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The Medial Temporal Lobe, the Hippocampus, and the Memory Systems of the Brain

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ABSTRACT   This chapter focuses on the memory systems of the brain, a continuing major theme in behavioral and cognitive neuroscience. One major topic is conscious declarative memory, which depends on the medial temporal lobe and its interaction with the neocortex. Another major topic is retrograde amnesia. The facts about retrograde amnesia provide the key evidence for a lengthy process of reorganization and stabilization within declarative memory that begins after learning has been completed. A related topic concerns how the anatomical components of the medial temporal lobe, including the hippocampus itself, might contribute differently to declarative memory. Another topic centers on the distinction between remembering and knowing. This distinction, which concerns two forms of declarative memory, is of interest because it provides one of the best methods for assessing episodic and semantic memory function in humans. Finally, new information is available about several forms of nondeclarative memory, including the phenomenon of priming, skill and habit learning, artificial grammar learning, category learning, and classical conditioning. New lesion studies and functional neuroimaging studies are illuminating the nature and organization of these forms of memory.

Declarative versus nondeclarative memory

The distinction between declarative (explicit) and nondeclarative (implicit) memory continues as a major theme in behavioral and cognitive neuroscience. This distinction is based on converging evidence from studies of experimental animals, neurological patients, and normal individuals (Schacter and Tulving, 1994; Squire and Zola, 1996). Declarative memory refers to memories for facts and events that are recollected consciously. This type of memory depends on the integrity of medial temporal lobe structures, including the hippocampus, as well as midline diencephalic nuclei. Nondeclarative memory is expressed through performance without any requirement

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for conscious memory content. Nondeclarative memory is independent of the medial temporal lobe and diencephalic structures that support declarative memory. Nondeclarative memory is not a single entity but rather describes a collection of abilities: memory for skills and habits, simple forms of conditioning, and priming.

Describing the properties of declarative and nondeclarative memory independently of their neuroanatomy is an important goal. Declarative memory is well suited for storing information about single events. The knowledge is flexible and applied readily to novel situations. In general, nondeclarative memory is inflexible and bound to the learning situation. Unlike declarative memories, nondeclarative memories cannot be accessed readily by response systems that did not participate in the original learning (Eichenbaum, Mathews, and Cohen, 1989; Reber, Knowlton, and Squire, 1996; Saunders and Weiskrantz, 1989).

Retrograde amnesia

The brain system that supports declarative memory has only a temporary role in the formation of long-term memory. Retrograde amnesia, the loss of memories that were acquired before the onset of amnesia, usually is graded temporally so that recent memories are more impaired than remote memories (Ribot, 1881). Retrograde amnesia sometimes can be ungraded and extensive, as in conditions such as encephalitis and head trauma, when damage typically occurs beyond the brain system that supports declarative memory (e.g., Damasio et al., 1985; Cermak and O'Connor, 1983; Reed and Squire, 1998). Nevertheless, in patients with restricted damage to the CA1 zone of the hippocampus proper, such as patient R.B. (Zola-Morgan, Squire, and Amaral, 1986) and patient G.D. (Rempel-Clower et al., 1996), retrograde amnesia is brief, perhaps covering 1 or 2 years at most. Other patients with more complete damage to the hippocampal formation also have temporally limited
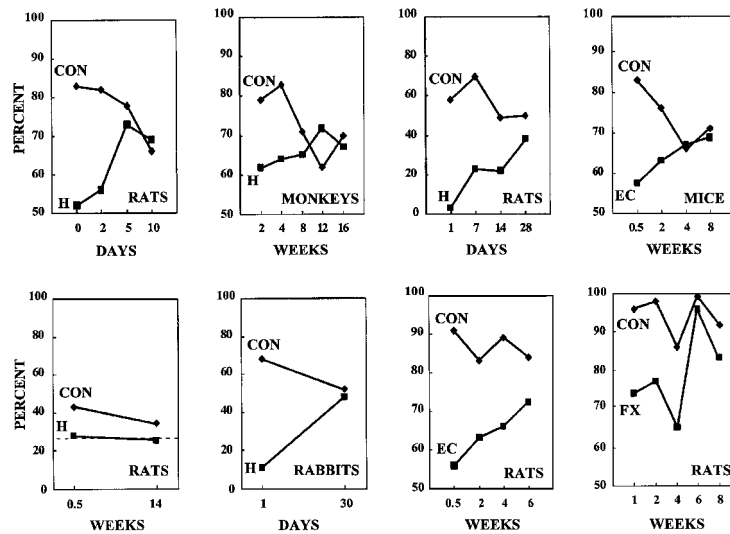
FIGURE 53.1 The panels show all the studies through 1998 in which an equivalent amount of training was given at each of two or more times before hippocampal formation damage, and retention was assessed shortly after surgery. The eight studies involve eight different tasks and four species. In each case, the data show the performance of control (CON) and operated animals (H = hippocampus, EC = entorhinal cortex, FX = fornix) as a function of the interval between training and surgery. Control animals typically exhibited forgetting as the interval between training and surgery increased. In seven of the eight studies, operated animals exhibited temporally graded retrograde amnesia. They were impaired at retaining material they had learned recently, but they retained re- motely learned material as well as control animals. In addition, the operated animals typically retained remotely learned material better than recently learned material. In the lower left panel, both groups of operated animals performed at chance levels (dotted line), which could have obscured a temporal gradient of amnesia if one were present. From left to right, beginning on the top row, the studies are by Winocur (1990); Zola-Morgan and Squire (1990); Kim and Fanselow (1992); Cho and associates (1993); Bolhuis and associates (1994); Kim and colleagues (1995); Cho and Kesner (1996); and Wiig and coworkers (1996). (From Milner, Squire, and Kandel, 1998. Reprinted with permission of Cell Press.)

retrograde amnesia (Reed and Squire, 1998), but graded loss of memory can extend back a decade or more (Rempel-Clower et al., 1996).

Because the study of human retrograde amnesia is based almost entirely on findings from retrospective tests, the clearest evidence about retrograde amnesia gradients comes from studies using experimental animals, where the delay between initial learning and a lesion can be manipulated directly (figure 53.1). These studies make three important points: (1) temporal gradients of retrograde amnesia can occur within long-term memory (i.e., retrograde amnesia does not reflect simply the vulnerability of a short-term memory that has not yet been converted into a long-term memory); (2) after a lesion, remote memory can be retained better than recent memory; and (3) lesions can spare weak memories while disrupting strong ones. To illustrate these three points, consider the case of rabbits given trace eyeblink conditioning. Trace conditioning is a variant of classical conditioning in which the conditioned stimulus (CS), such as a tone, is presented and terminated, and then a short interval is imposed before the presentation of the unconditioned stimulus (US). In normal rabbits, forgetting occurs gradually after training; thus, retention of the conditioned response is much poorer 30 days after training than after only 1 day. Nevertheless, complete aspiration of the hippocampus 1 day after training abolished the strong 1-day-old memory, whereas the same lesion made 30 days after training had no effect on the weaker, 30-day-old memory (Kim, Clark, and Thompson, 1995; figure 53.1).

