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Very Long-Term Amnesia in Association with Temporal Lobe Epilepsy: Evidence for Multiple-Stage Consolidation Processes

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The temporal fractionation of long-term retention remains a relatively uncharted area in human memory research, and in particular there is little in the way of neuropsychological data that address this issue. We describe a patient with temporal lobe epilepsy who complained of amnesia for important events that had occurred in the previous 3–24 months, but who reported that her short-term and medium-term memory were normal. She displayed normal performance on traditional tests of short-term and long-term retention, performing at a very similar level to that of age- and sex-matched healthy control subjects on immediate and half-hour delayed recall measures. Forty days later, however, she showed a dense amnesia for recall of such information, whereas control subjects could readily recall much of the original stimuli. She also showed evidence of memory loss for news events that had occurred over the previous few years. MRI scanning and EEG brain mapping indicated left temporal lobe pathology, with a possible epileptogenic focus in the left anterior hippocampus. These data provide empirical evidence for the existence of a distinct very long-term consolidation process in human episodic memory and point to its neural correlates in the temporal lobe. Transfer of information into a permanent long-term memory store may entail multiple-stage consolidation processes rather than a single-stage, unitary consolidation process. © 1997 Academic Press

INTRODUCTION

The fractionation of human memory into various subsystems has now been well established (Schacter & Tulving, 1994). Such fractionation has tradi-

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tionally been along the lines of the particular cognitive domain that characterizes a specific memory subsystem. Fractionation of human memory along temporal domains was initially attempted in the early 1960s, with the distinction made between short-term and long-term memory. Data from the classical, pure amnesic syndrome were initially used to help bolster the distinction between short-term memory and long-term memory (Baddeley & Warrington, 1970). Although the importance of delineating a short-term or ''working memory'' system is fairly well established, little hard evidence exists on the temporal characterization of memory systems beyond the short term. Information that has been successfully stored in the brain and that is more than a few minutes old has traditionally been considered to have transferred from short-term memory into a long-term episodic memory system (Baddeley, 1990; Parkin, 1993). The classical view, dating back to the ''dual trace'' hypothesis of Hebb (1949), has assumed that consolidation into such a permanent memory store comes about as a result of a single-stage, unitary process rather than a multiple-stage process (Weingartner & Parker, 1984). More recently, Rose (1992) has stated that ''. . . for declarative memory there is a transition, over a period of minutes to hours, from the initial and labile short-term phase to long-term stable memory'' (1992, p. 208). Roland (1993) has noted that the ''peculiar thing about long-term memory is that it takes about one hour to be established'' (1993, pp. 303–304).

There are a number of scattered pieces of evidence that question the simple division between a short-term or working memory system, which covers time periods of a few seconds or minutes, and a long-term memory system that covers all intervals thereafter. Firstly, as early as 1966, McGaugh noted that ''there may be three memory trace systems: one for immediate memory; one for short-term memory which develops within a few seconds or minutes and lasts several hours; and one which consolidates slowly and is relatively permanent . . . There is increasing evidence for a 'tri-trace' system, and our findings are at least consistent with such a view'' (1966, p. 1537).

Secondly, in a paper that reviewed some of the work on the effects of ECT on memory and related research, Squire (1986) noted that ''consolidation can proceed for as long as several years, during which time memory depends on the integrity of the neural systems that have been damaged in amnesic patients'' (1986, p. 1615). Some patients with focal medial temporal lobe or diencephalic pathology (Zola-Morgan, Squire & Amaral, 1986; Kapur, Scholey, Moore, Barker, Mayes, Brice & Fleming, 1994) appear to have a short retrograde amnesia that covers a period of months, or at the most a few years, lending further support to a temporally graded long-term consolidation mechanism.

In addition, there have been several recent papers which suggest that certain brain damaged patients may show normal memory functioning at intervals of a few minutes or even a few hours, yet after a day or longer their memory performance for the same type of material is significantly impaired.

Martin, Loring, Meador, Lee, Thrash, and Arena (1991) found that, on a word-list learning test, patients with temporal lobe epilepsy performed normally in their word-list recall after 30 min, but showed impaired retention after 24 hr. De Renzi and Lucchelli (1993) reported a case of focal retrograde amnesia where there appeared to be good memory for items after 4 hr but poor memory after 13 days.

