8

The Medial Temporal Region and Memory Consolidation: A New Hypothesis

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The concept of memory consolidation—the idea that memory changes with the passage of time after learning—has been discussed and debated throughout this century in the disciplines of experimental psychology, physiological psychology, and neuropsychology. What is striking about these various inquiries is that each has had its own developmental history and that there has seldom been good correspondence among the disciplines in how memory consolidation should be viewed. It will be our contention here that converging evidence from all three disciplines now permits a new and coherent view of memory consolidation. This chapter presents evidence that memory changes for a long time after learning and describes a new framework in which the concept of memory consolidation can be placed.

Consolidation theory had its beginnings in experimental psychology as a way of explaining the detrimental effects on retention of a learning experience interpolated during the retention interval (Muller & Pilzecker, 1900). The shorter the interval between original learning and interpolated learning, the greater the deficit. It was supposed that the formation of stable memory required some change to occur after learning and that interpolated learning interfered with this stabilizing process. However, such an account of these data was eventually replaced by interference theory (see Keppel, this volume), which was deemed to provide a better explanation of both these and many other data. Current work on memory within cognitive psychology has largely ignored consolidation, focusing instead
on the levels-of-processing approach to learning and memory (Craik & Lockhart, 1972) and the encoding specificity principle (Tulving & Thomson, 1973). These approaches emphasize processes operating at the time of information acquisition and at the time of retrieval and have had little to say about processes that might operate during the retention interval. What evidence exists concerning changes in memory over long time intervals (Bartlett, 1932; Freud, 1930; Rumelhart & Norman, 1978) has received little attention.

In physiological psychology, now sometimes termed behavioral neuroscience, consolidation theory grew out of and thrived on an explicit interest in processes that might operate after learning. Sherrington (1906) was among the first to appreciate the observation that nervous activity often outlasts a stimulus. Later, reverberating, self-reexciting neural circuits were postulated as a possible basis for memory storage (Hilgard & Marquis, 1940). Hebb (1949) embraced this idea as a possible mechanism for short-term memory and suggested that more stable, structural changes eventually occur in the same neural circuits to support long-term memory: “To account for permanence, some structural change seems necessary, but a structural growth presumably would require an appreciable time. . . . A reverberatory trace might cooperate with the structural change, and carry the memory until the growth change is made. . . . The conception of a transient, unstable reverberating trace is therefore useful, if it is possible to suppose also that some more permanent structural change also reinforces it [p. 62].”

A similar view, that memory takes time to be “fixed” after learning, was considered at about the same time by Gerard (1949, 1955). McGaugh and Herz (1972), commenting on these views, noted that “the hypothesized dual-trace mechanism accounted for the development of permanent or long-term memory and at the same time allowed for an initial “labile” period during which the neural processes underlying memory are subject to interference [p. 4].”

A large literature supporting this idea has come from the study of retrograde amnesia in laboratory animals. Certain experimental manipulations such as electroconvulsive shock or anoxia disrupt memory only when treatment is administered soon after training. Treatments administered at progressively longer intervals after training exert progressively less disruptive effects (for reviews, see Glickman, 1961; McGaugh & Herz, 1972). This work seemed to promise that determination of the interval during which a treatment is disruptive would lead to an estimate of the time course of consolidation. Unfortunately, it has not proven possible to identify a specific length of time during which consolidation occurs. Retrograde amnesia gradients in experimental animals vary widely in length, from seconds to hours, and sometimes days, depending on experimental conditions. These gradients have therefore come to be viewed more as evidence for changing susceptibility of memory to disruption than as a direct measure of consolidation time. Indeed, in comprehensive reviews of this work that have
considered both the logic of retrograde amnesia studies as well as the available data, it was concluded that these studies do not permit measurement of the maximal time course of memory consolidation (Chorover, 1976; McGaugh & Gold, 1976). McGaugh and Gold (1976) wrote: "RA [retrograde amnesia] gradients do not provide a direct measure of the time required for the consolidation of long-term memory. . . . These results need not imply that there is a maximal amnesic gradient, but may simply indicate that the disruptive effectiveness of a given treatment is limited under the particular experimental conditions used [p. 550]." Though it has proven difficult in this tradition to address the temporal features of consolidation, much research continues to seek its neurobiological substrate (Gold & McGaugh, this volume). At the same time, because the time course of disruptive effects in experimental animals is usually short (i.e., seconds to hours), it has been possible on this evidence to maintain the view that such disruption occurs when memory is in a labile form, prior to its fixation.

In neuropsychology, the facts of human amnesia have also led to ideas about memory consolidation. Retrograde amnesia in man has long been known to affect recent events more than remote events (Ribot, 1882), and these observations have been taken in support of the idea that memory consolidates or changes in some way as time passes after learning (Burnham, 1903; McDougall, 1901; Russell & Nathan, 1946). In the case of amnesia associated with electroconvulsive therapy (ECT), formal studies have shown that memory for material learned immediately before treatment is worse than memory for material learned hours before treatment (Zubin & Barrera, 1941). The first systematic studies of traumatic amnesia also reported a temporally limited retrograde memory loss (Russell & Nathan, 1946). In 83% of 840 cases exhibiting retrograde amnesia, the period of time prior to injury that was affected was less than 30 min.

