Some Relationships Between Global Amnesias and the Memory Impairments in Alzheimer’s Disease

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The question addressed by this chapter is whether the deficits in learning and remembering shown by amnesic patients with pathology in the medial temporal zone and related structures are like or unlike the patterns of memory loss seen in Alzheimer’s disease. In the latter group, cell loss is found not only in the medial temporal region but occurs in the neocortex and subcortical structures as well; as a result the memory disorder is accompanied by a general dementia. In order to determine if memory disorders that occur in relative isolation from other cognitive deficits can be distinguished from memory disorders that form part of a general cognitive decline, comparisons were made between patients with global amnesia and patients with Alzheimer’s disease. The latter group was subdivided on clinical grounds into those with mild, moderate, or severe disability in activities of daily living for the purpose of seeing whether or not different patterns of memory deficit would emerge for these subgroups. A group of healthy elderly subjects was also included in the comparison because normal aging produces changes in brain and behavior that are qualitatively similar to those in Alzheimer’s disease, but markedly attenuated. Results concerning short-term retention, encoding processes, and learning processes are described below.

SUBJECTS

The 47 subjects of this investigation included 5 patients with global amnesia, 15 healthy elderly subjects, and 28 patients with Alzheimer’s disease (Tables 1 and 2).

Patients with Global Amnesia

The amnesic group consisted of 5 men who ranged in age from 24 to 55 years (Table 1). Four of them were college graduates, and the other had finished high school. The two instances of ruptured anterior communicating artery aneurysm had
<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Education (years)</th>
<th>Duration of amnesia (years)</th>
<th>WAIS vocabulary (scaled score)</th>
<th>Token test: receptive (max. = 36)</th>
<th>Reporter's test: expressive (max. = 26)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>W.A.</td>
<td>48</td>
<td>M</td>
<td>16</td>
<td>2</td>
<td>13</td>
<td>35</td>
<td>26</td>
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<tr>
<td>J.N.</td>
<td>55</td>
<td>M</td>
<td>16</td>
<td>3</td>
<td>14</td>
<td>35</td>
<td>22</td>
</tr>
<tr>
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<td>54</td>
<td>M</td>
<td>12</td>
<td>27</td>
<td>12</td>
<td>22</td>
<td>17.5</td>
</tr>
<tr>
<td>P.H.</td>
<td>42</td>
<td>M</td>
<td>16</td>
<td>22</td>
<td>12</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>A.G.</td>
<td>24</td>
<td>M</td>
<td>15</td>
<td>3</td>
<td>11</td>
<td>34</td>
<td>13</td>
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<td>Healthy elderly (N = 15)</td>
<td></td>
<td></td>
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<tr>
<td>(55–81)</td>
<td>66.9</td>
<td>4F, 11M</td>
<td>15.2</td>
<td>(10–19)</td>
<td>(10–19)</td>
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<tr>
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<td>5F, 6M</td>
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<td>(8–13)</td>
<td>29.3</td>
<td>17.8</td>
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<td>(51–75)</td>
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<td>(56–78)</td>
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<td>Patient</td>
<td>Etiology of amnesia</td>
<td>Verbal I.Q.</td>
<td>Performance I.Q.</td>
<td>Full scale I.Q.</td>
<td>Memory quotient</td>
<td>Delayed recall</td>
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<td></td>
</tr>
<tr>
<td>W.A.</td>
<td>Ruptured anterior communicating artery aneurysm</td>
<td>123</td>
<td>119</td>
<td>124</td>
<td>105</td>
<td>5</td>
<td>8</td>
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<tr>
<td>J.N.</td>
<td>Ruptured anterior communicating artery aneurysm</td>
<td>134</td>
<td>107</td>
<td>125</td>
<td>100</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>H.M.</td>
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<td>97</td>
<td>108</td>
<td>104</td>
<td>64</td>
<td>1</td>
<td>0</td>
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<tr>
<td>P.H.</td>
<td>Encephalitis</td>
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<td>123</td>
<td>114</td>
<td>80</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>A.G.</td>
<td>Cardiac arrest with ischemic anoxia</td>
<td>85</td>
<td>92</td>
<td>87</td>
<td>56</td>
<td>2</td>
<td>0</td>
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</table>
Patients with Alzheimer's Disease

