CHAPTER 3. CONTRIBUTIONS OF THE PSYCHOLOGICAL SCIENCES

3.4 BIOLOGY OF MEMORY

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The topic of memory is fundamental to the discipline of psychiatry. Memory provides the essential substrate for the cognitive activities that define human experience, it allows one to connect the present moment to what came before, and it is the basis of cultural evolution.

An individual's personality reflects habits and dispositions that have developed from experience. Adaptive and maladaptive coping strategies, anxieties, and phobias are largely products of learning. Neurotic or psychotic symptoms can be the consequences of specific experiences or repeated patterns of experience. Psychotherapy is a process by which new behaviors are acquired through the accumulation of new experiences. Thus, memory is at the heart of psychiatry's concern with the effects of early experience, the development of the individual, and the possibility of change.

Disorders of memory and complaints about memory lapses are pervasive in both neurology and psychiatry. Memory problems are also of special concern as side effects of psychopharmacological treatments and electroconvulsive therapy. Accordingly, the effective clinician needs to understand memory, its psychological and neurological foundations, the varieties of memory dysfunction, and how memory can be evaluated. The biological perspective on memory developed here rests on a growing body of neuroscientific evidence that relates mental events to the functioning of the brain.

MEMORY AS SYNAPTIC CHANGE

Memory is a special case of the more general phenomenon of *neural plasticity*. Neurons can show

history-dependent behavior by responding differently as a function of recent input, and this plasticity of nerve cells and synapses is the basis of memory. In the last decade of the nineteenth century, researchers proposed that the persistence of memory could be accounted for by nerve cell growth. Others have restated this idea, developing the hypothesis that the synapse is the critical site of change. In principle, there are many possible ways for such structural change to be realized, including alterations in the number of synaptic contacts or in the strength of existing contacts.

Plasticity Neurobiological evidence from animal studies supports two basic conclusions about the biology of memory. First, specific synaptic events, including an increase in neurotransmitter release, are responsible for short-lasting plasticity, which may last for seconds or minutes. Second, long-lasting memory depends on new protein synthesis, physical growth of neural processes, and an increase in the number of synaptic connections.

A major source of information has been the extended study of the marine mollusc *Aplysia californica*. A sufficient number of individual neurons and connections between neurons have been identified to allow the wiring of some simple behaviors to be diagrammed. *Aplysia* is capable of both associative learning (including classical conditioning and operant conditioning) and nonassociative learning (habituation and sensitization). Figure 3.4-1 shows the circuitry responsible for the gill-withdrawal reflex, a defensive reaction whereby tactile stimulation causes the gill and siphon to retract. When tactile stimulation is preceded by stimulation to the head, gill withdrawal is facilitated. The cellular mechanisms underlying this sensitization are based on an enhanced release of neurotransmitter by the facilitatory neuron (labeled "Int" in Fig. 3.4-1) and accompanied by covalent modifications of preexisting proteins. Under some training conditions, sensitization can persist for weeks, and these longer-lasting changes can also be produced by repeated applications of serotonin, distributed over a period of 1½ hours. Although both short- and long-lasting plasticity are based on enhanced transmitter release, the long-lasting change uniquely requires the expression of genes and the synthesis of proteins. In addition, the long-term change, but not the short-term change, is accompanied by the growth of neural processes of neurons within the reflex circuit.

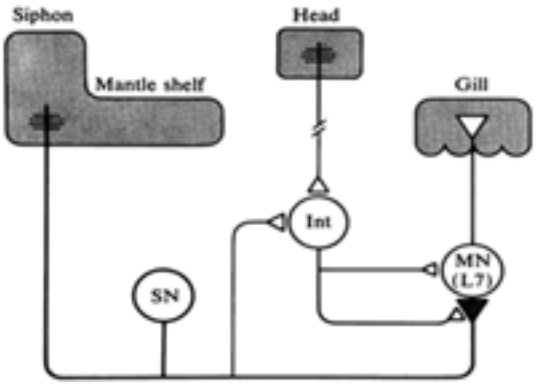


FIGURE 3.4-1 A schematic diagram of the neuronal circuit underlying behavioral habituation and sensitization of the gill-withdrawal reflect in *Aplysia*. The relative simplicity of the nervous system of *Aplysia* makes it a valuable organism for studying cellular and synaptic mechanisms of memory. The synapse between the sensory neuron (SN) and the motor neuron (MN) is an important site of habituation. Sensitization results from activation of the interneuron (Int) pathway. (Reprinted with permission from Kandel ER: *Cellular Basis of Behavior*. Freeman, San Francisco, 1976.)