Individual cases of traumatic amnesia have also been described in which retrograde amnesia appears to cover six months or more prior to injury (Barbizet, 1970; Russell & Nathan, 1946). Moreover, the well-known amnesic case H.M., who in 1953 sustained bilateral excision of the medial temporal region for relief of intractable seizures (Scoville & Milner, 1957), has been reported to have had retrograde amnesia covering one to three years prior to surgery (Milner, Corkin, & Teuber, 1968). Yet evaluation of individual patients on the basis of clinical interviews cannot provide a compelling case that retrograde amnesia actually extends in a temporally limited way over a time course of many months or more. Coons and Miller (1960) argued forcibly that such impressions may result from sampling bias inherent in clinical interviews. That is, questions about recent events tend to be more detailed and to sample shorter time periods than questions about more remote events. Accordingly, an individual having long retrograde amnesia might always appear to have a temporally limited deficit, even if all past time periods were affected equally. It is now clear, however, on the basis of formal memory testing, that retrograde amnesia can extend a year or two into the
past without affecting more remote time periods (Squire & Cohen, 1982). Following five treatments of bilateral ECT, patients developed a temporally limited retrograde amnesia that covered a few years prior to treatment without affecting earlier years. These results were consistent both with the idea that memory changes with the passage of time after learning and that these changes can occur over a time course of years.

This brief historical review shows that different points of view about memory consolidation have developed in three relevant disciplines. In experimental psychology, memory consolidation has been passed over to some extent in favor of processes that operate at the time of learning and at the time of retrieval. In behavioral neuroscience, memory consolidation has tended to refer to a relatively short-lived process that operates during an initial labile period while memory is being fixed. In neuropsychology, memory consolidation has been related to the facts of retrograde amnesia in patients, and would seem to proceed for a very long time.

In this chapter, our intention is to present a new hypothesis of memory consolidation that draws heavily on data from neuropsychological studies of amnesia and is compatible as well with developments in experimental psychology and behavioral neuroscience. A crucial aspect of this hypothesis is the idea that memory consolidation proceeds for a long time, up to several years, and that it depends on the integrity of the medial temporal region of the brain.

RELEVANT OBSERVATIONS

Retrograde Amnesia

Our assertion that memory consolidation can continue for as long as a few years after learning is based on the fact that temporally limited retrograde amnesia can occur on this time scale, affecting memories formed one or two years ago without affecting memories formed prior to that time. This section explicitly develops these inferences and shows how an alternative class of interpretations is ruled out by the data.

There have been many clinical reports of temporally limited retrograde amnesia spanning several years. The argument to be developed here, however, depends on features of the impairment that can be revealed only by objective testing. The present discussion therefore will focus on a few studies in which retrograde amnesia has been measured with formal memory tests and where quantitative aspects of the memory impairment can be considered. The relevant data come from studies of retrograde amnesia in psychiatric patients receiving bilateral ECT. Fig. 8.1 shows the results of two such studies. These studies asked patients questions about television programs broadcast for no more than one season during the past many years (Squire & Cohen, 1979; Squire, Slater, & Chace, 1975). Before ECT, the patients exhibited a forgetting curve across the
time period measured by the test, performing best for the recent time periods and worst for the more remote time periods. One hour after the fifth treatment, there was a selective impairment in the ability to answer questions about programs broadcast one to two years previously and no impairment of memory for programs broadcast from 2 to 17 years previously. Similar results have been obtained in a third study involving the names of television programs (Squire, Chace, & Slater, 1976) and a fourth study involving details about past public events (Cohen & Squire, 1981).

These findings show that the susceptibility of memory to disruption decreases as time passes after initial learning. The validity of this conclusion depends on how well these testing methods overcome Coons and Miller’s (1960) concern about sampling bias. Specifically, the test must satisfy the criterion of equivalence (Squire & Cohen, 1982), whereby the material tested from different time periods is likely to have been learned about to the same extent and then forgotten at similar rates. This critical requirement has now been validated by repeated testing with the television test during seven years (Squire & Fox, 1980).

The finding that a one- or two-year-old memory can be affected by ECT, while an older memory is spared, leads us to conclude that memory changes over long periods of time and becomes resistant to disruption as a result of this change. This conclusion depends on the specific pattern of the data, not on the mere fact that ECT affected one-year-old memories but not five-year-old memories. This point follows from consideration of the hypothetical data shown in Fig. 8.2. Here ECT has impaired one- and two-year-old memories without impairing older memories, but recall of one- or two-year-old memories after ECT is a little better than recall of three- to four-year-old memories and much better than recall of five- to six-year-old memories. These data would not require the conclusion that memory changes with time over the years. Suppose first that in each time period memories of varying durability are formed. Some of these memories concern details and will soon be forgotten; others concern important events and will last for a long time. Then, one need suppose only that ECT disrupts the less durable memories that would ordinarily be soon forgotten and spares the more durable memories that would ordinarily be retained for a long time. If this were the case, ECT would take its greatest toll on recent memories, and results like those depicted in Fig. 8.2 could be obtained. Importantly, with this scenario, ECT could never affect recent memories to such an extent that the score for the recent time period is actually lower than the score for more remote time periods. Durable, long-lasting memories are equally abundant in all time periods. If ECT disrupted only weak, easily forgotten memories, then all the durable memories should remain after the weak ones were disrupted, and performance at worst should be equivalent across time periods.

However, what can actually occur after ECT (See Fig. 8.1) is that the score for the most recent time period is significantly worse than the score for a more remote time period. To the extent that performance after ECT is worse for recent
time periods than for remote time periods, the data demonstrate that changes must occur in memory on this time scale. These changes cause some memories, which can be disrupted by ECT when they are one to two years old, to become resistant to disruption during subsequent years. It is our view that these changes reflect memory consolidation. Thus, memory consolidation is a process that continues long after learning and that develops and maintains stable memory representations.

The basic idea that changes in memory continue for a long time after learning was first stated many years ago on the basis of clinical reports of extensive retrograde amnesia (Burnham, 1903): "In normal memory a process of organization is continually going on—a physical process of organization and a psychological process of repetition and association. In order that ideas may become a part of permanent memory, time must elapse for these processes of organization to be completed [p. 396]."