A recent paper by Ahern, O'Connor, Dalmau, Coleman, Posner, Schomer, Herzog, Kolb, and Mesulam (1994) also described a patient with normal memory for events after a few hours but very poor memory after a few days. Their patient was a 38-year-old man who had a three year history of depression, memory loss, decreased libido and increased appetite. He also had a two year history of temporal lobe epilepsy, with 20–30 seizures per day at time of presentation. Investigations showed a testicular tumor and a paraneoplastic limbic encephalitis. Initial MRI scans in 1987 showed abnormal signals in the medial temporal regions, more in the left than the right, and also some ventricular dilatation. MRI scans in 1989 and 1990 showed left anteromedial temporal lobe atrophy. The patient had a Wechsler Memory Scale—Revised *General Memory Quotient* of 120 and a *Delayed Memory Quotient* of 111, and yet he presented with a significant degree of retrograde amnesia. Although no formal very long-term retention test data were reported, Ahern et al. noted that on many occasions, he was ''able to learn and retain new information across relatively long delay intervals ranging from 30 minutes to several hours . . . In marked contrast, J.T. was unable to remember major autobiographical and current events that had occurred days or weeks before each test session . . . J.T.'s anterograde amnesia was characterized by an unusually rapid rate of forgetting over a time course of hours to days'' (1994, p. 1271). Their patient had a subsequent right temporal lobectomy that left him densely amnesic, with the features of a more classical amnesic syndrome.

In this paper, we describe a patient whose memory dysfunction was similar to the patient described by Ahern et al., but with evidence of more focal memory deficits, in that retrograde amnesia was not present to a significant degree. In our case, we were able to gather data from a specially designed test of very long-term retention and to complement this with data from tests of public events memory. We were also able to gather evidence from a range of imaging procedures that offered clues as to the pathological mechanisms underlying our patient's memory disorder.

CASE REPORT

P.A., a 62-year-old woman initially presented in November 1991 with amnesia for holidays that she had taken over the previous 18 months. For example, she had been to France in September 1990, but she had no recollection at all of the holiday. Autobiographical memory for pre-illness events was normal or only mildly impaired. A range of neurological, imaging and neuropsychological investigations carried out in 1992 and early 1993 were normal. Her memory symptoms persisted, and in 1994 she also developed minor absence seizures. Although there was no evidence of these in previous years, it remains possible that they had been present but not readily detectable by the patient or her neurologist. In June 1994, EEG brain mapping was carried out using a 29-electrode montage that allowed for more focused mapping of the temporal lobes. Although abnormal discharges were occasionally seen in the right temporal lobe, the most frequent spikes were considered to arise from left inferior-anterior temporal lobe structures (Fig. 1).

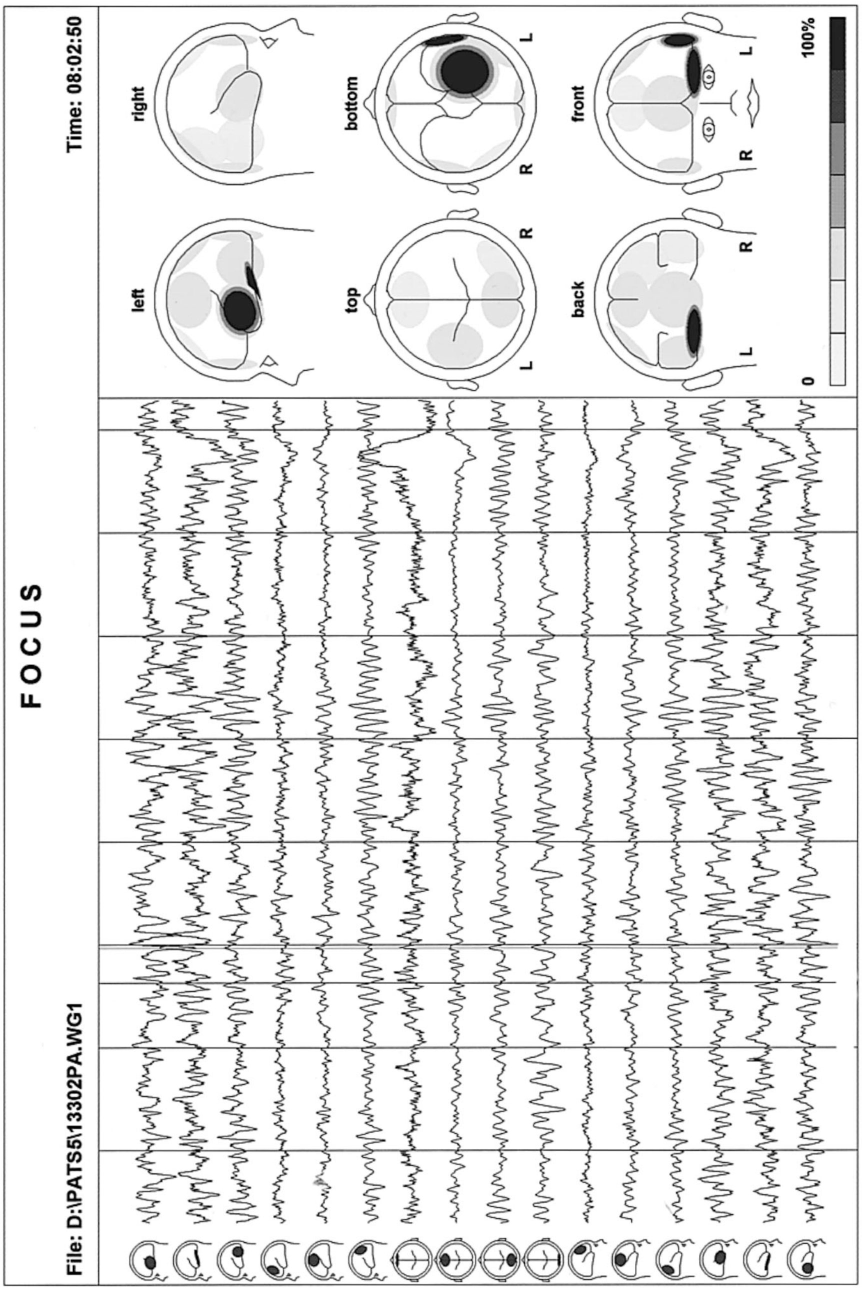
MRI scanning was carried out using sequences that focused on temporal lobe and limbic-diencephalic structures. The scan images were compared with those of an age-matched control subject, who was scanned using an identical set of imaging sequences. Ratings of a wide range of anatomical structures, including the hippocampus and temporal lobe gyri, were made using an established protocol (Kapur, Barker, Burrows, Ellison, Brice, Illis, Scholey, Colbourn, Wilson, & Loates, 1994). These ratings were made independently by two experienced neuroradiologists, who were blind to the neuropsychological test data. The scans were also reviewed independently by a third neuroradiologist. Using this procedure, a focal area of abnormality in the left anterior hippocampus was found (Fig. 2). It was not possible to delineate the precise aetiology or pathological nature of this abnormality. An FDG PET scan was found to be normal.