The results from experimental animals provide evidence for a gradual process of reorganization and stabilization in the neocortex whereby long-term memory eventually becomes independent of the medial temporal lobe. The medial temporal lobe is the target of highly processed information originating from a variety of cortical regions, and it returns projections to these same cortical regions. The hippocampal formation may direct a process of reorganization in the neocortex by gradually binding together the multiple, geographically separate cortical regions that together store memory for a whole event (Alvarez and Squire, 1994; Squire and Alvarez, 1995; McClelland, McNaughton, and O'Reilly, 1995). The lengthy time period required by this process suggests that morphological growth and change may be required at the synapses within the corticocortical projections that comprise a representation.

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There is precedent for gradual changes in neuronal morphology occurring as the result of behavioral experience. Specifically, gradual morphological changes can occur in visual cortical neurons as the result of a small retinal lesion. These changes serve to reduce the size of the visual scotoma and are likely driven by continuing sensory input (Darian-Smith and Gilbert, 1994). To explain why this long process occurs in the organization of long-term memory, McClelland and associates (1995) suggested on computational grounds that the hippocampal system itself can learn specific instances rapidly but that information can be incorporated into the neocortex only gradually. The gradual incorporation of information into neocortex minimizes disruption of existing knowledge structures. Much more needs to be learned about this gradual process. Interestingly, measured against life span, a 30-day gradient of retrograde amnesia in a mouse or rat is equivalent to a gradient of a few years in a human. Whether such a comparison is meaningful must await parametric studies of retrograde amnesia in experimental animals and the identification of which task factors can influence the severity and extent of retrograde amnesia.

Components of the medial temporal lobe memory system

Studies with monkeys and humans have identified the brain structures within the medial temporal lobe that are important for declarative memory. These structures are the hippocampus, the entorhinal cortex, the parahippocampal cortex, and the perirhinal cortex (figure 53.2). The amygdala, although critical for aspects of emotional learning (Davis, 1994; LeDoux, 1996) and for the enhancement of declarative memory by emotion (Adolphs et al., 1997), is not critical for declarative memory itself (Zola-Morgan, Squire, and Amaral, 1989).

The question whether these medial temporal lobe structures play different roles in declarative memory follows naturally from the fact that anatomical connections from different parts of the neocortex enter the medial temporal lobe at different points (Suzuki and Amaral, 1994a, b). For example, the visual association cortex, including area TE, projects more strongly to the perirhinal cortex than to the parahippocampal cortex, whereas the parietal cortex projects to the parahippocampal cortex but not to the perirhinal cortex.

The evidence from monkeys and humans at first might seem to count against the idea that the different structures of the medial temporal lobe have distinct functions. The data are that the severity of memory impairment increases as more components of the medial
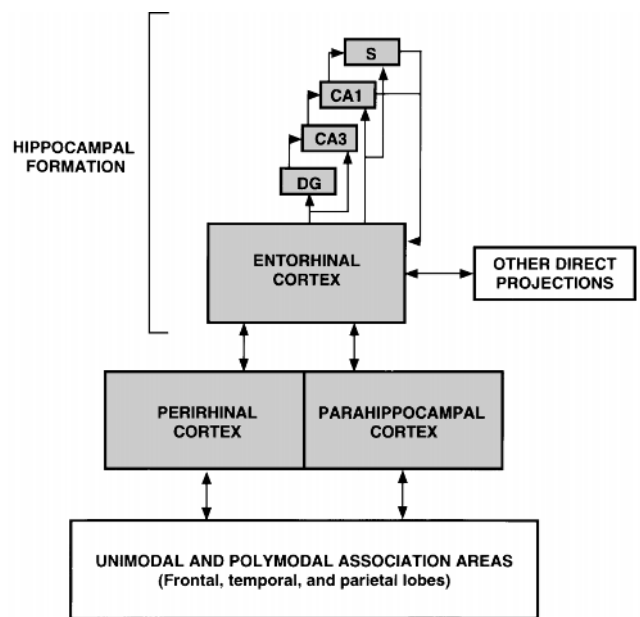

FIGURE 53.2 Schematic view of the medial temporal lobe memory system. The entorhinal cortex is a major source of projections to the hippocampal region (which includes the dentate gyrus, the cell fields of the hippocampus proper, and the subicular complex). Nearly two thirds of the cortical input to the entorhinal cortex originate in the adjacent perirhinal and parahippocampal cortices, which in turn receive projections from unimodal and polymodal areas in the frontal, temporal, and parietal lobes. The entorhinal cortex also receives other direct inputs from the orbital frontal cortex, the insular cortex, the cingulate cortex, and the superior temporal gyrus. All these projections are reciprocal. (From Squire and Zola, 1996. Copyright 1996 National Academy of Sciences, U.S.A.)

temporal lobe are damaged (Rempel-Clower et al., 1996; Zola-Morgan, Squire, and Ramus, 1994). However, these findings are compatible with the idea that different components of the medial temporal lobe contribute to memory in different ways. As damage increases, fewer strategies may be available for storing memory, resulting in more severe memory impairment.

Direct comparisons of the separate effects of perirhinal and parahippocampal lesions suggest that these structures may play distinct roles, as the neuroanatomical findings first suggested. Visual recognition memory appears to be more dependent on the perirhinal cortex than the parahippocampal cortex (Squire and Zola, 1996), whereas spatial memory appears to be more dependent on the parahippocampal cortex than the perirhinal cortex (Malkova and Mishkin, 1997; Parkinson, Murray, and Mishkin, 1988; Teng, Squire, and Zola, 1997).

There also has been interest in which, if any, memory functions can be identified that are specific for the hippocampus. Anatomically, the hippocampus lies at the end of the medial temporal lobe system and is a recipient of convergent projections from each of the

structures that precedes it in the hierarchy (figure 53.2). This arrangement has suggested to some that the hippocampus has a special role in memory tasks that depend especially on relating or combining information from multiple sources, such as spatial information or information about specific events, as opposed to factual knowledge (Mishkin et al., 1997; Nadel, 1991; Eichenbaum, Otto, and Cohen, 1994). These possibilities are active topics of investigation. Three observations seem warranted at this point.