In vertebrates, behavioral manipulations can also result in measurable changes in the brain's architecture. For example, rats reared in enriched environments show an increase in the number of synapses ending on individual neurons in neocortex. These changes are accompanied by small increases in cortical thickness, in the diameter of neuronal cell bodies, and in the number and length of dendritic branches. New synapses may be formed directly or synapses may be selectively preserved from a population that is continuously being replaced. Behavioral experience thus exerts powerful effects on the wiring of the brain.

Many of these same structural changes have been found in adult rats exposed to an enriched environment, and some have been found in adult rats given extensive maze training. In this case opaque contact-lens occluders were used to restrict vision to one eye, and the corpus callosum was transected to prevent information received by one cerebral hemisphere from reaching the other hemisphere. In these monocularly trained animals, increases in the size of dendritic fields of pyramidal neurons of occipital cortex were found only in the trained hemisphere. This finding rules out a number of nonspecific influences including motor activity, indirect effects of hormones, and overall level of arousal. Therefore it seems likely that long-term memory in vertebrates is generally based on specific changes within the neurons that lie along specific pathways.

Long-Term Potentiation The phenomenon of *long-term potentiation* (LTP) is a form of neural plasticity likely to be important for memory in vertebrates. LTP is observed when a postsynaptic neuron is persistently depolarized following a brief burst of high-frequency stimulation. LTP has a number of properties that make it a promising candidate as a physiological substrate of memory. First, it is established quickly and then lasts for a long time. Second, it is associative in that it depends on the co-occurrence of presynaptic activity and postsynaptic depolarization. Third, it occurs only at the potentiated synapses, not at all the synapses terminating on the postsynaptic cell. Finally, LTP occurs prominently in the hippocampus, a structure with important memory functions. The induction of LTP is known to be mediated postsynaptically and to involve activation of the *N*-methyl-D-aspartate (NMDA) receptor, which permits influx of calcium into the postsynaptic cell. The mechanism whereby LTP is maintained is not clearly established, but evidence has been presented in favor of a presynaptic locus of change (increased transmitter release). Rapidly developing structural changes in the dendritic spines of the postsynaptic neuron have also been described in association with LTP.

A new method for studying molecular mechanisms of memory relies on introducing specific mutations into the genome. For example, by altering a single cloned gene, a mutant strain of mice can be produced with specific receptors or cell-signaling molecules inactivated or altered. This knock-out technique can provide greater specificity than pharmacological blocking methods. Recently, it has been possible to study mice with a selective deletion of one type of NMDA receptor in the CA1 field of the hippocampus. Although many aspects of CA1 physiology remain intact, the CA1 cells do not exhibit LTP. In addition, an impairment is observed on a learning task. If reversible gene knock-outs can be achieved, it will be possible to induce specific molecular changes in a developmentally normal adult.

Associative Learning Additional insights into memory have been gleaned from the study of the neural circuitry underlying classical conditioning of the eyeblink-nictitating membrane response in rabbits. Repeated pairings of a tone (conditioned stimulus) and an airpuff to the eye (unconditioned stimulus) lead to a conditioned eyeblink in response to the tone. Reversible lesions of the deep nuclei of the cerebellum eliminate the conditioned response without affecting the unconditioned response, which indicates that the cerebellum contains part of the essential circuitry for learned association, the conditioned stimulis–unconditioned stimulus link. Reversible lesions of the deep nuclei also prevent learning from occurring, and the rabbits begin learning from the naive state when the lesion is reversed. This finding does not mean that all the changes occurring in the animal during conditioning involve the cerebellum; it means only that essential neural changes responsible for the conditioned stimulus–unconditioned stimulus link depend on this circuitry. The relevant plasticity appears to be distributed between the cerebellar cortex and the deep nuclei (Fig. 3.4-2). An analogous pattern of plasticity is thought to underlie motor learning in the vestibulo-ocular reflex, and perhaps associative learning of motor responses in general. Based on the idea that learned motor responses depend on coordinated control of changes in both timing and strength of response, it has been suggested that synaptic change in the cerebellar cortex is crucial for learned timing, whereas synaptic change in the deep nuclei is crucial for learned changes in the strength of the response.