Detailed neuropsychological testing was carried out in 1994. On standard neuropsychological tests, P.A. displayed excellent performance, both on standard memory tests and on other cognitive tasks. For example, on the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981) she had a Verbal IQ of 133, a Performance IQ of 131, and a Full Scale IQ of 138. On the Wechsler Memory Scale—Revised (Wechsler, 1987), she had a General Memory Quotient of 116 and a Delayed Recall Quotient of 116. On other general cognitive tasks, including tests of naming (McKenna & Warrington, 1983), face perception (Benton, Van Allen, Hamsher, & Levin, 1975), card sorting (Nelson, 1976) and verbal fluency (Lezak, 1983), she also performed well within the normal range. Recognition Memory Test (Warrington, 1984) performance was excellent for words (49/50) and for faces (49/50).

EXAMINATION OF VERY LONG-TERM MEMORY: WMS-R

Method

Very long-term memory (VLTM) was tested in three ways. First, 6 weeks after initial testing with subtests from the Wechsler Memory Scale—Revised (WMS-R), P.A. was presented with specially designed versions of the items in the recall tests. We selected two subtests from the WMS-R that were used in the delayed, 30-min recall testing—the story recall (logical memory) and visual design (visual reproduction) subtests. These subtests yielded the most reliable very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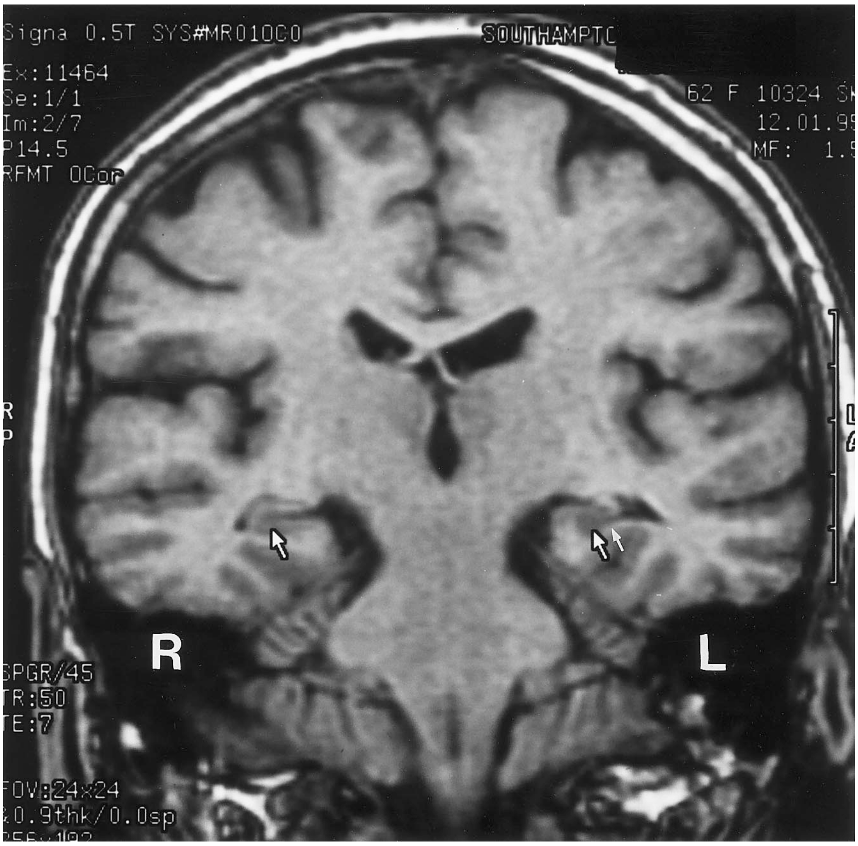

