form, with WB-I having the highest mean scaled score, followed by WB-II and WAIS-R. Comprehension scores did show a marginally significant ($P < 0.1$) interaction between test form and time, with scores for the WAIS-R increasing across time (Fig. 8). The Vocabulary subtest showed a marginally significant ($P < 0.1$) negative relation with Time (pooling test forms and after removal of the nonsignificant interaction term). Individual correlations of Vocabulary and Time for each test form were, however, nonsignificant. For all four dependent variables (Information, Comprehension, Similarities, and Vocabulary), the lag 1 autocorrelation among residuals from the GLM model was nonsignificant, thus supporting the validity of *P* values from the GLM. These data therefore do not provide evidence for a significant change in lexical memory across time (Fig. 8).

We also compared H.M.'s 1997 performance on these four subtests of the WAIS-R to that of CON. H.M. was within 1 SD of the CON mean on all four subtests, giving no indication of a lexical or semantic memory impairment (Fig. 9). An ANOVA comparing performance across the four tests showed no effect of subject task, or subject ζ task interaction ($P > 0.5$).

DISCUSSION

The purpose of this investigation was to determine whether bilateral damage largely restricted to medial temporal-lobe structures 1) disrupts lexical processing of already-learned words (words

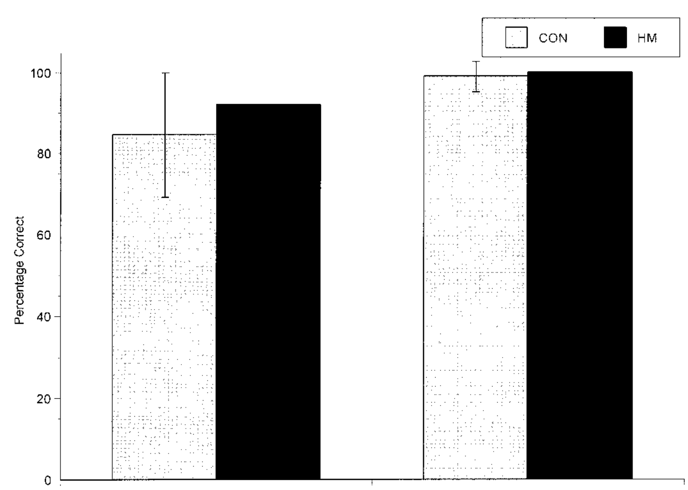

FIGURE 7. **H.M. performed within 1 SD of the CON mean on syntax comprehension tasks. Bars indicate ±2 SD.**