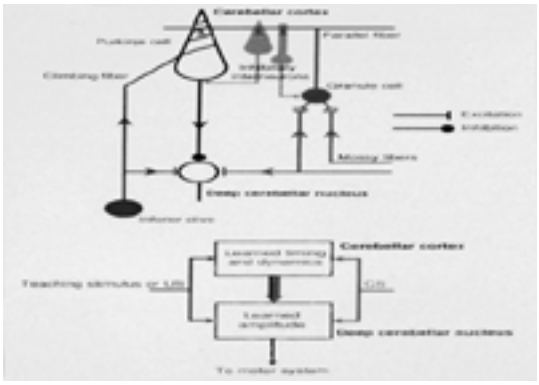


FIGURE 3.4-2 A schematic diagram of the circuitry of the mammalian cerebellum (**top**). In the classically conditioned blink response, input from the air-puff unconditioned stimulus and input from the auditory conditioned stimulus comes in through parallel pathways to the cerebellar cortex and to the deep cerebellar nucleus, and plasticity occurs in both pathways (**bottom**). (Reprinted with permission from Raymond JL, Lisberger SG, Mauk MD: The cerebellum: A neuronal learning machine? Science *272:*1126, 1996. © 1996 American Association for the Advancement of Science.)

Understanding the biology of memory requires more than just an understanding of the synaptic events that store memory. It is also essential to understand how and where synaptic events are organized in the brain. Many levels of analysis can be identified between synaptic change and behavioral memory, and many important questions about memory address levels of biological analysis that are intermediate to synapses and behavior.

CORTICAL ORGANIZATION OF MEMORY

The question of where memories are stored in the brain has long been a major research issue. In the 1920s Karl Lashley carried out a series of experiments that were directed at this problem. Lashley

recorded the number of trials that rats needed to relearn a preoperatively learned maze problem after removal of different amounts of cerebral cortex. The deficit was proportional to the amount of cortex removed and, further, it seemed to be qualitatively similar, regardless of what region of cortex was removed. Lashley concluded that memory for the maze habit was not localized in any one part of the brain, but instead was distributed equally over the entire cortex. Subsequent work has led to a revision of this idea. Maze learning in rats depends on many forms of information, including visual, tactual, spatial, and olfactory information. These various forms of information are processed and stored in different areas. Thus, the correlation between retention score and lesion size that Lashley observed reflects the progressive encroachment on specialized cortical areas serving the many components of cognition important to maze learning.

The specialized cortical areas responsible for processing and storing visual information have been studied most extensively in nonhuman primates. Nearly half of the primate neocortex is specialized for visual functions. Cortical pathways for visual information processing (Fig. 3.4-3) begin in primary visual cortex (V1) and proceed from there along parallel pathways or streams. One stream projects ventrally to the inferotemporal cortex (area TE in the monkey) and processes information about the quality of visual percepts. Another stream projects dorsally to the parietal cortex and processes information about spatial location. Electrophysiological studies in the monkey show that neurons in area TE register specific and complex features of visual stimuli, like shape, and may even respond selectively to patterns and objects. These specific visual processing areas, along with connections to corresponding regions in dorsolateral prefrontal cortex, are involved in the immediate experience of perceptual processing, and in what has been called *immediate memory* or *working memory*. These areas also serve as the ultimate repositories of the memories that result from their activity. Accordingly, lesions in these areas lead to impairments in visual perception as well as in visual learning and memory, although elementary visual functions such as acuity remain intact. Inferotemporal cortex can thus be thought of both as a higher-order visual processing system and a storehouse of the visual memories that result from that processing. These stored visual memories can be used and manipulated according to current processing demands, and they can also be quite long-lasting.