FIG. 2. Left hippocampal abnormality (twin arrows) as evident on coronal view of MR imaging sequence, compared to the normal right hippocampus (single arrow).

FIG. 1. ''Brain map'' representing data from EEG recordings carried out using a 29-electrode placement protocol that enabled detailed monitoring of abnormal electrical activity from the temporal lobes. EEG recordings were transformed into signals of source activity using a software package that provided source montages (FOCUS EEG Source Imaging and Review Software (1994), Dr M Scherg, Schinkelstrasse 37, D-80805, Munich). These source montages are the weighted combinations of the recorded scalp EEG signals, with weights being selected on the basis of multiple dipole models to enhance the activity from one brain region while suppressing the contribution of other brain regions. The vertical lines indicate the point from which the particular image montage was determined. The greatest abnormality is in the left anterior-inferior temporal lobe.

long-term retention data in pilot studies. For each subtest, free recall and recognition recall versions of the test were constructed. The second and third procedures involved the use of news events.

Story recall. Very long-term memory (VLTM) for the two WMS-R Logical Memory passages consisted of a request, 6 weeks after initial testing, for free recall of each of the two stories (following standard administration procedures for 30-min delayed-recall, without any cues). Recognition memory for the story content was then tested in the following manner. Each story was divided into nine ''idea units,'' and a set of four-choice recognition questions was constructed for each item. For example, the first recognition item for story A was *What was the woman's name?* (A) *Anna Thomas,* (B) *Anna Thompson,* (C) *Anita Thompson,* or (D) *Anita Thomas*. The subject was asked to indicate which one of these four items (A–D) came from the story. The location of the correct item amongst the three distractors, presented after each question, was systematically varied within each of the nine sets.

Visual design recall. The assessment of VLTM for the four WMS-R Visual Reproduction stimuli consisted of a request, 6 weeks after initial testing, for free recall of the designs according to standard administration procedures, followed by visual design recognition testing. As with recognition memory assessment for the two stories, each subject was shown an array of four designs, consisting of the original and three distractors. The subject was asked to choose the one design that had been originally presented. A total of five arrays were shown (see Figs. 3a–3e), one array for each of the first three WMS-R Visual Reproduction test items and one array for each of the two parts of the fourth test item. The location of the target item within each array was systematically varied.

Results

The performance of both P.A. and control subjects on the VLTM version of the Wechsler Memory Scale—Revised is shown in Table 1. Four control subjects were matched for sex, age (mean age = 65.3 years, range = 62–68 years), socioeconomic background, and performance on the National Adult Reading Test (mean IQ estimate score = 121.1, range = 120–122). At the time of testing, P.A. was 62 years old and had a NART IQ score of 124. As can be seen in Table 1, the two sets of scores, between P.A. and the control subjects, were closely matched for the immediate and 30-min delayed recall conditions, but P.A. showed poor free recall of both the stories and designs after a 6-week delay period. In addition, although she was also impaired in her performance on the verbal recognition memory test, her performance on the visual recognition memory test was similar to that observed for the control subjects. Of note, the immediate and 30-min delayed recall data obtained for the four control subjects, for both the stories and designs, were similar to those reported in the standardization data published in the WMS-R manual (Wechsler, 1987). The slight functional asymmetry in P.A.'s memory performance, noted above, may relate to the left temporal lobe focus of her lesion.