First, it is clear that animals with neurotoxic damage limited to the hippocampus are impaired at nonspatial memory tasks (Bunsey and Eichenbaum, 1996). Spatial tasks are simply a good example of the large category of declarative memory abilities that are impaired after hippocampal damage (Squire, 1992). Second, in monkeys and humans, damage limited to the hippocampal region (hippocampus, dentate gyrus, and subicular complex) impairs simple tasks of recognition memory (Reed and Squire, 1997; Zola et al., 1998). For example, monkeys with circumscribed, radiofrequency lesions of the hippocampal region were impaired in the visual paired-comparison task (Zola et al., 1998). This task measures familiarity for recent stimuli by taking advantage of the natural (untrained) tendency that monkeys have to look longer at novel pictures than familiar pictures. Third, formal tests suggest that amnesic patients with hippocampal region damage have difficulty learning new facts just as they have difficulty learning about new events (Hamann and Squire, 1995; also see Squire and Zola, 1998).

These considerations suggest that the hippocampal region is important for both spatial and nonspatial memory, for both recognition memory and recall, and for both fact and event memory. This is, in fact, the impression that one gains through study of amnesic patients like R.B. and G.D., who had bilateral damage limited to the CA1 region of the hippocampus. If the hippocampus has some unique function that can be detected in behavioral measures, then there should be some memory task that G.D. and R.B. would have performed as poorly as patients with CA1 damage plus damage to other medial temporal lobe structures (e.g., the well-studied amnesic patient H.M. [Scoville and Milner, 1957]). However, G.D. and R.B. appeared simply to be less severely affected than patients like H.M. One possibility is that the hippocampus makes a unique contribution to declarative memory, but that this contribution will become clear only when the intrinsic circuitry of the hippocampus is better understood computationally. Another possibility is that the hippocampus, as the result of its placement at the end of the processing hierarchy of the medial temporal lobe (figure 53.2), combines and ex-

tends the functions of the structures that are positioned earlier in the hierarchy. In this view, the hippocampus supports and extends the operations of the structures that send projections to it, and studies of lesions and behavior would not reveal deficits unique to the hippocampus that could not also be observed by damaging the perirhinal cortex, the parahippocampal cortex, or the entorhinal cortex.

The distinction between remembering and knowing

When an item evokes a conscious recollection that includes specific information about the item and the context in which the item was learned, a subject is said to "remember" (R). When a subject is confident an item is familiar and was seen before, but is unable to remember anything about the item in its original learning context, the subject is said to experience "knowing" (K) (Tulving, 1985). In some respects, the distinction between remembering and knowing is similar to the distinction between declarative and nondeclarative memory, and R and K responses can be dissociated in a number of ways that are reminiscent of that distinction (Gardiner and Parkin, 1990). However, recent work shows that both R and K responses are impaired in amnesia (Knowlton and Squire, 1995; figure 53.3; Kroll, Yonelinas, and Knight, 1997). Accordingly, the evidence suggests that remembering and knowing are two different expressions of declarative memory.

In another study, event-related potentials (ERPs) from recently presented items that elicited R responses were similar to ERPs from recently presented items that elicited K responses until 500 ms after each item was presented (Smith, 1993). However, items that were endorsed as having been presented before (i.e., all the items that received either R or K responses) could be distinguished from items that were endorsed as new items beginning approximately 350 ms after item presentation. Smith (1993) suggested that both R and K responses result from a common process of recollection dependent on declarative memory. The distinction between R and K responses then arises from a postrecollective process, when subjects attend to the products of their retrieval efforts.

The nature of this postrecollective component of memory has been described in a number of ways. Tulving (1989) originally described remembering and knowing as measuring episodic and semantic memory, respectively. Items that are "remembered" after a short study-test delay are likely to become merely "known" after a long delay, and this transition has been likened to the transition between episodic and semantic memory (Conway et al., 1997).
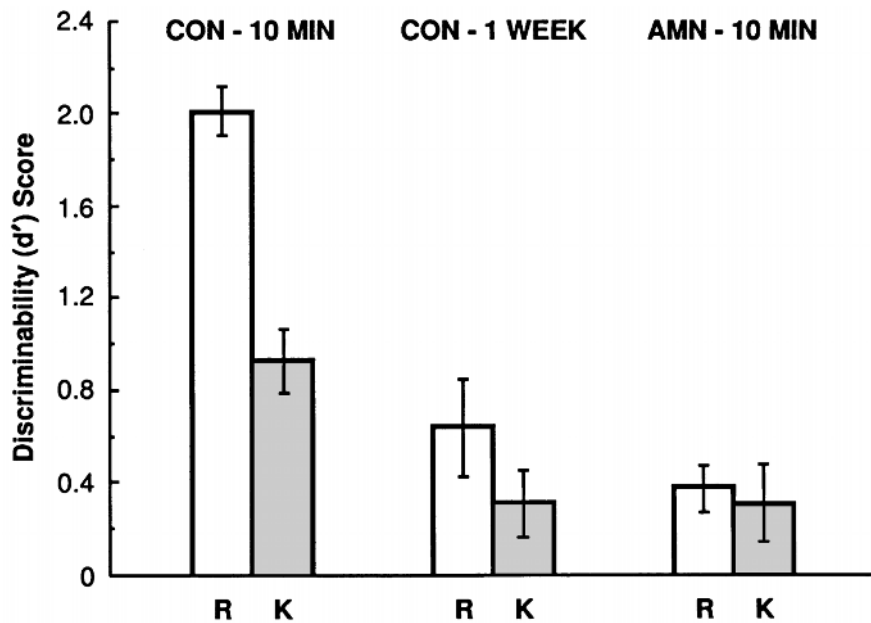
FIGURE 53.3   Recognition memory (measured by d', discriminability) for test items labeled *remember* (R; open bars) or *know* (K; closed bars) by amnesic patients (AMN) and two control groups (CON). The amnesic patients ($n = 13$) were tested 10 minutes after the study phase, and the control groups were tested 10 minutes ($n = 14$) or 1 week after the study phase ($n = 11$). For amnesic patients, the accuracy of both R responses and K responses were impaired. Brackets show standard errors of the mean. (From Knowlton and Squire, 1995.)

This line of thinking leads to the idea that although remembering and knowing are both forms of declarative memory, they nevertheless can be distinguished in a fundamental way. Whereas both remembering and knowing are dependent on the medial temporal lobe and diencephalic brain structures that support declarative memory, remembering depends additionally on the frontal lobes (Schacter, Harbluk, and McLachlan, 1984; Janowsky, Shimamura, and Squire, 1989). In one study, elderly individuals were impaired in remembering (i.e., making accurate R responses) in proportion to the extent that they exhibited neuropsychological signs of frontal lobe dysfunction (Parkin and Walter, 1992).