The well-studied neurosurgical case H.M. (Scoville & Milner, 1957) connects these ideas about memory consolidation to the medial temporal region. Case H.M. has had a profound anterograde amnesia since he sustained bilateral excision of the medial temporal region in 1953. Though it has yet not been possible to identify retrograde amnesia in this individual with formal tests, clinical interviews have given the consistent impression that he has a retrograde amnesia of one to three years, i.e., for the period 1950–1953 (Milner, Corkin, & Teuber, 1968). His memory for earlier time periods (1920–1950) is known to be good (Marslen-Wilson & Teuber, 1975). The findings from ECT show that temporally limited retrograde amnesia can occur on this time scale and raise the level of certainty that, as a result of his medial temporal surgery, H.M. indeed has this sort of retrograde amnesia. If so, it follows that the medial temporal region has a necessary role in the development and maintenance of memory that continues for as long as a few years after learning. Beyond that time, this region is less involved or not at all involved in memory. Because forgetting also occurs during this same period after learning, the changes that occur during this period apparently result in some information that has not been forgotten becoming more resistant to disruption. Of course, memory for many if not most experiences does not endure as long as a few years. We presume that the role of the medial temporal region in the consolidation of such experiences continues while information is being forgotten, during the reorganization and stabilization of what remains.

FIG. 8.1. Temporally limited retrograde amnesia for events that occurred one to two years previously in psychiatric patients receiving ECT.
A. Recognition memory for the names of former, one-season television programs.
B. Recall of details about former, one-season programs. (From Squire, Slater, & Chace, 1975: Squire & Cohen, 1979). These findings support the conclusion that memory changes during the first few years after learning and becomes resistant to disruption as a result of this change (see text).
Because of its time course, memory consolidation must by our view depend on changes in the neural substrates of long-term memory storage, not on transfer out of a short term, labile memory system. At the same time, this conclusion in no way denies the possible importance for long-term memory storage of events occurring during or shortly after learning. Thus it has been suggested that protein synthesis, hormonal release, and other short-term physiological consequences of training play a critical role in the formation of memory (Barondes, 1975; Gold & McGaugh, 1975; Kety, 1970; Livingston, 1967; Squire, 1975). In addition to whatever events occur near the time of training, other events continue to affect memory for a long time afterwards.

In the case of the one- to two-year retrograde amnesia associated with ECT, the memory impairment is largely temporary and is recovered substantially during the months following treatment (Squire, Slater, & Miller, 1981). Thus ECT does not erase these memories but causes them to be temporarily inaccessible in a way that depends on their age at the time of treatment. Recovery from prolonged
retrograde amnesia can also occur following head trauma (Russell & Nathan, 1946). The fact that these effects of ECT are largely temporary rather than permanent is not critical to the present discussion. Apparently, the stage of resistance that memory has reached at the time of ECT will determine whether or not memory becomes inaccessible. Thus ECT reveals differences among memories of different ages that must be related to the neurological organization of these memories at different times after acquisition.

The recovery from retrograde amnesia that occurs following convulsive treatment in humans is quite compatible with the permanent retrograde amnesia reported in laboratory animals when the interval between learning and convulsive stimulation is short (McGaugh & Gold, 1976). In humans, both traumatic amnesia and ECT can also lead to long-lasting, probably permanent retrograde amnesia for information acquired just prior to the precipitating event (Russell & Nathan, 1946; Squire, Slater, & Miller, 1981). Thus these facts of amnesia are all consistent with the idea that memory grows more resistant to disruption with the passage of time. If a disruptive treatment is given sufficiently long after learning, memory will not be affected; if the treatment is given at an intermediate time after learning, memory may be reversibly affected; if the treatment is given shortly after training, memory can be permanently lost.

Rapid Forgetting

Another feature of amnesia pertinent to discussion of memory consolidation is rapid forgetting. We have described memory consolidation as a process occurring after learning that maintains and stabilizes memory representations, strengthening those that are not forgotten. In the absence of such a process, information in memory should be forgotten at an abnormally rapid rate. This possibility has now been explored rather thoroughly. Rapid forgetting was first reported experimentally by Huppert and Piercy (1979), who also developed the experimental method on which the demonstration was based. Normal subjects and case H.M. were shown 120 pictures, one at a time. The exposure duration was 1 sec for the normal subjects and 16 sec for H.M., long enough to equate his retention performance at 10 min after learning to that of the normal subjects. Having equated performance in this way, they then observed that H.M. forgot abnormally rapidly between 10 min and 7 days after learning. This method has recently been applied to patients receiving ECT who also forgot at an abnormal rate (Squire, 1981). The results with ECT confirm our expectation that temporally limited retrograde amnesia should be associated with rapid forgetting of newly learned material. H.M. exhibits rapid forgetting and presumably one- to three-year retrograde amnesia as well: therefore, dysfunction of the medial temporal region may underlie both these deficits. In the case of ECT, however, it is not possible to speak with any certainty about which brain areas are most affected by the seizure and therefore most related to the memory disorder. Nevertheless.
some indirect evidence has linked ECT to medial temporal lobe dysfunction (Inglis, 1970).

In contrast to the rapid forgetting associated with dysfunction of the medial temporal region, the amnesia associated with damage to the diencephalic midline does not include this deficit. Huppert and Piercy (1978) first showed that patients with Korsakoff syndrome exhibit a normal rate of forgetting. Normal forgetting has also been observed in a second group of patients with Korsakoff syndrome, and in the case of N.A., who has a known lesion in the region of the left dorsomedial thalamic nucleus (Squire, 1981). When patients receiving ECT and Korsakoff patients all saw 120 pictures for 8 sec each, they had identical retention scores at 10 min after training. Yet during the next 32 hours, the ECT patients rapidly forgot the material; the Korsakoff patients exhibited little forgetting.