EXAMINATION OF VERY LONG-TERM MEMORY: PUBLIC EVENTS

Methods and Results

The second and third procedures for testing P.A.'s very long-term memory involved the use of public events test materials. P.A.'s memory for whether

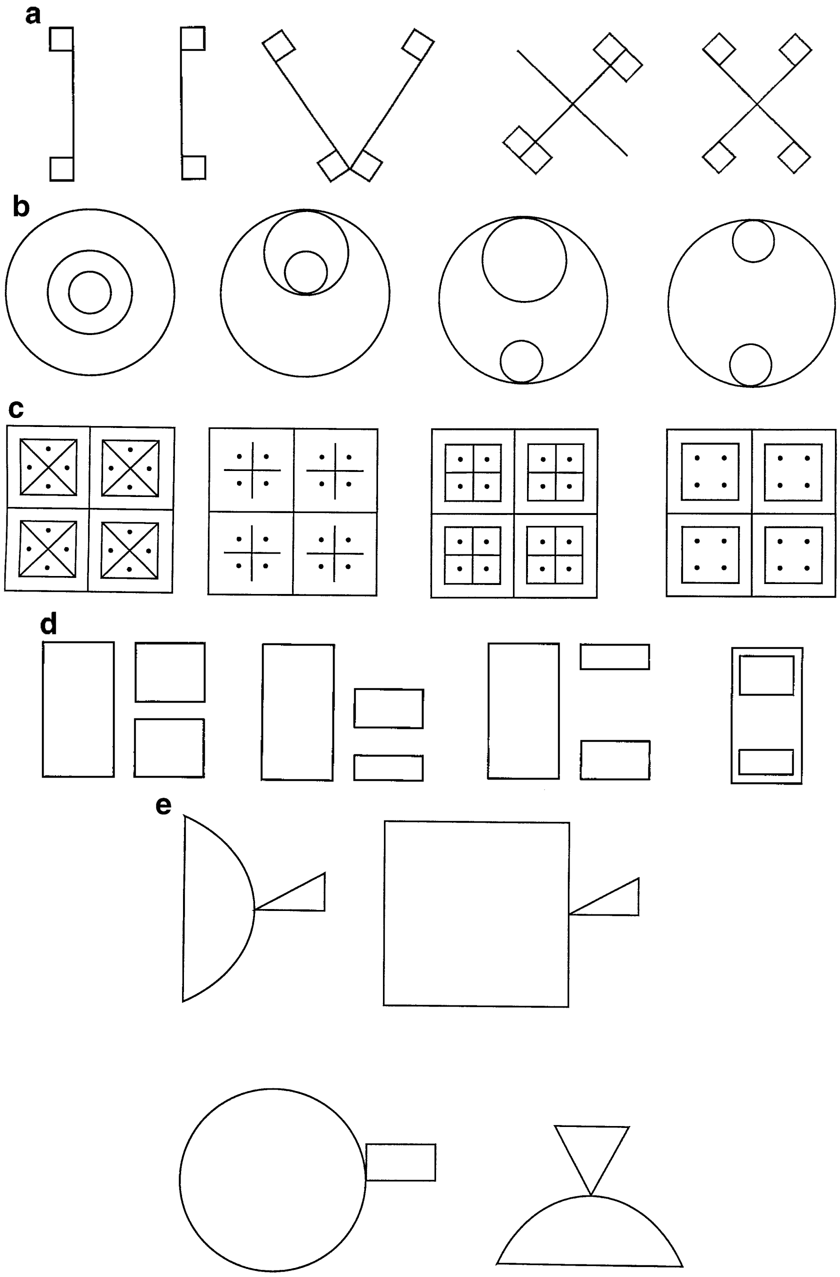

FIG. 3. (a–e) Sets of visual designs used in the 40-day delayed recognition memory test.

TABLE 1
P.A.'s Immediate Recall, 30-Min Delayed Recall, Very Long-Term Recall, and Very Long-Term Recognition Memory Performance on Story and Visual Design Subtests from the Wechsler Memory Scale—Revised

			Six weeks	
	Immediate recall	30-min recall	Recall	Recognition
Story retention				
Patient P.A.	26/50	20/50	0/50	2/18
Control subjects	24.5/50 (range = 18–34)	19.75/50 (range = 14–24)	11/50 (range = 9–16)	11.5/18 (range = 9–13)
Visual design retention				
Patient P.A.	36/41	35/41	0/41	4/5
Control subjects	31.5/41 (range = 22–37)	23/41 (range = 16–28)	7.0/41 (range = 5–10)	4.25/5 (range = 4–5)

famous personalities were dead or alive was assessed using a procedure that has been shown to be useful in detecting very long-term memory deficits (Kapur, Young, Bateman, & Kennedy, 1989). In addition, she completed a test of her memory for specific news events that had taken place over the past 40 years. The four control subjects for this portion of the study were also closely matched to P.A. for age and performance on the NART (mean age = 61 years; mean NART IQ score = 118).