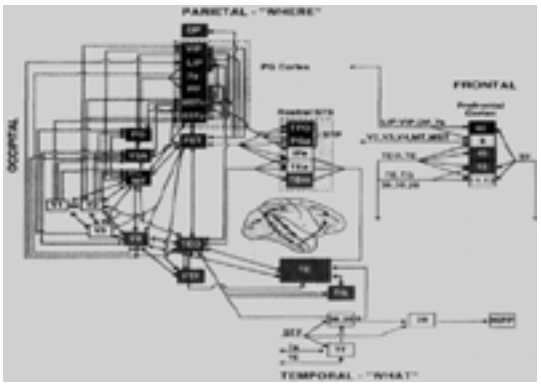


FIGURE 3.4-3 Summary of cortical visual areas and some of their connections. There are two major pathways from striate cortex (V1). The processing stream for object vision follows a ventral route into the temporal lobe via V4 (dark gray boxes) and the processing stream for spatial vision follows a dorsal route into the parietal lobe via MT (light gray boxes). Solid lines indicate connections arising from both central and peripheral visual field representations; dotted lines indicate connection restricted to peripheral field representations. Shaded region on the lateral view of the brain represents the extent of the cortex included in the diagram. Abbreviations: DP, dorsal prelunate area; FST, fundus of superior temporal area; HIPP, hippocampus; LIP, lateral intraparietal area; MSTc, medial superior

temporal area, central visual field representation; MSTp, medial superior temporal area, peripheral visual field representation; MT, middle temporal area, MTp, middle temporal area, peripheral visual field representation; PO, parieto-occipital area; PP, posterior parietal sulcal zone; STP, superior temporal polysensory area; VIP, ventral intraparietal area; STS, rostral superior temporal sulcus; and VTF, visual responsive portion of area TF. (Reprinted with permission from Ungerleider LG: Functional brain imaging studies of cortical mechanisms for memory. Science *270:*769, 1995. © 1995 American Association for the Advancement of Science.)

Many parts of the nervous system participate in storing representations of an event in memory. During an event, visual information is stored in inferotemporal cortex so that the same visual material can later be recognized as familiar. Concurrently, other components of the event—including spatial, temporal, tactile, olfactory, emotional, and other sorts of information—are processed and stored separately. Memory storage in the cerebral cortex thus depends on a fractionation of experience as follows. First, any particular event or learning task is composed of a number of components. Second, each component engages a particular processing site or set of sites. Third, each processing site stores information as an outcome of the processing that is done.

Thus, memory is both distributed and localized in the nervous system. It is distributed in the sense that, as Lashley concluded, there is no unitary cortical center dedicated solely to the storage of memories. Yet, memory is localized in the sense that different aspects or dimensions of events are stored at specific cortical sites—the same regions specialized to analyze and process those particular aspects or dimensions of information.

INSIGHTS FROM AMNESIA

The idea that the functional specialization of cortical regions governs both information processing and information storage is important, but it does not provide a complete account of the organization of memory in the brain. If it did, then particular cortical injuries would disrupt only particular domains of learning and memory (i.e., visual memory or spatial memory) and no global disruption of memory would occur. Brain injury would always produce a difficulty in learning a restricted type of new information along with a loss of previously learned information of that same type. Yet common neurological syndromes of memory impairment conflict with these expectations.

The hallmark of neurological memory impairment is a profound anterograde amnesia, or loss of new learning ability, that extends across all sensory modalities. Typically, this occurs together with retrograde amnesia, a memory loss for information acquired prior to the onset of amnesia. The retrograde deficit often has a temporal gradient, such that recall for recent events is impaired, but recall for remote events is intact. Other cognitive functions are preserved, including attention, immediate memory, personality, and social skills.