Despite this evidence for an association between rapid forgetting and medial temporal dysfunction, neuropathological information for these amnesic cases is not available. More direct evidence for this association comes from recent studies with operated monkeys (Zola-Morgan & Squire, 1982). They used the delayed nonmatching-to-sample task, which is sensitive to amnesia in man, and employed a procedure analogous to that used in the human studies. Normal monkeys were tested in the conventional way, in that they saw the sample stimulus once and then after a delay saw the sample stimulus together with a novel stimulus. Food reward was given for selecting the novel stimulus. Operated monkeys were given 10–12 successive exposures to the sample stimulus to equate their performance to that of normal monkeys at 10 min after training. Forgetting was then assessed at 1 hr and at 24 hr after acquisition. Normal monkeys remembered the sample stimulus across these delays. Monkeys with combined hippocampal-amygdala damage, who at histological examination had no abnormality in diencephalic structures, exhibited rapid forgetting. Monkeys with bilateral medial thalamic lesions that included the dorsomedial nucleus exhibited normal rates of forgetting. These results, together with the data from amnesic patients, make a strong case for the existence of two distinct entities in amnesia—diencephalic and bitemporal, and for an association between bitemporal amnesia and rapid forgetting. The normal forgetting associated with diencephalic amnesia seems to reflect a different kind of deficit (Squire, 1982; Squire & Cohen, 1982).

If both rapid forgetting and temporally limited retrograde amnesia are related deficits caused by medial temporal dysfunction, then patients with diencephalic lesions—who forget at a normal rate—might not exhibit temporally limited retrograde amnesia. Although the available data from formal tests do not yet permit a clear test of this prediction, they are consistent with it. Patients with Korsakoff syndrome exhibit an extensive remote memory deficit covering many decades, rather than temporally limited retrograde amnesia (Albert, Butters, & Levin, 1979; Cohen & Squire, 1981; Squire & Cohen, 1984). This deficit appears to depend on gradually developing anterograde amnesia and a general

Case N.A., who became amnesic in 1960, exhibits generally good memory for events that occurred prior to that time (Cohen & Squire, 1981). Moreover, in two tests that revealed some deficit in his memory for the premorbid period, the deficit covered the entire period and was not temporally limited (Cohen and Squire, 1981; Zola-Morgan, Cohen, & Squire, 1983). Nevertheless, N.A. has seemed on the basis of informal conversations to have particular difficulty remembering things several months prior to his accident (Teuber, Milner, & Vaughan, 1968; Kaushal, Zetin, & Squire, 1981). Yet, these impressions, even if accurate, cannot by themselves settle the question of whether his retrograde amnesia is the type that can result from an impairment in memory consolidation. The critical issue then in reaching conclusions about memory consolidation is not whether a temporally limited retrograde amnesia occurs at all, but whether it takes the form illustrated in Fig. 8.1 rather than the form illustrated in Fig. 8.2.

If a patient had a reconstructive deficit affecting past memories, as diencephalic amnesic patients may have (Cohen & Squire, 1981), then this deficit should affect most severely the fragile memories that will be forgotten most rapidly. Because these memories are necessarily most abundant in recent time periods, patients with diencephalic amnesia should have a retrograde amnesia that affects recent memories somewhat more than remote memories. By our view, however, this amnesia would be of the type illustrated in Fig. 8.2. Only patients with bitemporal amnesia should have the kind of retrograde amnesia illustrated in Fig. 8.1, which requires the conclusion that memory changes with time after learning.

The data reviewed here suggest that rapid forgetting and temporally limited retrograde amnesia (as in Fig. 8.1) occur together in amnesia. The amnesia associated with ECT causes both these phenomena. Medial temporal dysfunction appears to be associated with rapid forgetting, and presumably with temporally limited retrograde amnesia as well. Taken together, the data suggest that the diencephalic and medial temporal regions affected in amnesia make different contributions to normal memory functions (Squire & Cohen, 1982). The medial temporal region appears to have a role in postencoding processes that operate during the retention interval and that are required for memory to develop and be maintained in a normal way. It is these processes that we here term memory consolidation, and it is for this reason that we have related the medial temporal region to memory consolidation.

Anterograde Amnesia and Retrograde Amnesia

It has long been recognized that a correlation exists between the severity of anterograde amnesia and the extent of retrograde amnesia (Russell & Nathan, 1946), and this correlation has suggested that the same deficit might underlie both phenomena (Cohen & Squire, 1981; Wickelgren, 1979). Recent compute
simulation of bitemporal amnesia makes this same point more convincingly, because it links in a formal way the particular features of anterograde and retrograde amnesia that characterize medial temporal dysfunction. The simulation demonstrated that a deficit in the same mechanism can produce both rapid forgetting of newly learned material and temporarily limited retrograde amnesia, as in Fig. 8.1 (McClelland & Rumelhart, 1982, personal communication). The view presented here, and explored by computer simulation, also accounts for a related feature of bitemporal amnesia—the longer the anterograde amnesia persists, the longer will be the permanent retrograde amnesia that persists after anterograde amnesia has diminished. Four related observations are consistent with this conclusion. In traumatic amnesia where the period of anterograde amnesia is often limited to a few days, the period of permanent retrograde amnesia is usually brief, involving just the seconds or minutes prior to injury (Russell & Nathan, 1946). In ECT, where anterograde amnesia can persist for several weeks, and temporary retrograde amnesia can cover the previous one or two years, there can be permanent retrograde amnesia for events that occurred during the several days prior to treatment (Squire, Slater, & Miller, 1981). In tuberculous meningitis, where anterograde amnesia can persist for a few months, permanent retrograde amnesia has been reported for events that occurred up to many months prior to illness (Williams & Smith, 1954). Finally, in case H.M., who has a permanent anterograde amnesia, retrograde amnesia appears to cover a number of years prior to surgery (Milner, Corkin, & Teuber, 1968). These observations help to clarify further the relationship between anterograde and retrograde amnesia. If the function of the medial temporal region is interrupted before its role in the development of memory is completed, memory can be irretrievably lost. The longer the disruption of function persists, the greater the loss. Unless memory is fully developed (i.e., consolidated), it will be lost at an abnormally rapid rate during the period of disruption.