The diagnosis of Alzheimer's disease required a history of progressive intellectual deterioration and the exclusion of other conditions that are known to produce dementia (14). Accordingly, all patients underwent physical examination, CT scan, and a battery of laboratory tests. The group of 13 women and 15 men, whose ages ranged from 51 to 78 years, was divided into three subgroups: mildly demented, moderately demented, and severely demented (Table 1). The criteria for judging the severity of the dementia were qualitative and focused on how well the patient could function independently in everyday life. Memory capacities were de-emphasized, and test scores were not used in this determination. A rating of mild dementia indicated that the patient could be left alone at home for extended periods of time and might even live alone, could travel to MIT alone, and could perform all of the neuropsychological tests that were included in the protocol. The term moderate dementia implied that the patient could not perform a number of activities at home without assistance, could not get to MIT alone, had periods of confusion, and did not understand some testing procedures. A patient with severe dementia was one who needed help in dressing, grooming, and other activities of daily living, could not travel to MIT alone and once there was disoriented, and could not perform some tests. Institutionalized patients were excluded from this study, but presumably they would have fallen into a fourth category, very severe dementia. This global classification is crude but seemed worthwhile as a preliminary attempt to define subgroups of Alzheimer patients.

The subgroups of patients with Alzheimer's disease were comparable to the group of healthy elderly subjects in years of formal education but significantly inferior to them in terms of their scores on the WAIS Vocabulary subtest, the Token Test, and the Reporter's Test (Table 1). Within the Alzheimer group, the severely demented patients were significantly more handicapped on the Reporter's Test than were the mildly and moderately demented patients (Duncan's Multiple Range Test, alpha level = 0.05).

COGNITIVE TESTS AND RESULTS

The choice of cognitive measures for the comparison of amnesic patients, patients with Alzheimer's disease, and healthy elderly subjects was dictated in part by what tests the Alzheimer group could perform (8). Beyond that, an attempt was made to sample several memory processes. Three areas were investigated: short-term retention, encoding processes, and learning processes.

Short-term Retention

Because it is likely that different mechanisms govern the capacity of short-term memory as compared with forgetting in short-term memory, we administered tests to determine if they could be dissociated, either within the amnesic group or among groups. In addition, we compared short-term memory capacity for verbal and non-
verbal material. Three measures of short-term retention were digit span, block span, and the Brown-Peterson distractor paradigm.

**Digit Span and Block Span**

The immediate-memory span for digits was established for each subject by presenting strings of digits at the rate of 1 digit per sec and determining with Wechsler's (28) procedure the longest string that could be recalled correctly. The immediate-memory span for blocks was measured using a nonverbal test modeled after the digit span test (19, and P. Corsi, unpublished observations). The apparatus consisted of nine black blocks (cubes) attached to a black board in an impartial arrangement. The examiner tapped the tops of the blocks with a white pen in a particular sequence and, immediately thereafter, the subject tried to tap the blocks in exactly the same pattern. Block span was defined as the maximum number of blocks the subject was able to tap in the correct order.

One-way analyses of variance showed highly significant differences among the five groups for both digit span ($p = 0.0003$) and block span ($p = 0.0001$) (Table 3). Post hoc comparisons of mean digit span scores indicated that the amnesic patients and healthy elderly subjects did not differ from each other but were significantly superior to the moderately and severely demented, who performed equally badly. The mean of the mildly demented group fell in the middle of the distribution and did not differ significantly from the other four means. In post hoc analyses of mean block span scores, the amnesics and healthy elderly subjects were comparable and significantly superior to the mildly and moderately demented, who again did not differ from each other but who significantly surpassed the severely demented.