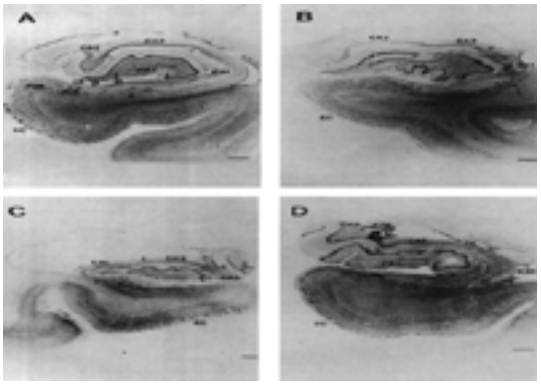
The selectivity of the memory deficit in amnesia implies that the brain has isolated intellectual and perceptual functions from the ability to lay down a record of information processing. The cognitive dysfunction experienced by amnesic patients affects memory storage but does not affect a wide range of other intellectual capabilities. The fact that memory storage is affected for all sensory modalities without a parallel disruption of perception implies that the memory function is superimposed on normal cortical processing. The fact that anterograde amnesia often occurs together with intact remote memory implies that viable retrieval mechanisms are intact, and also that the brain structures damaged in amnesia are not the ultimate repositories of memory. Detailed studies of amnesic patients and models of amnesia in nonhuman animals have illuminated these issues considerably.

Specialized Memory Function Amnesia results from damage to either of two brain regions: the medial temporal lobe or the midline diencephalon. Early studies of a severely amnesic patient known as HM markedly stimulated investigation of the role of the medial temporal lobe.

H.M. became amnesic in 1953, when he sustained a bilateral resection of the medial temporal lobe to relieve severe epilepsy. The removal included approximately half of the hippocampus, most of the amygdala, and the neighboring entorhinal and perirhinal cortices. Following the surgery, H. M.'s seizure condition was much improved. Moreover, he retained normal language, normal intellectual functions, and normal immediate memory (e.g., as tested with a digit span test). However, he exhibited profound forgetfulness, and this deficit has persisted for more than 40 years.

Extensive investigations of other amnesic patients have also been used to explore the memory functions of the medial temporal lobe. For example, patient R.B. became amnesic following an episode of global ischemia. He suffered from a moderately severe anterograde amnesia with minimal retrograde amnesia. After his death 5 years later, extensive histological study of his brain revealed a circumscribed bilateral lesion of hippocampal field CA1, whereas the minor additional pathology that was found could not reasonably explain the memory impairment. Similar pathological findings in the hippocampus have also been observed in other amnesic patients (Fig. 3.4-4). Magnetic resonance imaging (MRI) with high-resolution protocols can reveal pathology in the hippocampal region of amnesic patients in vivo. Two conclusions about the anatomical correlates of amnesia follow. First, damage limited to the hippocampus itself can result in clinically significant memory impairment; second, medial temporal regions in addition to hippocampal field CA1 also make a critical contribution to memory.

FIGURE 3.4-4 Coronal sections through the hippocampal region stained with thionin in a normal subject (**A**) and three amnesic patients with bilateral damage to the hippocampal formation (**B-D**). The hippocampus proper can be divided into three distinct fields, designated *CA1*, *CA2*, and *CA3*. The CA1 field extends to the subiculum (*S*). Other structures include the dentate gyrus (*DG*), presubiculum (*PrS*), parasubiculum (*PaS*), and entorhinal cortex (*EC*). In patient GD (**B**), damage included CA1; in patient LM (**C**), damage included CA1, CA2, CA3, DG, and EC; in patient WH (**D**), damage included CA1,



CA2, CA3, DG, S, and EC. For additional details, see Rempel-Clower N, Zola SM, Squire LR, Amaral DG: Three cases of enduring memory impairment following bilateral damage limited to the hippocampal formation. J Neurosci *16:*5233, 1996. (Reprinted with permission from Squire LR, Zola SM: Memory, memory impairment, and the medial temporal lobe. In *Cold Spring Harbor Symposia on Quantitative Biology*, vol 61. Cold Spring Harbor Laboratory Press, Plainview, New York, 1996.)

The findings from human amnesia inspired the development of models of amnesia in experimental animals. Early animal studies yielded contradictory findings that could not be easily related to memory impairment. In part, the difficulty was that human amnesia itself was poorly understood. Memory is now known to be a collection of different abilities and not a unitary mental faculty. Human amnesia does not affect all kinds of memory. Until researchers understood this, selecting memory tasks for making comparisons across species was problematic. Indeed, obtaining memory performance measures that reflect parallel memory functions in humans and experimental animals requires a high degree of control over the cognitive strategies used.