**Spared Learning in Amnesia.**¹

A final feature of amnesia relevant to this discussion of memory consolidation and the medial temporal region: The capacity for some kinds of learning and memory is preserved in amnesic patients. The best known examples of preserved learning and memory lie in the domain of perceptual-motor skills. For example, day-to-day learning of the hand-eye coordination skills needed for the pursuit-rotor task occurred in case H.M. (Corkin, 1968; Milner, 1962), patients with Korsakoff syndrome (Brooks & Baddeley, 1976; Cermak, Lewis, Butters, & Goodglass, 1973; Cohen, 1981), postencephalitic patients (Brooks & Baddeley, 1976), patients receiving bilateral ECT (Cohen, 1981), and case N.A. (Cohen, 1981). Of particular importance is the fact that, for some patients, learning occurred at an entirely normal rate and their performance seemed qualitatively

¹This aspect of the issues under discussion was developed in a Ph.D. thesis by Cohen (1981).
indistinguishable from that of control subjects (Brooks & Baddeley, 1976; Cermak, et al., 1973; Cohen, 1981). This observation means that acquisition of perceptual-motor skills in amnesia cannot be explained merely by continued and extensive repetition of information. If repetition were responsible for the gradual acquisition of a skill over many trials, then the amnesic patients should be inferior to normal subjects during the early learning trials and catch up to normal subjects only in later trials. Yet this does not occur. Instead, the learning curves of amnesic patients and normal subjects are often superimposable. This observation of superimposable learning serves as a compelling demonstration that some form of learning is spared in amnesia and does not depend on the brain regions damaged in amnesia.

The capacity for preserved learning in amnesia appears to extend beyond perceptual-motor tasks to perceptual skills like mirror reading (Cohen & Squire, 1980) and purely cognitive skills such as the learning of a numerical rule (Wood, Ebert, & Kinsbourne, 1982) and the solution to certain puzzles (Cohen, 1981; Cohen & Corkin, 1981). A particularly clear example involves a mirror-reading task that has been studied extensively in normal subjects (Kolers, 1976, 1979). Subjects see mirror-reversed words and are asked to read them aloud as normal words. Amnesic patients (case N.A., patients with Korsakoff’s syndrome, and patients receiving ECT) improved their mirror-reading skill at a normal rate on three successive days and then retained the skill at a normal level after three months. This occurred despite the fact that many patients denied having performed the task previously and all of them were amnesic for the words they had read (Cohen & Squire, 1980). It appeared that although the amnesic patients could learn the skills required for mirror reading, they could not learn the facts they would ordinarily acquire in using these skills, i.e., the words they read. Another example of preserved learning in amnesia comes from the ability of patients, including H.M., to learn the cognitive skills required for optimal solution to the Tower of Hanoi puzzle (Cohen, 1984; Cohen & Corkin, 1981), a complex problem-solving task involving at least 31 steps.

These findings have suggested to us that a significant domain of learning and memory, including motor, perceptual-motor, and cognitive skills, does not depend on the integrity of the medial temporal region. Accordingly, the ability to establish and use knowledge comprising skills can proceed normally in the brain in the absence of what we are here calling consolidation. By contrast, the development and consolidation of knowledge comprising the facts, words, faces, and shapes of conventional memory experiments depend on the integrity of the medial temporal region. We do not deny that the stabilization of memories that are independent of the medial temporal region may take some time. Nevertheless, the data do require the conclusion that the role of this region in memory consolidation applies only to some kinds of learning and memory.

The distinction between skills, which can be learned in amnesia, and the explicit knowledge gained in using those skills, which cannot be learned, is reminiscent of the distinction between knowing how and knowing that (Ryle.
Similar distinctions have been proposed to address these findings from amnesia (Cohen, 1981; Cohen & Squire, 1980 [procedural/declarative]) as well as other findings in behavioral neuroscience (O'Keefe & Nadel, 1978; [taxon, locale]), cognitive psychology (Bruner, 1969 [memory without record/memory with record]), and artificial intelligence (Winograd, 1975; [procedural/declarative]). Though different in some respects, the similarity among these versions has guided our understanding of what has been termed knowledge-how. It is often acquired in an incremental rather than in an all-or-none fashion, as with skill learning. It appears to be represented implicitly rather than explicitly, made accessible only by engaging in the skill in which the acquired knowledge is embedded. Thus, many skills develop despite poor access to the particular instances or events through which the skill was acquired.

We believe that, in the absence of the medial temporal region, organisms maintain the ability to acquire skills, but cannot establish a memory of the specific events that led to the perfection of the skills. That is, representations can develop that change how organisms respond to the environment, without affording access to information about the events that led to this change. Moreover, in the absence of the medial temporal region, facts that would ordinarily be acquired from such events, and knowledge that such events occurred, do not appear to be available.

In this regard, it is useful to remember that the deficit in amnesia manifests itself not merely as a breakdown of memory for specific instances of time-place information, but also includes the failure to acquire new semantic knowledge, e.g., information about public events and famous faces (Cohen & Squire, 1981; Marslen-Wilson & Teuber, 1975). In temporally limited retrograde amnesia, memory for both episodic and semantic knowledge is impaired from the period one to two years before amnesia, and both kinds of knowledge are available from earlier time periods (Zola-Morgan, Cohen, & Squire, 1983). It is now clear that both semantic and episodic memory are concerned with “knowledge that,” whereas skill learning lies outside this classification (Cohen, 1981; Schacter & Tulving, 1982; Squire & Cohen, 1984; Tulving, Schacter, & Stark, 1982).