One critical component of "remember" judgments seems to be the availability of source memory. Individuals often describe an item as "remembered" because they have a specific memory of the learning context for that item. They remember the source of the item. Source memory is sensitive to frontal lobe damage (Schacter, Harbluk, and McLachlan, 1984; Janowsky, Shimamura, and Squire, 1989), consistent with the idea that remember "judgments" depend on the integrity of the frontal lobes. However, remember judgments are not fully equivalent to source judgments, broadly defined, because even when individuals recognize an item by familiarity (a "know" response), they still are indicating in their endorsement of the item that they believe the items were presented during the study phase. Thus, remem-

bering and knowing both require knowledge that a test item was encountered recently in the study context, but remembering additionally requires that specific information be available about a particular moment in recent time when the item was encountered.

Nondeclarative memory

PRIMING   Priming refers to the enhanced ability to identify or produce a stimulus as a result of its recent presentation. The first encounter with an item results in a representation of that item, which then allows it to be processed more efficiently than items that were not encountered recently. Priming is not merely the activation of previously existing representations because priming can occur for novel material, including orthographically illegal nonwords such as KHSF (Keane et al., 1995b; Hamann and Squire, 1997) and for newly associated word pairs (Gabrieli et al., 1997; Poldrack and Cohen, 1997). Some of the best evidence that priming is a distinct form of memory comes from the finding that amnesic patients exhibit intact priming (see Schacter, Chiu, and Ochsner, 1993, for a review).

The dissociation between intact priming and impaired recognition memory in amnesic patients is particularly compelling. One study investigated priming in a patient who is so severely amnesic that he exhibits no detectable declarative memory (Hamann and Squire, 1997). Patient
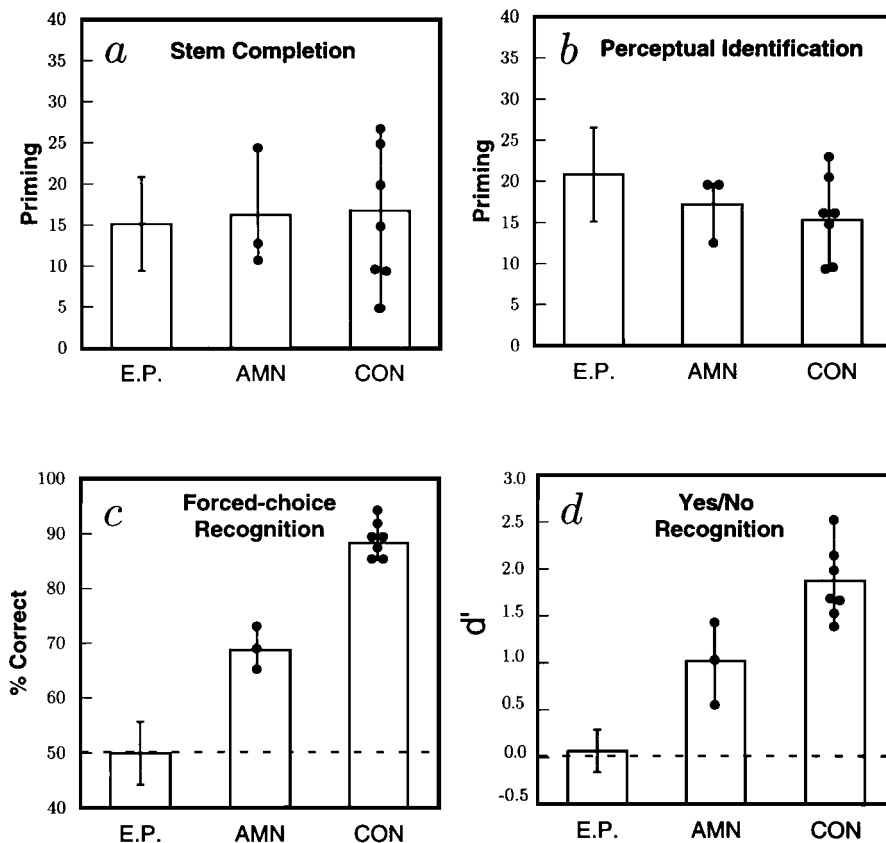
FIGURE 53.4 Performance on four different memory tests after studying 24 simple English words. (A) Stem completion priming. Six priming tests were given to the severely amnesic patient E.P., other less severely affected amnesic patients (AMN, $n = 3$), and normal controls (CON, $n = 7$). Priming scores were calculated as percentage correct for studied items minus percentage correct for nonstudied items. (B) Perceptual identification priming. Twelve tests were given to all participants. Priming scores were calculated as percentage of correct identifications of studied items minus percentage of correct identifications of nonstudied items. (C) Two-alternative, forced-choice recognition. Percentage correct across six tests for each participant. (D) Yes–no recognition. Discrimination accuracy (d') is shown across six tests for each participant. Percentage correct scores (hits plus correct rejections) were 52%, 65%, and 81% for E.P., AMN patients, and CON participants, respectively. Brackets for E.P. indicate the standard error of the mean; the data points for AMN and CON groups indicate individual participant means across all the tests. Dashed lines indicate chance performance. (From Hamann and Squire, 1997.)

E.P. sustained complete bilateral damage to the medial temporal lobe as the result of herpes simplex encephalitis. Two tests of priming were given–perceptual identification of words and word-stem completion. Two parallel tests of recognition memory for words were also given–two-alternative forced-choice and yes–no recognition. Each test was given 6 to 12 times to obtain a robust measure of performance. The result: E.P. performed entirely normally on the two priming tests but performed at chance on the recognition tests (figure 53.4). These results support the idea that priming depends on brain structures independent of the medial temporal lobe memory system. In addition, the fact that E.P. performed at chance on the recognition tests shows that he was unable to benefit his recognition performance by using the information available to him from priming.

The anatomical locus of perceptual priming appears to be in posterior neocortex. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have shown that primed items result in less activation in the posterior neocortex than do unprimed items (Schacter and Buckner, 1998). For example, in a word-stem completion task, volunteers showed reduced activation of the right posterior cortex while completing stems of words that had been presented recently, for example, study BRIDE, complete BRI__ (Squire et al., 1992). This decrease in activation likely reflects a decrease in the resources required to process material when it recurs because the material left a trace in the visual pathways after its first presentation.

Two patients with unilateral extrastriate lesions have been identified who performed poorly on visual percep-

tual priming tasks, but who exhibited intact recognition memory for the same stimuli (Gabrieli et al., 1995; Keane et al., 1995a). These patients also exhibited intact nonvisual priming and intact semantic priming. This dissociation of priming and recognition memory provides further support for the idea that these two forms of memory depend on different brain systems. The patients may have achieved normal recognition memory performance by accessing different information than is used to support priming. Whereas perceptual priming depends on the visual features of the stimulus items, recognition memory could draw on phonetic or semantic information that was established in parallel with and independently of information about visual features.