Nonetheless, a model of human amnesia in the nonhuman primate became available in the early 1980s, and subsequent investigations identified the crucial structures and connections. In the medial temporal lobe, these include the hippocampus proper (CA fields, dentate gyrus, and subiculum) and adjacent regions of entorhinal, perirhinal, and parahippocampal cortex. Monkeys with surgical damage to specific structures were trained to perform tasks analogous to tasks sensitive to memory impairment in humans. Large medial temporal lesions intended to approximate the damage that occurred in patient H.M. caused monkeys to exhibit many features of human amnesia. For example, the impairment occurred in more than one sensory modality, short-term memory was intact, the deficit was enduring, skill learning was preserved, and retrograde amnesia was temporally graded.

Within the medial temporal lobe separate contributions can be identified for memory and emotion. The participation of the medial temporal lobe region in emotional expression was first studied systematically in 1937 by Heinrich Kluver and Paul Bucy, who found that monkeys with bilateral temporal lobectomy became tame, approached animals and objects without reluctance, examined objects by mouth instead of by hand, and exhibited abnormal sexual behavior. Subsequent studies have indicated that emotional behavior is related not to the hippocampus but to the adjacent set of nuclei known collectively as the amygdala. In addition, other work has shown that the amygdala is part of a set of structures essential for fear conditioning.

Amnesia can also result from circumscribed damage to structures of the medial diencephalon, including the mammillary nuclei, the dorsomedial nucleus of the thalamus, the anterior nucleus, the internal medullary lamina, and the mammillothalamic tract. Korsakoff's syndrome is the best studied example of diencephalic amnesia. Patients with alcoholic Korsakoff's syndrome typically have frontal lobe

pathology in addition to diencephalic damage. Frontal lobe pathology produces a pattern of cognitive impairment that is dissociable from amnesia itself. In the case of the patient with Korsakoff's syndrome, frontal lobe pathology is superimposed on severe memory impairment (Table 3.4-1).

Test	Amnesia	Korsakoff's Syndrome	Frontal Lobe Damage
Delayed recall	+	+	–
Dementia rating scale: memory index	+	+	–
Dementia rating scale initiation/ perseveration index	–	+	+
Wisconsin Card-Sorting Test	–	+	+
Temporal order memory	+	+ +	+ +
Metamemory	–	+	+
Release from proactive interference	–	+	–

Table 3.4-1 Associated and Dissociated Deficits in Amnesia

One limitation of conventional methods for assessing neuropathology is that remote functional damage may be overlooked. For example, standard MRI scans may show structural damage limited to a particular region, but this damage may lead indirectly to disrupted functioning in other regions. Accordingly, functional neuroimaging may be useful for characterizing more fully the neural dysfunction responsible for amnesia. In Korsakoff's syndrome, results from positron emission tomography (PET) have revealed functional damage in widespread cortical regions (Fig. 3.4-5). Accordingly, diencephalic amnesia may often reflect a disruption of thalamocortical connections that are critical for memory storage.

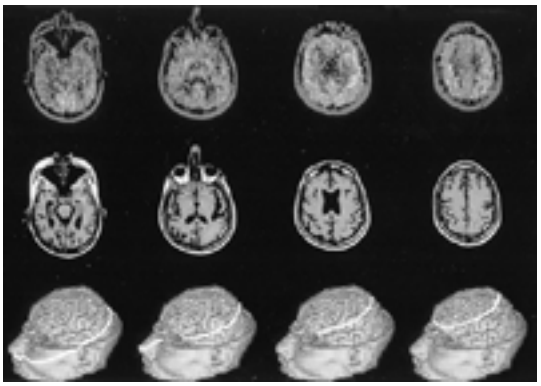


FIGURE 3.4-5 PET and MRI scans in a patient with Korsakoff's syndrome. Neural dysfunction was evident as reduced glucose utilization in multiple cortical regions in the frontal and parietal lobes, and in the cingulate. Functional neuroimaging can reveal brain dysfunction that might otherwise not be evident if limited to structural neuroimaging results. In Korsakoff's syndrome, the memory impairment probably reflects a disruption of thalamocortical circuitry. (Reprinted with permission from Paller KA, Acharya A, Richardson BC, Plaisant O, Shimamura AP, Reed BR, Jagust WJ: Functional neuroimaging of cortical dysfunction in alcoholic Korsakoff's syndrome. J Cogn Neurosci *9:*277, 1997.)