One question that needs to be asked about the kind of knowledge available to amnesic patients is how specific it can be. Are amnesic patients in a mirror-reading task acquiring and representing knowledge merely about the generic skill of reading words backwards while knowledge specific to individual words is lost or absorbed into the generic representation? Or, might amnesic patients acquire more specific information about the material that is presented? Kolers’ (1976) work suggested that normal subjects not only could learn general skills of reading-transformed text but also could acquire knowledge more specific to the particular text presented. Kolers viewed both kinds of knowledge as skills because they were independent of recognition memory. Recent data suggest that

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2 This idea was developed in a book, coauthored by O’Keefe and Nadel (1978).
stimulus-specific information can also be available to amnesic patients under certain circumstances, and that this information might be still another example of their preserved capacity for skill learning. In one study, five patients with Korsakoff syndrome and five normal subjects were asked a question involving a homophone, e.g., "What is an example of a reed instrument?" Later, when asked to spell read/reed, the amnesic patients gave the low-frequency spelling (reed) that had been biased by the preceding question and did so with a normal, or even greater-than-normal likelihood (Jacoby & Witherspoon, 1982). Yet, the patients failed in recognition memory tests involving the same homophones. We have obtained similar results in a modified word fragment completion task (Graf, Squire, & Mandler, 1984). These results indicate that the preserved capacity for learning in amnesia can extend to specific information about the material that is presented and that the knowledge acquired by amnesic patients is not limited to generic information that is accumulated across many trials. The availability of such information need not imply the availability of episodic or semantic knowledge about these events.

In summary, the facts of spared learning and memory show that the medial temporal region is involved only in the development of a particular kind of memory. Such memory seems to afford the basis for what we have been calling "knowledge that:" knowledge about specific events, the time and place of their occurrence, and facts about the world obtained in the course of such experiences. By contrast, the medial temporal region is not required for consolidation of what has been called "knowledge how:" knowledge implicit in skills and procedures.

The Medial Temporal Region and the Hippocampal Formation

There has been great interest in the possibility of identifying specific structures within the medial temporal region that are involved in memory functions. In H.M. and in another patient who also sustained a medial temporal resection, the removal included the uncus, amygdala, and the anterior two-thirds of the hippocampus (Scoville & Milner, 1957). Several lines of evidence have suggested that damage to the hippocampal formation is responsible for the amnesia in these cases. In five of six cases, when the bilateral excision extended posteriorly only far enough to include uncus, amygdala, and anterior hippocampus, the memory loss was not so severe as in case H.M. In another case, where the excision was limited to uncus and amygdala, no memory deficit was observed (Scoville & Milner, 1957). In the case of unilateral temporal lobe resections, which are associated with verbal or nonverbal memory deficits, the severity of the deficit is correlated with the extent of involvement of the hippocampal zone (Milner, 1974). Although the medial temporal resections described above included amygdala, study of patients with circumscribed, unilateral amygdala lesions has not revealed verbal or nonverbal memory deficits (Andersen, 1978). A possible role
of the temporal stem in the amnesic effects of medial temporal surgery has been ruled out in studies with monkeys (Zola-Morgan, Mishkin, & Squire, 1982). The temporal stem is a band of white matter lying in close proximity to the hippocampus. Finally, many additional examples of amnesia have been described (e.g., postencephalitic cases, vascular cases, cases of anoxic encephalopathy) that include bilateral damage to the hippocampal region.

Nevertheless, there have not been cases of bitemporal amnesia with damage clearly restricted to hippocampal formation. Based on studies of monkeys, it is possible that entorhinal cortex damage would mimic many of the effects of hippocampal damage (Moss, Mahut, & Zola-Morgan, 1981). Moreover, Mishkin (1978) has suggested that bitemporal amnesia in monkeys depends not on damage to hippocampus, but on conjoint damage to hippocampus and amygdala. His studies of a memory task given to monkeys with separate or combined lesions of these structures support this suggestion. One possibility is that these two structures contribute differently to memory functions. It also remains possible that hippocampal damage alone can cause significant memory impairment (for review, see Squire & Zola-Morgan, 1983). Because of this uncertainty about whether the hippocampal formation is the critical structure in bitemporal amnesia or whether other related brain structures also contribute to the deficit, we here use the term medial temporal region to identify the crucial brain area involved in memory consolidation. This terminology should not obscure the fact that the available data point to a necessary and important role for the hippocampal formation in this process. The next section develops some specific ideas about what memory consolidation is and how the medial temporal region might participate in consolidation.

A NEW FRAMEWORK FOR MEMORY CONSOLIDATION

Memory Storage

We presume that memory storage occurs in networks of neurons, primarily in neocortex, such that the specificity of memory is determined by which ensembles of neurons change, not by the kind of change that occurs. Plasticity depends on changes in synaptic efficacy within these ensembles. Which groups of neurons participate in memory storage is determined largely by what functions these neurons ordinarily participate in. That is, memory is stored in the same circuitry that ordinarily is involved in the perception and processing of the kind of information that is to be stored. In invertebrates like Aplysia, where the cellular correlates of information storage for simple forms of behavioral plasticity can be investigated rather directly, plasticity occurs as changes in circuitry that is already specialized for organizing the response that is to be modified (Kandel, 1976). Other evidence has been reviewed elsewhere (Squire & Schlapfer, 1981).
It is our contention that the neural elements participating in memory storage can undergo reorganization with the passage of time after learning. The most general way to state how this reorganization might occur is to suppose that although some elements are lost through forgetting, those that survive increase their synaptic efficacy. This notion is formally similar to the principle of competition (Purves & Lichtman, 1980), whereby when some neural elements are lost, those that remain increase their influence on target sites. By the present view, forgetting involves an actual loss of connectivity among the neural elements participating in a representation, i.e., disappearance of at least some of the changes in synaptic connectivity that originally embodied the information. In the case of long-term habituation in *Aplysia*, the relevant synaptic changes gradually disappear over a period of days and weeks in parallel with behavioral forgetting (Kandel, 1976). In this case, the neural elements remain present, but their functional connectivity changes. Loss of connectivity among elements due to forgetting is accompanied by, causes, or results from a process of reorganization of that which remains. Because there is considerable redundancy in such a representation, and because memory involves representation of many different features of an event, it is not necessary to suppose that all elements composing the memory of an event are ever lost irretrievably. Conversely, occasional success in retrieving an old memory does not require the conclusion that no connectivity has been lost among elements in the original representation. Loss of connectivity should lead, on average, to reduced efficiency, speed, or completeness of recall. As time passes after learning, one's representation of distant events loses detail through forgetting but becomes more schematized, organized, and related to other material in memory (Bartlett, 1932) during the process of consolidation.