For the Dead-or-Alive test, P.A. was shown a series of 135 names that had been famous over the past 50 years, mixed up with a further 49 fictitious names. She was first asked to read through the list of names and to mark those that were familiar to her. Having done this, she was then asked to go through those items that she had marked, and indicate which individuals were dead. She was then required to indicate the cause of death from four choices (natural causes, killed, accident and suicide), and also the decade in which the person died. A composite score (percentage of correct answers) was obtained that was based on these four types of responses. P.A.'s performance on these items, together with that of four matched control subjects, is shown in Fig. 4. As can be seen, she showed a temporally graded memory loss, which consisted of impaired performance for personalities who had died in the 1990s ($t = 5.85, p < .05$).

For the verbal news events test, P.A. and matched control subjects were presented with 94 news events that had occurred between the 1950s and the present. Each news event was paired with two other plausible but fictitious news events. The subject had to indicate which of the three events actually occurred. If she was correct, she was also asked a further specific question in relation to the news event, and she was also required to allocate the event to a particular decade. A composite score (percent correct) was computed, based on these three responses (Fig. 5). Consistent with her performance on

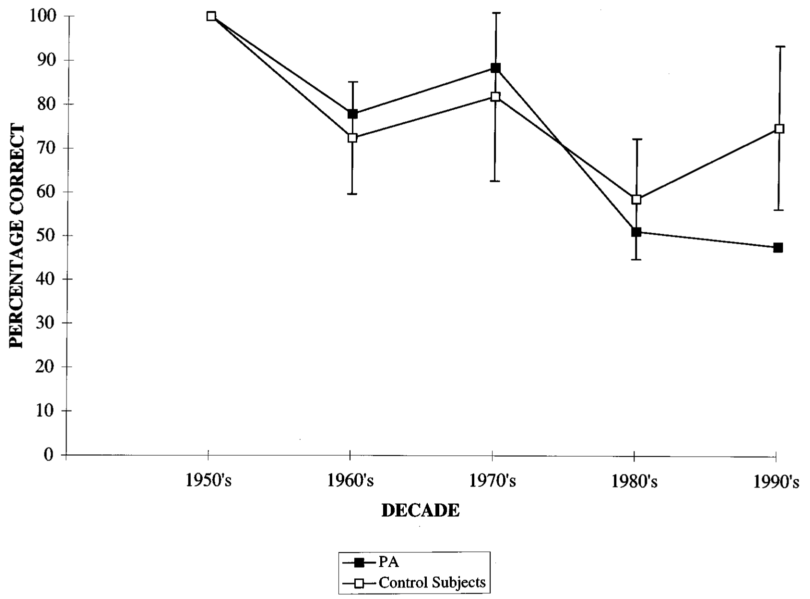

FIG. 4. Performance of P.A. and control subjects on Dead-or-Alive test. Error bars indicate two standard deviations.

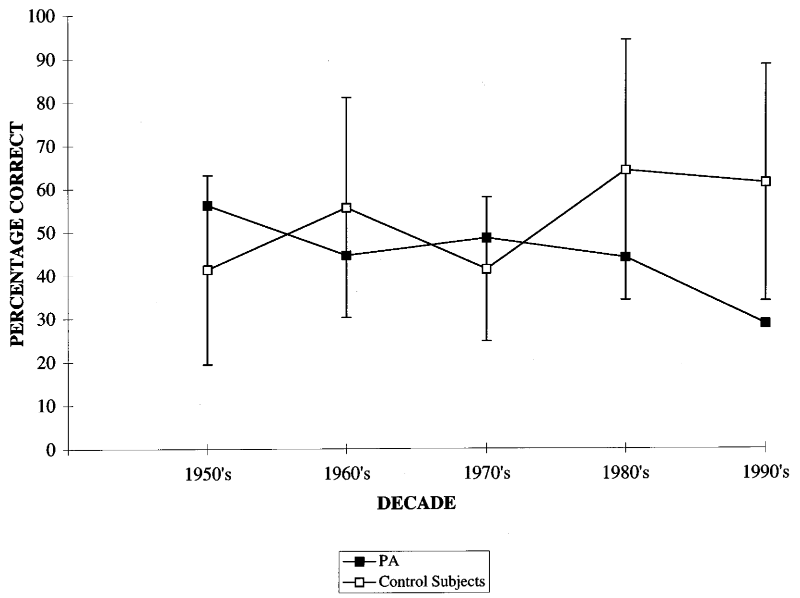

FIG. 5. Performance of P.A. and control subjects on Verbal News Events Test. Error bars indicate two standard deviations.

the Dead-or-Alive test, a significant memory loss for news items from the 1990s was found ($t = 5.34$, $p < .05$).