**Brown-Peterson Distractor Task**

Forgetting in short-term memory was assessed using the Brown-Peterson method (2, 22). This procedure required subjects to hear a consonant trigram and to report it after having performed a distractor task. The distractor task, counting backward from a particular three-digit number, was intended to prevent rehearsal of the trigram during retention intervals of 3, 6, 9, 15, and 30 seconds. Trials were blocked by

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Digit span</th>
<th>Block span</th>
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<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
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<tr>
<td>Global amnesia</td>
<td>5</td>
<td>7.2</td>
<td>6–9</td>
</tr>
<tr>
<td>Healthy elderly</td>
<td>14</td>
<td>7.1</td>
<td>4–9</td>
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<tr>
<td>Alzheimer’s disease</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mild</td>
<td>11</td>
<td>5.9</td>
<td>3–7</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
<td>5.8</td>
<td>5–6</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>4.7</td>
<td>4–6</td>
</tr>
</tbody>
</table>
retention intervals. In a distractor-free, immediate-recall condition, subjects heard the trigram, repeated it aloud, heard the word “recall,” and attempted to recall the trigram.

In order to compare the performance of the 5 groups at each delay interval, 6 one-way analyses of variance were carried out (Fig. 1). There were no significant group differences at 0 delay, but all of the other comparisons were statistically significant (3 sec, $p = 0.0038$; 6 sec, $p = 0.0466$; 9 sec, $p = 0.0061$; 15 sec, $p = 0.0001$; 30 sec, $p = 0.0236$). Duncan’s Multiple Range Tests, performed on the data at each delay interval, showed the amnesic patients and healthy elderly subjects to be indistinguishable except at the 15-sec delay where the 4 patient groups achieved comparable scores, all significantly inferior to that of the healthy elderly group. Their achievement significantly surpassed that of the Alzheimer groups: of all 3 groups at the 3-, 9-, and 15-sec delays, of the moderately demented at the 6-sec delay, and of the moderately and severely demented at the 30-sec delay.

In summary, short-term memory capacity as measured by digit span and block span was preserved in global amnesia. Forgetting in short-term memory, measured by the Brown-Peterson distractor method, was relatively normal in some amnesics but not in others. Patients with Alzheimer’s disease were impaired in both capacity and forgetting measures of short-term memory. Performance on digit span and block span was roughly correlated with the severity of the dementia.

Encoding Processes

Verbal Recognition Memory

The levels of processing framework of Craik and Lockhart (9) embodies the idea that the subject’s activity at the time of stimulus input determines how well an item is encoded and, therefore, remembered. Thus, semantic processing of a stimulus should promote better recall than mere attention to its surface details. Although this theoretical approach has been widely criticized, the method is useful for com-

![Graph showing performance on the Brown-Peterson distractor task](image)

**FIG. 1.** Brown-Peterson distractor task: Performance of patients with global amnesia, healthy elderly subjects, and patients with Alzheimer’s disease.
paring different kinds of memory disorders and for understanding disturbances in long-term memory. The level of processing can be manipulated experimentally by requiring the subject to answer a question about each word in a list of words. We attempted to sample 3 levels of processing with the following types of questions presented orally: "Does a man/woman say the word?" (sensory level); "Does the word rhyme with ______?" (phonological level); "Is the word a type of ______?" (semantic level). The test consisted of 10 questions at each of the 3 levels; half of the questions at each level required a "yes" response and half required a "no" response. After the 30 trials had been completed, there was an unexpected test of verbal recognition memory, in which the examiner read 3 unrelated words and the subject had to choose which one he had heard before.

The expected advantage for semantically encoded information was apparent in the results for 2 of the amnesic patients, W. A. and P. H., and for the healthy elderly subjects (Fig. 2), whereas the Alzheimer groups performed poorly following all three types of questions. The most superficial processing condition did not distinguish the 5 groups of subjects (p = 0.1408), but the other two conditions did (rhyme, p = 0.0008; category, p = 0.0001). In the results of Duncan's Multiple Range Tests, the healthy elderly subjects stood out: Regardless of encoding strategy, they achieved significantly more correct responses than did the Alzheimer subgroups or the amnesic group.