**Memory Consolidation and the Role of the Medial Temporal Region**

One can imagine different formulations of how the medial temporal region is involved in consolidation. Two possibilities can be dismissed at the outset. In what might be termed a general retrieval view, the medial temporal region permits memory retrieval of all information that is stored elsewhere in the brain, e.g., in cortical cell ensembles. All memories are available in amnesia, but in the absence of the medial temporal region they cannot be retrieved. A second view is that the medial temporal region is the storage site for all memory. Neither of these views can explain why H.M. has poor memory for past events that occurred since 1953 and good memory for events that occurred prior to that time (Marslen-Wilson & Teuber, 1975). By either of these views, damage to the medial temporal region should result in a deficit in recalling all past memories, not just memories that were formed after a certain year.

By the view to be developed here, the medial temporal region plays a role that cannot be so easily labeled in terms of storage or retrieval notions. What is
crucial to the present view is that the medial temporal region is required for only a limited time after learning and that its role is selective to a particular domain of information. Our proposal is that the medial temporal region establishes a relationship with distributed memory storage sites at the time of acquisition. The medial temporal region maintains coherence of memory, permitting its retrieval during the consolidation period. Processes intrinsic to normal function at memory storage sites are responsible for consolidation, which results in changes in the system of coherent elements specified by the medial temporal region. Some elements in the representation are lost; those that remain develop better connectivity. Once this process is sufficiently complete, the medial temporal region is no longer needed either for the storage or retrieval of memory.

When the medial temporal region is damaged, the coherence of recently formed, as yet unconsolidated representations will not be maintained, and memory will be lost. Similarly, new representations cannot be established because the system that ordinarily maintains the organization of recently acquired memories and permits their retrieval and reorganization is not available. Although some neuronal changes related to memory storage may still occur when the medial temporal region is damaged, some of the information that would be embodied in the neuronal circuitry, and stabilized as a result of the participation of the medial temporal region, will be absent. That is, some of the neuronal events that subserve information storage, including changes in synaptic connectivity, will not be present.

The capacity to acquire "knowledge how" proceeds independently of the medial temporal region and, in our view, involves the modification or tuning of existing schemata or knowledge structures. The changes that underlie this kind of learning are contained entirely in the neural systems in which they develop, without need of the medial temporal region. In animals like Aplysia, with relatively uncomplicated nervous systems, habituation and sensitization can occur as modifications in synaptic efficacy in existing networks (Kandel, 1976) and can result in a specific change in how the organism responds to environmental stimuli. There is no evidence in such cases for the presence or availability of knowledge about the specific instances that cumulated in the behavioral change. Similarly, restricting an animal's early visual experience to horizontal lines will result in specific changes in the population of orientation-selective cells in visual cortex. Yet there is no sense in which these changes imply knowledge that the world was once composed largely of horizontal lines or knowledge of specific experiences with a horizontal world. Indeed, the capacity for this latter type of learning may have arisen relatively late in evolution with the development of the hippocampal formation. This brain region may confer upon the organism the ability to remember specific instances as separate events. That is, it affords contextual information, including information about time and place (Nadel & Willner, 1980; Nadel, Willner, & Kurz, 1984). In addition, it also affords the basis for acquiring new facts about the world which, though acquired in specific
places at particular times, do not necessarily include this information, i.e., semantic knowledge.

These considerations emphasize the dissociation among different domains of knowledge and the selective role of the medial temporal region in memory consolidation. Thus, one kind of knowledge (knowledge-how) is stored in neural circuitry that does not depend on the medial temporal region and is not subject to consolidation. This knowledge consists of skills or procedures that can be embedded in already existing knowledge structures. It is accessible only by using these skills or procedures and does not by itself afford any awareness that a previous event has occurred. A second kind of knowledge (knowledge-that) depends on the medial temporal region and is contained in the interaction between the medial temporal region and neocortical storage sites. This knowledge is comprised of facts and data, including both information about specific experiences that occurred at specific places and times (episodic knowledge) and factual information about the world that is acquired as a result of these experiences (semantic knowledge). With the participation of the medial temporal region, memory for this material is consolidated during the time after learning. When memory consolidation is interrupted by damage to the medial temporal region, the semantic and episodic knowledge represented in the interaction of this region with neocortex is lost in the sense that some of the changes in synaptic efficacy that subserve its storage disappear. The knowledge that is independent of the medial temporal region, however, remains unaffected. Thus the amnesic patient, who has sustained damage to the medial temporal region, will by our view be incapable of establishing and using one kind of knowledge but will be capable of establishing and using another. To summarize, our view involves four premises:

1. The medial temporal region interacts with neocortex (and possibly other regions) in memory storage.
2. Information is embodied both in neocortical representations and in the interaction between the medial temporal region and neocortex.
3. This interaction is necessary in memory storage and retrieval for a limited time period after learning of up to a few years.
4. This interaction occurs only for certain kinds of knowledge.

Our proposal is not entirely new. Others have stressed, either separately or together, the idea that memory involves interaction between the medial temporal region and the neocortex and that the medial temporal region is concerned with particular kinds of information (Halgren, Wilson, Squires. Engel, Walter, & Crandall, 1983; Hirsh, 1974; Mishkin, 1982; Nadel & O’Keefe, 1974; O’Keefe & Nadel, 1978; Wickelgren, 1979).