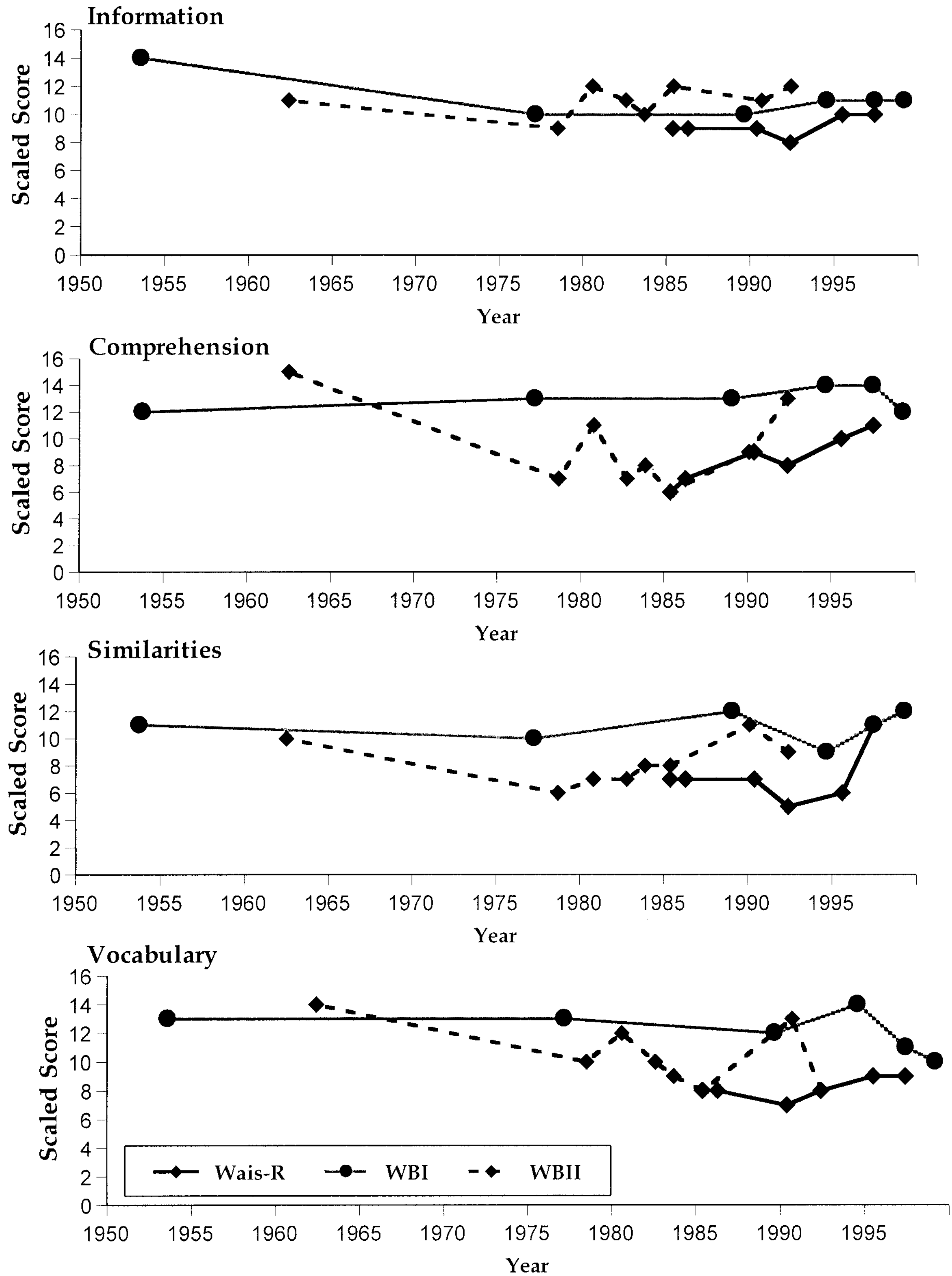

FIGURE 8. H.M. performed consistently across time on four tests of lexical memory. H.M. showed no significant decline across four subtests of the Wechsler-Bellevue I (WB-I), II (WB-II), and Wechsler Adult Intelligence Scale-Revised Edition (WAIS-R). The y-axis displays age-adjusted scaled scores.

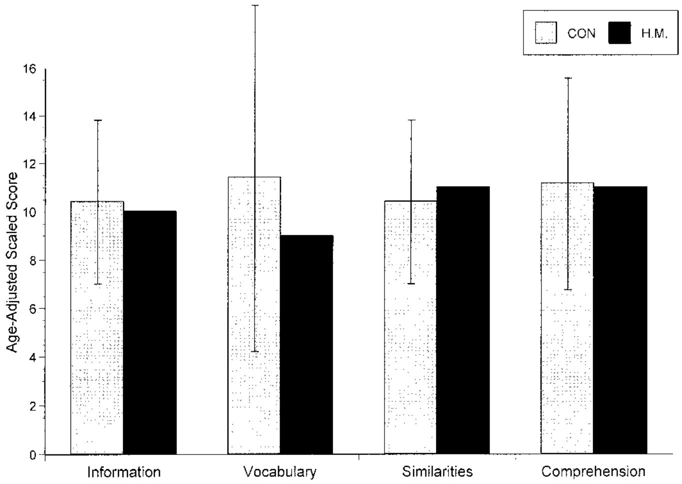

FIGURE 9. H.M. performed within 1 SD of the CON mean on the WAIS-R Subtests of Information, Vocabulary, Similarities, and Comprehension. Bars indicate ±2 SD.