The three amnesic patients who did not show the depth-of-processing effect attained scores on the Token Test and Reporter's Test that were below the lowest score achieved by a healthy elderly subject. This finding suggests that, as in Huntington's and Korsakoff's disease, deficits in verbal processing contribute to memory impairment (5). In a subsequent experiment with H. M. using shorter word lists,
the depth-of-processing effect was seen (Grove and Corkin, unpublished data). Patients with Korsakoff's disease also show differential recognition of words encoded as shallow and deep levels when the list length is short but not when it is long (6).

In summary, the normal effect of depth-of-encoding on subsequent verbal recognition memory for 30 words was seen only in healthy elderly subjects and in the amnesic patients whose other cognitive functions were clearly preserved. This effect was not found in 3 amnesic patients who had slight deficits in language capacities or in the Alzheimer groups.

**Learning Processes**

Learning was examined using 2 paired-associate-learning tasks, one verbal and the other nonverbal, and with the Gollin Incomplete-Pictures Test.

**Verbal and Nonverbal Paired-associate Learning**

The verbal test, which was designed specifically for use with elderly subjects (15), consisted of 3 stimulus-response pairs, which were read once by the examiner: for example, FLOWER-SPARK; TABLE-RIVER; BOTTLE-COMB. Then the stimulus words (flower, table, and bottle) were presented orally, one at a time, and the subject was asked to recall the appropriate response word (spark, river, or comb) within 10 sec. If the subject's answer was correct, the examiner said, "Right"; if wrong, the examiner said, "No" and supplied the correct word. This correction procedure was continued until the subject reached a criterion of 3 consecutive correct responses for each of the 3 stimulus words, or until each had been presented 30 times. The score was the total number of times the stimulus words were presented before the criterion was reached; scores could range from 3 to 93.

The nonverbal paired-associate learning test used geometric drawings that were moderately difficult to label verbally and therefore were likely to be coded visually. Like the verbal test just described, the nonverbal test consisted of 3 stimulus-response pairs that were shown once, one pair at a time on individual cards. In the remainder of the test, recognition was measured by presenting the 3 stimulus figures individually at the top of a card, with all 3 response figures below. During each such presentation, the subject was asked to choose the response figure associated with that stimulus. The correction procedure and criterion of learning were the same as in verbal paired-associate learning.

All 5 amnesic patients were able to achieve the criterion of learning with both the verbal and nonverbal paired-associates (Fig. 3), indicating that these tests make relatively light demands on learning processes. For all groups, the verbal task, which involved recall testing, was more difficult than the nonverbal one, which involved recognition testing. Recognition is typically, though not always, easier than recall (3).

The analysis of variance revealed statistically significant effects of group in both tests (verbal, \( p = 0.0001 \); nonverbal, \( p = 0.0023 \)). In verbal paired-associate learning, the healthy elderly subjects reached criterion in significantly fewer trials
FIG. 3. Verbal and nonverbal paired-associate learning: Comparison of patients with global amnesia, healthy elderly subjects, and patients with Alzheimer's disease.

than did all other groups. In nonverbal paired-associate learning, the healthy elderly subjects were significantly more efficient than were the moderately and severely demented Alzheimer groups, but there were no significant differences among the healthy elderly, amnestic, and mildly demented groups. On both tasks, the amnesics significantly surpassed the severely demented patients, but these two tests did not distinguish the 3 Alzheimer groups from each other.