SKILLS AND HABITS   The learning of motor, perceptual, and cognitive skills is largely nondeclarative in some circumstances, as evidenced by the fact that amnesic patients can learn some skills at an entirely normal rate. In one study, amnesic patients and control subjects performed a serial reaction-time task (Nissen and Bullemer, 1987) in which they responded successively to a sequence of four illuminated spatial locations. The task was to press one of four keys as rapidly as possible as soon as the location above that key was illuminated. Amnesic patients and normal subjects successfully learned a repeating sequence of locations, as indicated by gradually decreasing reaction times for key presses as the sequence repeated itself. When the sequence was changed, reaction times increased again. Amnesic patients learned the sequence even when they had little or no declarative knowledge of it, as measured by four different tests of declarative knowledge (Reber and Squire, 1994).

In a second study, the distinction between procedural knowledge for the sequence and declarative knowledge for the sequence was established in a different way. Amnesic patients received extended practice on a sequence (1200 trials), and control subjects were given no practice but attempted to memorize the sequence during a brief period of 60 observation trials (Reber and Squire, 1998). The result: control subjects answered questions about the sequence better than the amnesic patients, but the amnesic patients exhibited better nondeclarative knowledge of the sequence than the controls, as measured by their improved reaction times while performing the task.

Neuropsychological studies of skill learning point to the involvement of the neostriatum in many of the tasks. Patients with striatal damage, including patients with Huntington's disease or Parkinson's disease, are impaired at acquiring perceptuomotor skills (see Salmon and Butters, 1995, for a review). Functional neuroimaging also has implicated the neostriatum in the serial reaction time task (Doyon et al., 1996; Grafton, Hazeltine,

and Ivry, 1995; Hazeltine, Grafton, and Ivry, 1997; Rauch et al., 1997).

Habit learning refers to stimulus-response–based associations that are formed gradually and independently of declarative memory for the training episode (Mishkin, Malamut, and Bachevalier, 1984). In experimental animals, there is strong evidence that the neostriatum is essential for habit learning (White, 1997). To study habit learning in humans requires thwarting the tendency to memorize the structure of the task by using declarative memory. For example, in the win-stay radial-arm maze task, rats gradually learn the habit of entering a lit arm across many trials. However, humans could learn to enter a lit arm in a single trial by acquiring the declarative fact "light signals food."

We developed a task in which the probabilistic nature of what was to be learned made a declarative memorization strategy ineffective (Knowlton, Squire, and Gluck, 1994). Information learned on single trials is not nearly as useful as information abstracted across many trials. The task was presented to subjects as a weather prediction game in which a series of cues appear on a computer screen, and the subject must guess on each trial whether the cues predict sunshine or rain (figure 53.5). Subjects receive feedback on every trial, and memorization is minimized by requiring subjects to respond within 5 seconds. Although subjects often report that they are simply guessing, they nevertheless show evidence of learning. They begin the task performing at chance (50% correct), and they end up after 50 trials choosing the most associated outcome approximately 70% of the time.

As is the case with habit learning tasks studied in experimental animals, the medial temporal lobe memory system is not necessary for this type of learning. Amnesic patients were able to learn normally across the first 50 trials of this task (Knowlton, Squire, and Gluck, 1994). Further evidence that the probabilistic classification task is an example of habit learning is provided by the fact that patients with Parkinson's disease exhibited significant impairment on this task. In fact, a double dissociation was found between amnesic patients and Parkinson patients. Amnesic patients learned the task but then could not answer questions about the nature of the task and what they had done. Parkinson patients failed to learn the task but were normal at answering questions about the test episode (Knowlton, Mangels, and Squire, 1996; figure 53.6). These data provide evidence for the existence of a neostriatal habit learning system in humans.

ARTIFICIAL GRAMMAR LEARNING   In an artificial grammar learning task, subjects are presented with a
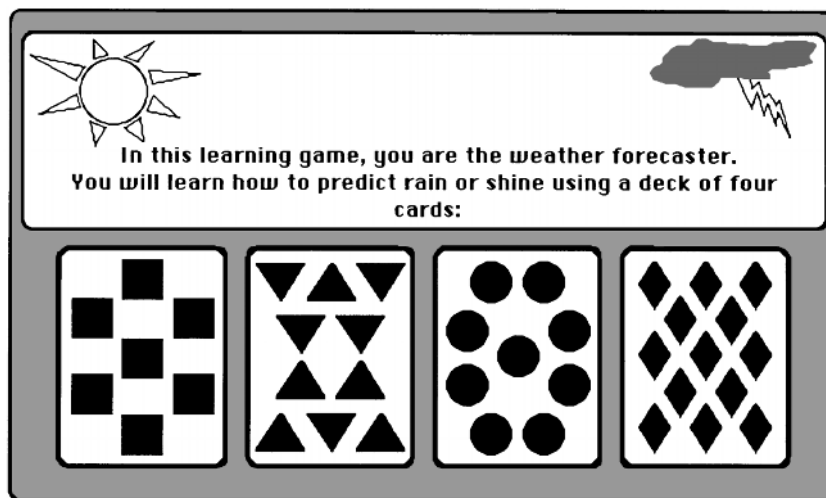
FIGURE 53.5 Appearance of the computer screen at the beginning of the probabilistic classification task. The four cues are shown along with the sun and rain icons. On each trial, one, two, or three of these cues were presented side by side (in 1 of the 14 possible combinations), and individuals predicted whether the outcome would be sunshine or rain by pressing one of two keys. Feedback was provided immediately to signal a correct or incorrect response. A particular cue was associated with the outcome sunshine either 75%, 57%, 43%, or 25% of the time, and thus either 25%, 43%, 57%, or 75% of the time with the other outcome (rain). For each person in the study, the four cues were randomly assigned one of these probabilities. Testing proceeded for 50 trials. (From Knowlton, Squire, and Gluck, 1994.)
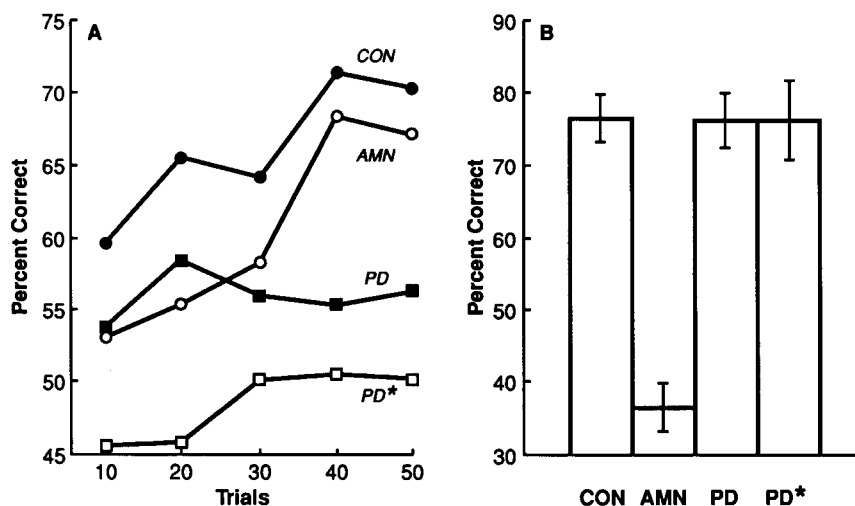