learned preoperatively), 2) impairs grammatical processing, or 3) results in a degradation of lexical processing over time. Additionally, by answering these questions, this study allowed clarification of whether lexical memory is dissociable into separable components for underlying the acquisition of new words, and the processing of previously learned words. To our knowledge, this study is the first extensive analysis of lexical memory and grammatical processing in global amnesia. Although a number of authors have broached the issue of language function in amnesia (Ostergaard, 1987; Gabrieli et al., 1988; Shapiro et al., 1992; MacKay et al., 1998a,b), these papers focused on only a few tasks to assess language capacity. In addition, no studies have looked at lexical or semantic memory longitudinally in global amnesia.

H.M. performed as well as control participants on a wide range of lexical memory tasks, including picture-naming tasks and morphological production and judgment tasks. The notable exception was H.M.'s impaired performance on the category fluency and letter fluency tasks. We do not believe that these deficits are related to his temporal lobe damage. Neocortical temporal lobe regions seem to be more important in category than letter fluency (Newcombe, 1969; Mummery et al., 1996; Gourovitch et al., 2000; Martin et al., 1994). If H.M.'s performance on these tasks were related to the extensions of his lesion to neocortical temporal regions, we would expect him to do worse on category fluency as compared to letter fluency. This pattern is not the case; H.M. did equally poorly on both tasks. It should be noted that the fluency tasks were the only tasks requiring declarative memory: Because H.M. orally generated responses, he had to be able to remember his prior responses so as to avoid repeating items. To clarify whether his lower fluency scores were related to declarative memory decrements, we looked at his performance on the Thurstone fluency task (administered during a separate testing session in 1998). This task gives participants 4 min to write as many four-letter words beginning with C as possible, and 5 min to write as many S words as possible. Because responses are written, declarative memory is not necessary to avoid repetition of words. On this task, within the first minute, H.M. wrote four words beginning with "C" and five words beginning with "S." These rates of generation are consistent with the verbal fluency scores he achieved. We therefore do not believe that H.M.'s impairment stems from a declarative memory deficit. Rather, H.M.'s impaired performance on this task is likely due to motor slowing. Because of years of antiepileptic medication (Dilantin), H.M. has cerebellar damage, affecting his motor speed, including speech output. This would be expected to affect the fluency tasks, as they were the only timed tasks in this investigation. The uniform rate at which he generated words (1–2 words per 15-s interval) contrasts with control participants' pattern of decreasing word production over time. This difference suggests that H.M.'s poor performance is due to slow responding, rather than an exhaustion of retrievable category exemplars.

Until this investigation, it was unclear whether H.M. had shown a decline of lexical memory across time. It had been alternatively claimed that H.M.'s preoperatively acquired semantic knowledge remained intact (Milner et al., 1985), and that evidence suggested an age-related lexical decline (Corkin, 1984). Our longitudinal data resolved this question, indicating that H.M.'s lexical memory has remained consistent since the time of his operation. While he did show a reduced lexical memory performance in the early- to mid-1980s, likely leading to Corkin (1984) reporting semantic memory reductions, the decline was transient; his scores from the late 1980s onward have been at the same level as he achieved preoperatively.

Importantly, this finding also suggests that lexical information can be maintained without explicit reinforcement. Even though H.M. was not consciously reminded about questions such as those that appear on the Information subtest of the WAIS (e.g., "Who was president during the Civil War?"), he is as likely to be able to correctly answer that question today as he was preoperatively.

Our results suggest that H.M.'s deficit on ambiguity detection (MacKay et al., 1998a,b; Schmolck et al., 2000b) does not result from a core deficit in either grammatical processing or lexical memory. It is possible that additional capacities, unrelated to the medial temporal lobe, are required by these tasks. This possibility is supported by findings that H.M. is more impaired at some aspects of ambiguity detection than are other amnesic patients with similar medial temporal-lobe damage (Schmolck et al., 2000, 2000b). In addition, patients who showed a deficit on ambiguity detection (including H.M.) have damage not only to the medial temporal lobe, but also at least some lateral temporal damage. The deficits in ambiguity detection may arise from this non-medial temporal-lobe damage. Alternately, these deficits may stem from factors unrelated to H.M.'s lesion, such as his upbringing or education.