Gollin Incomplete-Pictures Test

The Gollin Incomplete-Pictures Test (13,20,27) was used to assess both visual perception and perceptual learning. The stimulus materials consisted of simple line drawings of 20 animals and common objects, each in 5 degrees of fragmentation. In Trial 1, all 20 drawings were presented in their most fragmented version for about 1 sec each, and the subject was encouraged to guess what each one represented. This procedure continued in Trials 2 through 5, with the 20 drawings becoming more complete on each successive trial. Testing stopped when the subject identified all 20 drawings in a given trial or at the end of Trial 5. The recognition scores provided an index of competence in visual perception. Perceptual learning was assessed by repeating the test procedure with the same stimulus materials after delays of 1 hr and 24 hr, and then calculating the reduction in errors on retest.

The recognition-test data indicated that W. A. and H. M. recognized the 20 drawings correctly by the fourth trial, but that J. N. and P. H. required an additional trial to demonstrate errorless performance (Fig. 4). (A. G. has not yet been given this test.) The 4 who were tested showed steady improvement from trial to trial, suggesting that these patients did not have significant handicaps in visual form-recognition capacities. Their perceptual learning skills, assessed by retest scores
obtained at various times after the initial test (Fig. 5), showed maximum savings on the first retest, even when this session took place after 4 months (see P. H.’s data) rather than after 1 hr, as was typically the case. It appears that H. M. showed impressive savings in 1980, 13 years after his first test-retest session (20), and subsequent testing showed further improvement, although at no time did he remember having done the test before. This learning without awareness is consistent with H. M.’s capacity to acquire new motor skills (7). It is also reminiscent of the monkey’s ability after bilateral amygdalohippocampal resection to remember objects that had been presented in single trials 24 hr apart, despite severe deficits on other visual and somatosensory recognition tasks (M. Mishkin et al., *this volume*).

The statistical comparisons of the healthy elderly and the Alzheimer groups revealed significant effects at all 3 testing times and on all trials, except Trials 3 through 5 in the second-delay testing, when many subjects already had correctly recognized all 20 pictures (Fig. 5). The scores of the amnesic patients were not included in this analysis of delayed test results because these men had not been retested at precisely the same time intervals as had the healthy elderly and Alzheimer groups. Although the amnesic patients performed as well as the healthy elderly
FIG. 5. Gollin Incomplete-Pictures test: Mean test-retest scores of the healthy elderly and Alzheimer groups.

subjects on the initial test, the improvement between the initial test and the first retest was more marked in the healthy elderly subjects. This discrepancy seemed reasonable when one considered that after the initial test, the healthy elderly subjects might have been able to remember the pool of 20 objects and animals from which their responses would be drawn, whereas the amnesic patients might have had a smaller pool in memory to draw upon, or none at all, depending on the severity of the amnesia.

Trial-by-trial comparisons were made of the mean scores that the healthy elderly and 3 Alzheimer groups achieved in the 3 test sessions. In Trials 1 through 3, healthy elderly subjects made significantly fewer errors in the 2 retest sessions than they had in the initial test, indicating marked savings. The mildly demented patients also showed significant improvements in retest scores, though only on Trials 1 and 2. In contrast, analyses of the mean scores of the moderately and severely demented Alzheimer patients showed no statistically significant differences on any trial. Thus, their dementia prohibited perceptual learning.
In summary, learning processes were more impaired in Alzheimer patients than in amnesic patients, and within the Alzheimer group, impairment was related to the severity of dementia.

DISCUSSION

This chapter compares patients with a relatively pure global amnesia that was unaccompanied by substantial loss in other cognitive capacities and patients with Alzheimer’s disease, whose severe memory disorder occurred together with a marked disturbance of other cognitive functions. The results presented here indicated that, in general, patients with Alzheimer’s disease were more impaired both on short-term and long-term memory tests than were patients with global amnesia resulting from pathology in the medial temporal zone. The fact that patients with Alzheimer’s disease differed from amnesics not only in the presence of associated cognitive decline but also in the severity of the memory disturbance suggests that in dementia there is an interaction between memory capacities and other cognitive processes such that the deficits in both domains are more severe than they would have been in isolation. Support for this claim is provided by the finding that within the Alzheimer group, memory-test performance was correlated with the severity of the dementia. As an example of how memory disorders and other cognitive deficits might interact, it is reasonable to suppose that impairment in verbal comprehension could hinder the learning of word lists, while an inability to remember which strategies had failed in a problem-solving task might lead to an unsuccessful outcome.