There is at least one notion other than ours that could be compatible with all four premises. One might suppose that the medial temporal region does not merely permit consolidation but actually causes it to occur by exerting a neu-
romodulatory, or other extrinsic influence necessary for the fixation of memory (Wickelgren, 1979; McClelland & Rumelhart, 1982. personal communication). This idea supposes that the medial temporal region is the motive force for consolidation. It incorporates the selectivity of the medial temporal region’s role in memory consolidation insofar as it asserts that this function is necessary only for the consolidation of some kinds of information. This selectivity might be realized in two different ways. It may be that the medial temporal region stores information about which neocortical sites it should interact with (i.e., it stores “addresses” of memories stored elsewhere [Teyler & Discenna, 1984]) and thus actively directs its interaction with the neocortical storage sites. Alternatively, the selectivity could inhere in some property of the neocortical sites, with the medial temporal region playing a more passive, nonspecific role. By the latter view, only certain neocortical sites would have the capacity or need to respond to this nonspecific, extrinsic influence. It should be noted that the “address” version of this view is closely allied with our view that the medial temporal region maintains coherence of memory. Any “coherence” model would seem to require an addressing system that contained knowledge about which particular set of elements is to be maintained by the medial temporal region. In both views, the medial temporal region directs its interaction with selected neocortical storage sites, as a result of which consolidation occurs during the time after learning for a particular domain of knowledge.

Some Neuroanatomical and Neurobiological Considerations

Our view of the role of the medial temporal region and its interaction with neocortex demands extensive and precise neural interconnections between the two. The amygdala has direct, reciprocal connections with insular cortex, all parts of the temporal lobe, including hippocampal formation, and major parts of the frontal lobe, including the orbital and medial surfaces (Price, 1982; Van Hoesen, 1981). The hippocampal formation receives much of its input from entorhinal cortex via the perforant path. The entorhinal cortex itself receives multimodal information from temporal and frontal neocortex, from the olfactory system via the prepiriform area, and has been regarded as a final link between sensory areas of neocortex and the hippocampal formation (Van Hoesen, Pandya, & Butters, 1972). Efferents from the hippocampal formation via subiculum and presubiculum, and area TH-TP (parahippocampal gyrus), reach a variety of cortical associations areas; moreover the subiculum of the hippocampal formation has direct connections with amygdala, the medial surface of frontal cortex, perirhinal cortex, and cingulate cortex (Rosene & Van Hoesen, 1977). Considering the close relationship between the medial limbic structures, i.e., amygdala and hippocampal formation, and the majority of temporal neocortex, and the relationship between temporal neocortex and other association cortices, there
appears to be great opportunity for interaction between the medial temporal region and the neocortex. Thus there is evidence for the kind of connections this model would require.

Although consolidation need not continue for years for all kinds of information, the processes we are discussing last for a long time. Such processes would require neural mechanisms for maintaining and reorganizing information over long time intervals. Little is known about the neurobiological events that might underlie such processes, but examples of durable plasticity have been identified in mammalian brain. Thus, neurons in rat neocortex undergo extensive and durable changes in architecture in response to enriched environments or a series of daily training experiences (Rosenzweig, 1979; Greenough & Chang, 1984). These include changes in dendritic branching patterns, length of synaptic apposition, and number of dendritic spines—all of which could influence synaptic connectivity. In humans, growth of dendrites appears to continue throughout life (Buell & Coleman, 1979). In the medial temporal region itself and in the hippocampal formation specifically, physiological work has demonstrated a form of long-lasting synaptic plasticity, long-term potentiation (Bliss & Lomo, 1973). This effect, observed in vitro in hippocampal slices (Lynch & Shubert, 1980) and in the hippocampus of freely moving rats and monkeys alike (Swanson, Teyler, & Thompson, 1982) lasts for weeks or months and is associated with changes in dendritic spines (Lee, Schottler, Oliver, & Lynch, 1980). Although these forms of plasticity have not yet been clearly linked to behavioral memory, they provide potential bases for both the maintenance of an interaction between the medial temporal region and neocortex and for the changes at storage sites that we suppose subservient consolidation.

Some Cognitive Considerations

Our model of consolidation postulates that the medial temporal region maintains coherence within an ensemble of neocortical sites until such time as the coherence of these sites becomes an intrinsic property of the ensemble. It is our view that during this lengthy process certain aspects of memory for the original event are forgotten while those that remain are strengthened. But it would be simplistic to suggest that any single biological change is responsible for consolidation lasting as long as several years, as indicated by the data from retrograde amnesia. Rather, this time period, during which the medial temporal region maintains its importance, is filled with external events (such as repetition and activities related to original learning) and internal processes (such as rehearsal and reconstruction). These influence the fate of as-yet unconsolidated information through remodeling the neural circuitry underlying the original representation. The selection of which elements of a memory are forgotten and which survive and are strengthened depends on how these elements are affected by: 1) the particular events intervening between learning and retention; and 2) how the
elements fit into the organism's pre-existing knowledge. During memory consolidation, some elements of memory are incorporated into pre-existing schemata; others might form the basis for new schemata; still others will be lost.

These ideas differ from the view that memories are fixed entities, traces of prior experience, uninfluenced by subsequent or prior events, and changed only by slow erosion. Memory consolidation by our view is not a relentlessly gradual or passive process. The ideas developed here fit more comfortably with a view of memory as a dynamic process, which changes over time through reorganization and assimilation to pre-existing memories, and which is affected by subsequent memory-storage episodes. This view has precedents in the work of Bartlett (1982), Rumelhart & Norman (1978), and in psychoanalytic theory (see for example, Feldman, 1977). It should be clear that we view consolidation as subserving just this sort of dynamism in memory.

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