GENERAL DISCUSSION

Our findings corroborate clinical reports that indicate the presence of very long-term memory symptoms in the absence of amnesia on standard memory tests (Ahern et al., 1994; De Renzi & Lucchelli, 1993; Martin et al., 1991). In some of these reports, the range of neuropsychological deficits has been more diffuse, with additional cognitive impairments noted, or empirical data on memory functioning had not been gathered over a very long time period. Our case represents a unique presentation of focal cerebral dysfunction in association with a highly selective very long-term anterograde memory loss. In terms of neurological nosology, it may be necessary to consider the existence of a syndrome of ''very long term amnesia'' that complements the classical amnesic syndromes.

Our patient had been diagnosed with temporal lobe epilepsy, as was also the case in another similar patient that has been reported (Ahern et al., 1994). The precise role of the hippocampal abnormality seen on MR imaging is uncertain, although it may be making a direct contribution to the disruption of very long-term consolidation mechanisms. Subtle abnormalities, such as the one that we found in our patient, are similar to those described in other published studies of patients with temporal lobe epilepsy (Jackson, 1994); however, they must be treated with some caution in view of individual differences that probably exist in the normal population with regard to MR morphology, and in view of our patient's normal PET scan. It is possible that subclinical epileptiform activity may have been present over a several year period prior to this study, and that this may have interfered with very long-term consolidation processes. It is difficult to be certain if such disruption was at the level of storage areas in the temporal lobe, or at the level of pathways that interface the hippocampal formation with lateral white matter and neocortical areas. If the former is the case, one might have expected more in the way of major retrograde amnesia—similar to that found in other cases (Ahern et al., 1994; De Renzi & Lucchelli, 1993). However, we only found relatively mild retrograde memory deficits, which would support the possibility of a more medial locus for her lesion. It is possible that the hippocampal system itself does not have a direct role in very long-term storage, and that this function is rather mediated by structures that interface the hippocampal system with the neocortex (Squire, 1992).

The fractionation of multiple memory systems across cognitive domains is now well established (Schacter & Tulving, 1994; Warrington & McCarthy, 1992). Our data point to the fractionation of multiple stages of long-term memory processing across temporal domains. This fractionation may entail different stages of a single physiological consolidation process such as long term potentiation, or biologically distinct consolidation processes, each with its own particular time frame.

Our patient's pattern of deficits on the two public events memory tests corresponded both with her everyday symptoms and with her performance on ''episodic'' memory tasks relating to retention of story and visual design material. While it is not possible to be very precise as to the onset of her epileptiform lesion, it would seem likely that this became active around 1990–1991. This would mean that her various test deficits reflect anterograde rather than retrograde memory impairment, and this also is consistent with her own pattern of memory symptoms.

We should emphasize that, at the clinical level, our patient was very different from the ''run-of-the-mill'' amnesic patient. She had no difficulty in remembering appointments, what she had been told by friends, where she put things, etc. She was always oriented for time and place. She did, however, note that as a result of her very long-term memory symptoms she would on occasion find herself rather inhibited in her social conversation—for instance, she stated that she might hesitate to ask a friend about her husband's health in case he had died. This symptom has, of course, a clear parallel with our patient's performance on the Dead-or-Alive test. It remains possible that in future years her symptom profile may evolve to become similar to that of other patients (Kapur et al., 1989; Shallice & Kartsounis, 1993) in that she may display a more marked retrograde amnesia/semantic learning loss.

In summary, our findings challenge the established view that there is a simple transition from a short-term to a permanent long-term memory system. Even after information is encoded and learned, its preservation in long-term memory is not guaranteed. Our data suggest that the mechanisms governing the transfer of information into a ''stable,'' permanent store are part of an active, dynamic process or set of processes that continues for months or even years after learning (Mondadori, Hengerer, Ducret, & Borkowski, 1994), rather than a fixed process that is determined in the minutes or hours after initial acquisition. There may be distinct and dissociable long-term consolidation systems, each with its own time frame. At the clinical level, our findings also indicate a need for better, more refined instruments with which to assess very long-term retention.