There is an alternative explanation of the severe intellectual loss in dementia that does not assume an interaction among cognitive systems. This view holds that all cognitive functions are dampened uniformly in Alzheimer’s disease as a result of an impairment in some chemical or physiological mechanism that would cut across the behavioral repertoire in a nonspecific way. Although the present experiment was not designed to explore such a possibility, the more profound drop in mnemonic capacities compared to other cognitive processes in Alzheimer’s disease suggests that memory mechanisms are disproportionately affected.

It is of interest to know the extent to which patterns of impaired and preserved memory function in global amnesia coincide with the descriptions of and distinctions among human memory systems proposed by cognitive psychologists. A hypothesized difference among systems would be reinforced if these systems were dissociable in neurological disease; one such suggestion distinguishes short-term from long-term memory functions. There is now considerable evidence that both of these capacities are impaired in patients with Korsakoff’s disease (reviewed in 4) as they are in patients with Alzheimer’s disease. This finding, however, might occur only in amnesic populations in which the neuropathology is characterized by multiple atrophic changes involving both neocortex and subcortical structures (26), and where the memory impairment, not surprisingly, is accompanied and exacerbated by a variety of other behavioral deficits (21). In amnesic patients presumed to have
medial temporal disorders, the present study revealed a different pattern of sparing and loss, consisting of an alteration in long-term but not short-term memory function. These findings extend the observations made previously about H. M. (20,29) to other patients with amnesic syndromes in which structures in the medial temporal region are also implicated, but where the etiology is different. Nevertheless, the possibility exists that deficits will be detected when a greater variety of short-term memory processes are examined in these patients.

Another way of conceptualizing human memory capacities is to consider semantic memory (consisting of general knowledge, including rules) as distinct from episodic memory (comprising personal knowledge relating to individual past experiences having specific temporal and spatial tags) (25). The memory tests reported in this chapter are all measures of episodic memory capacities, and it is clear that both amnesic patients and patients with Alzheimer’s disease are impaired in this respect. The amnesic patients studied here, however, do not show evidence of a selective impairment of episodic memory concomitant with a preservation of semantic memory as others have suggested (16). First, there is adequate retrieval from episodic memory of information consolidated before the period of retrograde amnesia. For example, H. M. knows the name of the neurosurgeon who operated on him and can describe childhood vacations with his family. Quantitative tests of remote-memory function should be administered to the amnesic patients who served in this study as a further test of the integrity of premorbid episodic memory. Second, although the preservation of premorbid intellectual functions in amnesic patients indicates a sparing of semantic memory for that period, it is important to note that their fund of semantic knowledge acquired since shortly before the onset of amnesia is meager and clearly inferior to that of control subjects. The dissociation of impaired and preserved abilities following disturbances in the medial temporal region does not correspond to the hypothesized episodic and semantic memory systems. N. J. Cohen (unpublished observations) has suggested that the pattern of sparing and loss in amnesia highlights the distinction between procedural (knowing how) and declarative (knowing that) knowledge. The results described here support that view. The study of patients with memory disorders is a powerful tool in examining theoretical issues of this sort.

ACKNOWLEDGMENTS

I thank my collaborators, John H. Growdon and Edith V. Sullivan, for providing clinical assessments of patients and advice on dementia ratings. They also made insightful comments on the manuscript as did Neal J. Cohen, Brenda Milner, and Mary Jo Nissen. I am grateful to Lois Kellerman for the data analyses, to Karen Shedlack for her dedication to all aspects of the research, and to Harris Funkenstein, Brenda Milner, Michael S. Perlman, William B. Scoville, and John F. Sullivan for allowing their amnesic patients to be examined at the MIT Clinical Research Center. The administrative, nursing, and dietary staffs of the MIT Clinical Research
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