FIGURE 53.6 (A) Performance on the probabilistic classification task by controls (CON, $n = 15$), amnesic patients (AMN, $n = 12$), patients with Parkinson's disease (PD, $n = 20$), and a subgroup of the PD patients with the most severe symptoms (PD*, $n = 10$). None of the groups performed significantly above chance levels (50% correct) on the first block of 10 trials. The controls and amnesic patients gradually learned the cue–outcome associations during 50 trials. The PD patients exhibited no measurable learning across 50 trials. (B) Performance on a declarative memory task that asked about the testing episode. Both PD and PD* groups exhibited entirely normal declarative memory for facts about the testing episode, despite their poor performance on the classification task itself. In contrast, the amnesic patients exhibited a severe impairment in declarative memory for the testing episode but normal performance on the classification test. Brackets show standard errors of the mean. (Reprinted with permission from Knowlton, Mangels, and Squire, 1996. Copyright 1996 American Association for the Advancement of Science.)

series of letter strings that are formed according to a finite-state rule system like the one in figure 53.7. After viewing these letter strings, subjects are told for the first time that the letter strings were formed according to a set of rules and that their task is to decide for a new set of letter strings whether each one is formed by the same set of rules. Even though subjects typically report that they are simply guessing, they are able to classify new letter strings as "grammatical" or "non-grammatical" significantly above chance (see Reber,

Grammatical

MXV
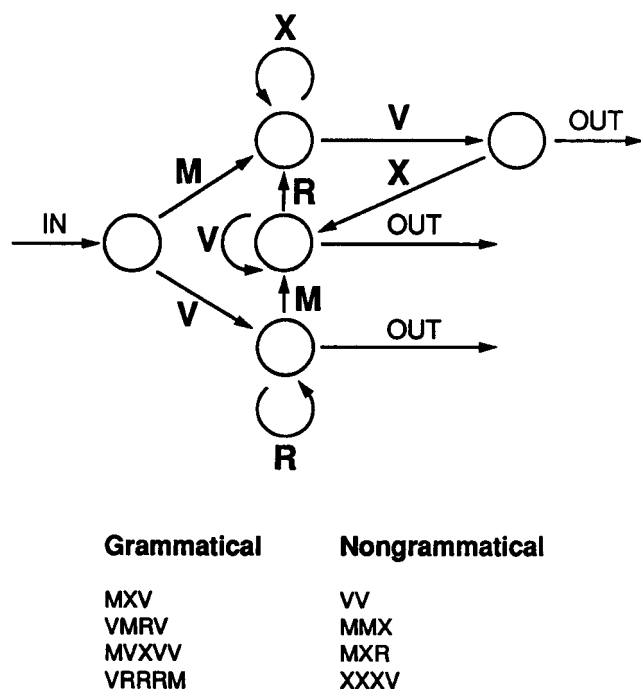VMRV
MVXVV
VRRRM

Nongrammatical

VV
MMX
MXR
XXXV

FIGURE 53.7 Artificial grammar learning. Letter strings are generated from a finite state rule system. Grammatical letter strings are formed by traversing the diagram from the in arrow to the out arrows, adding a letter at each transition from one node to the next. Nongrammatical letter strings are formed by introducing an error into a grammatical letter string. (From Knowlton and Squire, 1994.)

1989, for a review). Interestingly, amnesic patients classify items as grammatical or nongrammatical as well as normal subjects, despite being impaired at recognizing the letter strings that were used during training (Knowlton, Ramus, and Squire, 1992; Knowlton and Squire, 1994; 1996; figure 53.8).

The information that is acquired nondeclaratively in an artificial grammar learning task initially was assumed to be some veridical portion of the actual rule system that was used to form the exemplars. However, grammatical and nongrammatical letter strings differ in other ways besides their adherence to grammatical rules. For example, test letter strings that are grammatical are more likely to be composed of letter bigrams and trigrams (chunks) that appeared frequently in the training exemplars than are nongrammatical letter strings. In this sense, grammatical letter strings are considered to have a higher "chunk strength" than nongrammatical items. It turns out that subjects are likely to endorse as grammatical those test items with high chunk strength, regardless of whether the items follow grammatical rules. This finding demonstrates that the information learned about an artificial grammar includes very simple, concrete associations between features of the training items and the test

items (Knowlton and Squire, 1994; Servan-Schreiber and Anderson, 1990).

It also is true that subjects are able to transfer some knowledge about an artificial grammar to letter strings composed of entirely new letters, and they can even accomplish a change in sensory modality from training to testing (Altmann, Dienes, and Goode, 1995). Thus, it appears that subjects are able to learn some abstract information about the artificial grammar, which then allows them to transfer their knowledge to new test items that differ in surface structure. The question of whether learning on this task is abstract or concrete is orthogonal to the question of whether this learning is declarative or nondeclarative. Amnesic patients and normal subjects appear to exhibit the same sensitivity to chunk strength, and they both transfer to stimuli formed using new letters (Knowlton and Squire, 1996). Thus, both abstract and concrete information can be learned nondeclaratively.

Patients with basal ganglia dysfunction can accomplish artificial grammar learning (Knowlton et al., 1996; Reber and Squire, in press). The fact that much of artificial grammar learning is based on concrete, item-specific information about bigrams and trigrams raises the possibility that this type of learning could resemble priming or perceptual learning. For example, it was shown that subjects trained on an artificial grammar are able to perceive grammatical letter strings at a shorter exposure duration than nongrammatical letter strings, demonstrating that the grammatical letter strings enjoy enhanced perceptual fluency (Buchner, 1994). If so, artificial grammar learning may depend on changes within the neocortex.