Overall, we found that H.M. performed as well as control participants on lexical memory and grammatical processing tasks, giving no indication of a lexical or grammatical processing impairment. The results of this study suggest that medial temporal-lobe structures are not required for the retrieval and use of already-learned lexical information. This finding provides evidence for a dissociation within lexical memory. We know from prior investigations that H.M. is impaired at acquiring new lexical information (Gabrieli et al., 1988;

Postle and Corkin, 1998). Despite hundreds of testing sessions, H.M. was unable to learn new words, such as "xerox," that had entered the language after the time of his operation (Gabrieli et al., 1988). Similarly, he did not show priming to words that entered the language after the time of his surgery, despite normal priming for words learned preoperatively (Postle and Corkin, 1998). In contrast to this profound deficit in lexical acquisition, H.M. appears to have a spared capacity for retrieving lexical information acquired premorbidly. This result suggests a role for the medial temporal lobes in acquiring, but not retrieving or processing, already-established lexical information. Unlike posterior aphasics, who have substantial damage to neocortical temporal-lobe regions, and who show substantial impairments in lexical retrieval (Goodglass, 1993; Ullman et al., 1997, 2001), H.M.'s minimal damage to the temporal neocortex does not interfere with his capacity to retrieve lexical information and to use that information efficiently.

It is worthwhile comparing H.M.'s performance with that of patients with Alzheimer's disease (AD). AD participants have been found to have dramatic lexical memory deficits (Nebes, 1989; Ullman et al., 1997). In fact, semantic deficits have been shown to be an accurate measure for staging the disease (Locascio et al., 1995). AD is characterized by neocortical lesions in addition to medial temporal pathology. The difference between H.M.'s performance and AD patients' performance therefore must be related to the presence of cortical lesions in AD. Together with other evidence (for a discussion see Ullman, 2001), these results suggest that temporal/temporo-parietal regions, and not medial-temporal structures, subserve lexical memory retrieval. Our results from this investigation, coupled with those from previous studies of lexical memory (Ullman et al., 1997, 2001), suggest a dissociation within the mental lexicon, whereby medial temporal lobe structures are required for the acquisition of new lexical knowledge, while the neocortex is recruited for the retrieval and use of well-established lexical information. This dissociation parallels that of episodic memory as proposed by Squire and colleagues (Squire and Zola-Morgan, 1991; Squire, 1992; Zola-Morgan and Squire, 1990; but see Nadel and Moscovitch, 1997). They propose that the hippocampus and other medial temporal lobe structures are recruited for initial encoding and storage of an episodic memory trace, but are no longer needed for episodic memory retrieval after time has passed; instead, retrieval relies on surrounding neocortical structures.

In conclusion, we found that lexical and grammatical processing were preserved in amnesic patient H.M. His lexical memory has remained stable over the last 46 years, and he continues to perform as well as control participants on a range of language tasks. These results, in conjunction with other work from our laboratories (Postle and Corkin, 1998; Gabrieli et al., 1988; Ullman et al., 1997; Ullman, 2001), support a dissociation within lexical memory, with medial temporal-lobe structures required for the acquisition of lexical information, and the neocortex, in particular temporal/temporo-parietal regions, subserving the use of already-established lexical information.

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APPENDIX

The words included on the spelling test were: go, up, my, time, street, live, soft, five, saint, river, deep, stay, upon, could, track, buy, provide, goes, together, death, retire, objective, proper, carry, property, convict, visitor, drown, wreck, supply, accident, affair, associate, political, probably, application, offensive, extreme, emergency, foreigner, development, intelligent, leisure, size, orchestra, syllable, mortgage, persistent, investment, incessant.