REFERENCES

Ahern, G. L., O'Connor, M., Dalmau, D., Coleman, A., Posner, J. B., Schomer, D. L., Herzog, A. G., Kolb, D. A., & Mesulam, M. M. 1994. Paraneoplastic temporal lobe epilepsy with testicular neoplasm and atypical amnesia. *Neurology,* **44,** 1270–1274.

Baddeley, A. D., & Warrington, E. K. 1970. Amnesia and the distinction between long and short-term memory. *Journal of Verbal Learning and Verbal Behaviour,* **9,** 176–189.

Baddeley, A. 1990. *Human memory: Theory and practice*. Hove: Erlbaum.

Benton, A. L., Van Allen, M. W., Hamsher, K. D., & Levin, H. S. 1975. *Test of facial recognition, form SL.* Iowa City: Department of Neurology.

De Renzi, E. & Lucchelli, P. 1993. Dense retrograde amnesia, intact learning capability and abnormal forgetting rate: A consolidation deficit? *Cortex,* **29,** 449–466.

Hebb, D. 1949. *The organization of human memory*. New York: Wiley.

Jackson, G. D. 1994. New techniques in magnetic resonance and epilepsy. *Epilepsia,* **35** (Suppl. 6), S2–S13.

Kapur, N., Young, A., Bateman, D., & Kennedy, P. 1989. Focal retrograde amnesia: a long-term clinical and neuropsychological follow-up. *Cortex,* **25,** 387–402.

Kapur, N., Barker, S., Burrows, E. H., Ellison, D., Brice, J., Illis, L. S., Scholey, K., Colbourn, C., Wilson, B., & Loates, M. 1994. *Journal of Neurology, Neurosurgery and Psychiatry* **57,** 1334–42.

Kapur, N., Scholey, K., Moore, E., Barker, S., Mayes A., Brice, J., & Fleming, J. 1994. The mamillary bodies revisited: Their role in human memory functioning. In L. Cermak (Ed.), *Neuropsychological explorations in memory and cognition: Essays in Honor of Nelson Butters*. New York: Plenum Press.

Lezak, M. 1983. *Neuropsychological assessment*. New York: Oxford University Press. *Second edition*.

Martin, R. C., Loring, D. W., Meador, K. J., Lee, G. P., Thrash, N., & Arena, J. G. 1991. Impaired long-term retention despite normal verbal learning in patients with temporal lobe dysfunction. *Neuropsychology,* **5,** 3–12.

McGaugh, J. L. 1966. Time dependent processes in memory storage. *Science,* **153,** 1351–1358.

McKenna, P., & Warrington, E. K. 1983. *The graded naming test*. Windsor, Berkshire: NFER-Nelson.

Mondadori C., Hengerer, B., Ducret, T., & Borkowski, J. 1994. Delayed emergence of effects of memory-enhancing drugs: Implications for the dynamics of long-term memory. *Proceedings of the National Academy of Sciences,* **91,** 2041–2045.

Nelson, H. E. 1976. A modified card sorting test sensitive to frontal lobe defects. *Cortex,* **12,** 313–324.

Parkin, A. 1993. *Memory. Phenomena, experiment and theory*. Oxford: Blackwells.

Roland, P. 1993. *Brain activation*. New York: Wiley-Liss.

Rose, S. 1992. *The making of memory*. London: Bantam Press.

Schacter, D. L., & Tulving, E. (Eds.) 1994. *Memory systems 1994*. Cambridge, MA: MIT Press.

Shallice, T., & Kartsounis, L. 1993. Selective impairment of retrieving people's names: a category specific disorder? *Cortex,* **29,** 281–291.

Squire, L. R. 1986. Mechanisms of memory. *Science,* **232,** 1612–1619.

Squire, L. R. 1992. Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review,* **99,** 195–321.

Warrington, E. K. 1984. *Recognition memory test*. Windsor: NFER-Nelson.

Warrington, E. K., & McCarthy, R. 1992. Memory disorders. In: A. K. Ashbury, G. McKhann & W. I. McDonald (Eds.), *Diseases of the nervous system*. Philadelphia: Saunders. *Second ed., Vol. 1*.

Wechsler, D. 1981. *Wechsler adult intelligence scale—Revised*. San Antonio: Psychological Corporation.

Wechsler, D. 1987. *Wechsler memory scale—Revised*. San Antonio: Psychological Corporation.

Weingartner, H., & Parker, E. S. 1984. *Memory consolidation*. Hillsdale: Erlbaum.

Zola-Morgan, S., Squire, L. R., & Amaral, D. 1986. Human amnesia and the medial temporal lobe region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *The Journal of Neuroscience,* **6,** 2950–2967.