CATEGORY LEARNING   After exposure to several exemplars of a category, subjects are able to classify new items according to whether they are members of that category. In addition, subjects identify the prototype, or central tendency of the category, as a member of the learned category more readily than the items used during training, even when the prototype itself was not presented during training. Such findings originally were interpreted as showing that subjects abstract a prototype from the training exemplars and use the abstracted prototype to classify new items. However, computational work has shown that superior classification of prototypes also occurs when nothing is stored except the characteristics of individual exemplars (Medin and Schaffer, 1978). The prototype usually is similar to a large number of the training items so that it would be strongly endorsed if subjects were making their judgments by making comparisons between each test item and the exemplars stored in memory.
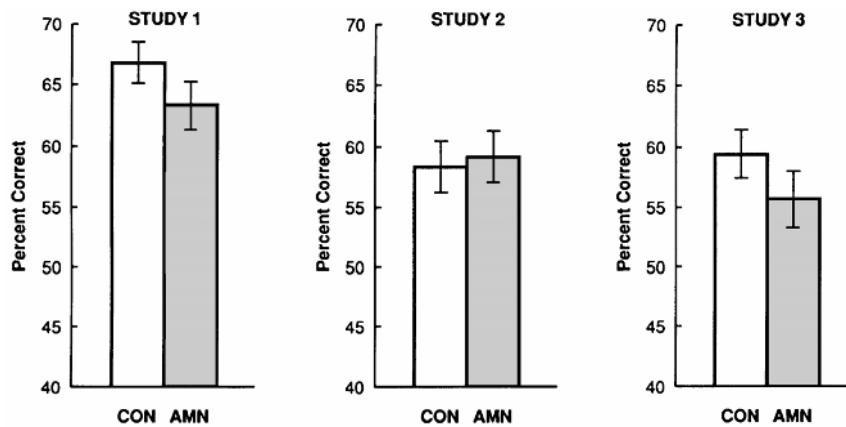
FIGURE 53.8 The results of three separate studies showing normal performance of amnesic patients (AMN) compared with control subjects (CON) on classification tasks based on ar-tificial grammars. Brackets show standard error of the mean. (From Knowlton, Ramus, and Squire, 1992, and Knowlton and Squire, 1994.)

The matter of whether category learning depends on abstracting a prototype or whether it is exemplar based is orthogonal to the issue of whether category learning is declarative or nondeclarative. Support for the idea that category learning is nondeclarative comes from the finding that amnesic patients are able to classify items according to a learned category, despite a severe deficit in recognizing the items that were used to train the category (Knowlton and Squire, 1993). The task was similar to one developed by Posner and Keele (1968). Amnesic patients and control subjects were shown a series of dot patterns formed by distorting a randomly generated pattern that was defined arbitrarily as the prototype of the category. Having seen a series of dot patterns, all of which were distortions of an underlying prototype, subjects then were able to discriminate new dot patterns that belonged to the training category from other dot patterns that did not (figure 53.9). Amnesic patients performed the same as control subjects, even though the patients were severely impaired at recognizing which dot patterns had been presented for training. These data demonstrate that category-level knowledge can be acquired nondeclaratively. Moreover, if category-level knowledge is exemplar based, then it is independent of the exemplar-based information used to support recognition memory.

A challenge to the notion that classification and recognition arise from independently acquired sources of knowledge comes from computational work showing how the performance of amnesic patients could depend on a single knowledge base. The key idea is that the function relating exemplar knowledge and classification performance is nonlinear. If a little exemplar knowledge is all that is needed to achieve near-normal classification performance, then amnesic patients could perform nearly
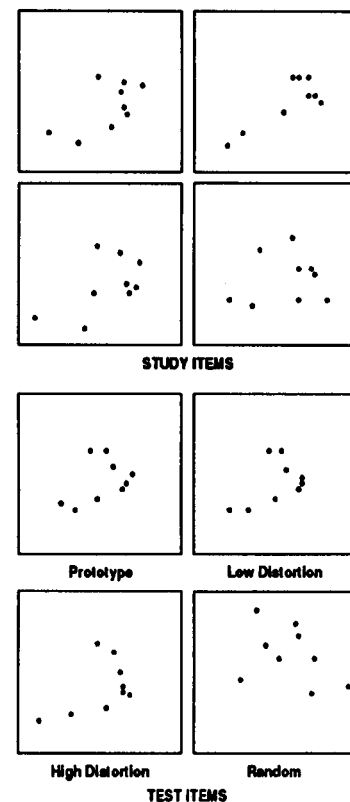

FIGURE 53.9 Examples of the 40 study items and 84 test items used to assess category learning of dot patterns. The study items were all distortions of a prototype dot pattern that was not presented. The test items were new dot patterns, either presentations of the prototype ($n = 4$), low distortions of the prototype ($n = 20$), high distortions of the prototype ($n = 20$), or random dot patterns ($n = 40$). (From Squire and Knowlton, 1995. Copyright 1995 National Academy of Sciences, U.S.A.)

normally on category learning, despite having impaired exemplar knowledge as assessed by recognition memory (Nosofsky and Zaki, 1998).

This possibility has been addressed in two ways. First, amnesic patients and patients with Parkinson's disease demonstrated a double dissociation between classification performance and recognition memory on the probabilistic classification task (figure 53.6). This finding shows that, for this task, knowledge stores appear to be independent. Classification is not simply easier than recognition because the patients with Parkinson's disease actually found classification more difficult than recognition (Knowlton et al., 1996).

Another way to test the independence of classification and recognition is to test the category-learning abilities of a patient who has no detectable declarative memory capacity. If normal category learning occurs in such a patient, then classification performance must be based on nondeclarative knowledge. This set of requirements was met with the severely amnesic patient E.P. (Squire and Knowlton, 1995). After viewing 40 different dot patterns, he classified new dot patterns as well as normal subjects (figure 53.10). Six different tests were given to obtain a robust performance measure. Despite his intact ability to classify new dot patterns, he failed to recognize a single dot pattern as familiar after it had been presented 40 times consecutively. This recognition test also was repeated six different times. It is not clear how to explain these results except to suppose that learning about categories can occur independently of declarative memory.

Category learning, like artificial grammar learning, may resemble priming effects with respect to the importance of perceptual fluency. Categorical dot patterns presented at test are similar to previously viewed patterns and therefore may be processed more rapidly and less effortfully than noncategorical patterns. Accordingly, the prototype of the trained category would benefit the most from perceptual fluency because it should be similar to a larger number of training items than any other individual dot pattern. Similarly, dot patterns that resemble the prototype should benefit more from perceptual fluency than random dot patterns. Neuroimaging data support this idea (Reber, Stark, and Squire, 1998). Volunteers studied 40 dot patterns that were distortions of an underlying prototype and then, while fMRI data were collected, they made yes–no category judgments about new dot patterns. Posterior occipital cortex (areas 17/18) exhibited less activity during processing of the categorical patterns than during processing of noncategorical patterns. This result suggests that category learning and perceptual priming may be based on similar mechanisms. That is, decreased activity in the posterior cortex may occur not only when a stimulus is repeated a second time but also when a stimulus is presented that is similar to one seen earlier.
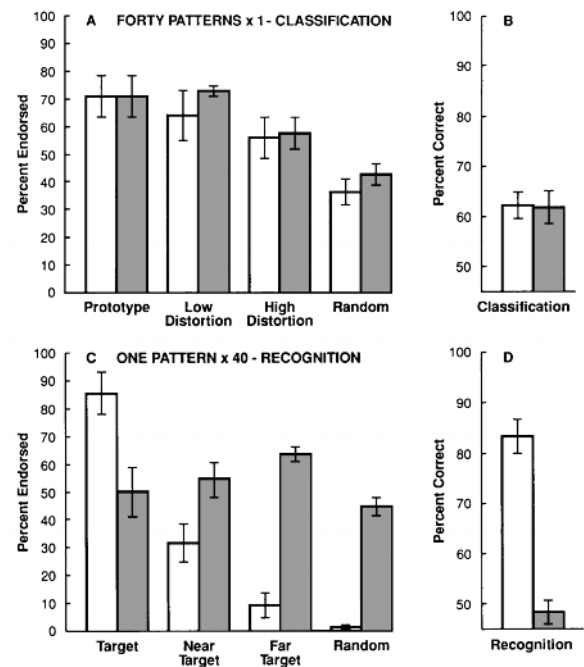

FIGURE 53.10   Performance on parallel tasks of categorization and recognition memory by the severely amnesic patient E.P. and control subjects. All subjects were tested six times on both tests. Brackets show standard errors of the mean. (A) Categorization. Classification of 84 novel dot patterns 5 minutes after studying 40 different training patterns that were distortions of a prototype dot pattern. Control subjects ($n = 4$, open bars) and E.P. (closed bars) performed similarly, endorsing test items as a function of how closely they resembled the prototype of the training category. There were four types of test items (4 prototypes, 20 low distortions, 20 high distortions, and 40 random dot patterns). (B) Overall percentage correct scores for classification. E.P. performed as well as control subjects at categorization. (C) Recognition. Recognition memory 5 minutes after 40 presentations of the same prototype dot pattern. The recognition test was structured identically to the categorization test (A), and only the instructions differed—that is, recognition instead of classification. Thus, at test there were 4 presentations of the prototype target pattern, 20 near targets, 20 far targets, and 40 random patterns. (D) Overall percentage correct scores for recognition. Correct responses consisted of endorsements of the training pattern (the 4 targets) and rejections of the other 80 patterns. E.P. performed at chance. (From Squire and Knowlton, 1995.)

CLASSICAL CONDITIONING   Classical conditioning is an extensively studied example of simple associative learning and, in its simplest form, is a quintessential example of nondeclarative memory. The best studied paradigm, delay conditioning of the eyeblink response (conditioned stimulus = tone; unconditioned stimulus = airpuff to the eye) is reflexive and automatic and depends solely on structures below the forebrain, including the cerebellum and associated brainstem circuitry (Thompson and Krupa, 1994). Amnesic patients also exhibit intact
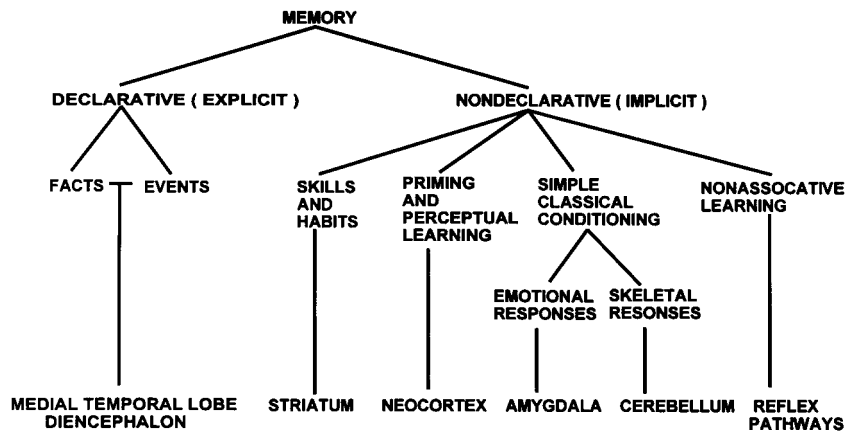
FIGURE 53.11 A taxonomy of mammalian long-term memory systems. The taxonomy lists the brain structures thought to be especially important for each form of declarative and nondeclarative memory. In addition to its central role in emotional learning, the amygdala is able to modulate the strength of both declarative and nondeclarative memory. (From Squire and Zola, 1996.)

acquisition and retention of delay eyeblink conditioning (Daum and Ackerman, 1994; Gabrieli et al., 1995).

In trace conditioning, an interval is interposed between the CS and the US. This form of conditioning requires the hippocampus in both rabbits (Solomon et al., 1986) and humans (McGlinchey-Berroth et al., 1997). Studies of elderly normal subjects (mean age = 67 years) given differential eyeblink conditioning (CS+ vs. CS–) suggest that trace conditioning is hippocampus dependent because it requires the acquisition and retention of conscious knowledge during the course of the conditioning session (Clark and Squire, 1998). Only subjects who became aware of the CS–US relationship acquired differential trace conditioning. The correlation between measures of awareness taken after trace conditioning and conditioning performance itself was $r = 0.74$ and $r = 0.69$ for two different trace-conditioning tasks. In contrast, in two tasks of delay conditioning, awareness bore no relationship to conditioning performance ($r = 0.10$ and $r = 0.16$).

Trace conditioning is dependent on the cerebellum as well as the hippocampus (Woodruff-Pak, Lavond, and Thompson, 1985). Thus, a nondeclarative learning circuit in the cerebellum presumably is required for the generation of the conditioned response. Trace conditioning likely requires the hippocampus (and an interaction between hippocampus and neocortex) because the existence of the trace interval makes it difficult for the cerebellum to process the CS and US in an automatic way. With the help of the hippocampus, the neocortex may develop a representation of the temporal relationship between the stimuli, which then can be available to the cerebellum in a format that the cerebellum can use.

Conclusion

It presently is possible to link particular brain regions and systems to particular kinds of memory (figure 53.11). Unlike declarative memory, nondeclarative memory does not depend on a single brain system. These different forms of nondeclarative memory have different properties and different functions. A common thread is their independence from declarative memory and the fact that they are nonconscious. As the functional neuroanatomy of memory is becoming better understood, it should become possible to discover where and how plasticity is occurring in the different circuits that comprise each memory system. This information also would illuminate a number of long-standing systems-level questions about memory: (1) What is a memory system? (2) How independent are the systems from each other? and (3) When memory loss occurs, is the information simply inaccessible or has it been erased?

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