Although amnesia can result from damage to either the medial temporal lobe or to the diencephalon, the distinctive functions of these two regions have been difficult to elucidate. It may be reasonable to expect the medial temporal lobe and diencephalic brain regions to make different contributions to normal

memory, but there is currently no compelling evidence for a corresponding qualitative difference in memory impairment. This could be because the two regions function together as one system that facilitates the formation of links between neocortical storage sites, or because the two regions function separately but each makes an essential contribution to linking neocortical storage sites. In any event, memory clearly relies on an elaborate complex of neural circuits extending across multiple brain areas; Figure 3.4-6 shows the chief components of this circuitry. Ongoing research continues to improve our understanding of the neuroanatomy of amnesia and the normal functions of this neural circuitry.

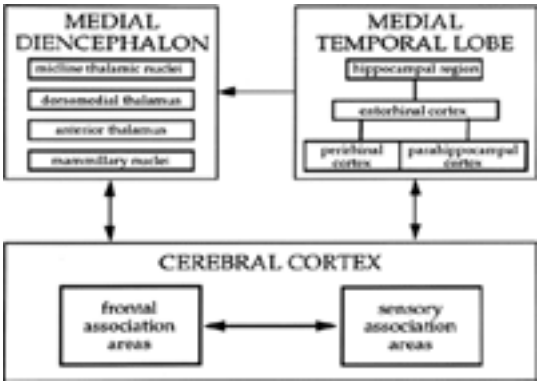


FIGURE 3.4-6 A schematic view of some of the chief brain regions critical for declarative memory. The entorhinal cortex is the major source of projections to the hippocampus, and nearly two thirds of the cortical input to the entorhinal cortex originates in the perirhinal and parahippocampal cortex. Entorhinal cortex also receives direct connections from cingulate, insula, orbitofrontal, and superior temporal cortex.

Retrograde Amnesia Memory loss in amnesia typically affects recent memories more than remote memories (Fig. 3.4-7). Temporally graded amnesia has been demonstrated retrospectively in studies of amnesic patients and prospectively in studies of monkeys, rats, mice, and rabbits. These findings have important implications for understanding the nature of the memory storage process. Memories are dynamic, not static. Apparently, memory storage can become more robust over time. As time passes after learning, some memories are forgotten while others become stronger because of a process of consolidation that depends on cortical, limbic, and diencephalic structures. The limbic-diencephalic contribution diminishes over time such that the neocortical component of the memory eventually becomes self-sufficient. In other words, the limbic-diencephalic structures are needed at the time of learning and during this gradual process. After sufficient time has elapsed, long-term memories can be retrieved whether or not limbic-diencephalic structures are intact. Thus, the permanent repositories of memory are the distributed neocortical regions, not diencephalic or hippocampal regions.

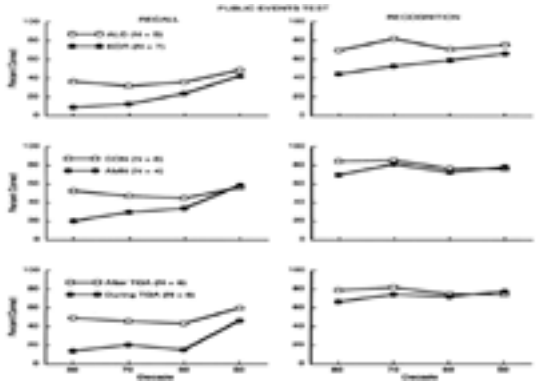


FIGURE 3.4-7 Remote memory performance of amnesic patients with Korsakoff's syndrome (KOR), alcoholic control subjects (ALC), amnesic patients with confirmed or suspected damage to the hippocampal formation (AMN), healthy control subjects (CON), and patients with transient global amnesia (TGA). The left column shows recall scores for past public events that had occurred in one of the four decades from 1950 to

1985. The right column shows performance on a multiple-choice test (four alternatives) involving the same public events. (Reprinted with permission from Kritchevsky M, Squire LR: Transient global ischemia: Evidence for extensive, temporally graded retrograde amnesia. Neurology *39:*213, 1989 and Squire LR, Haist F, Shimamura AP: The neurology of memory: Quantitative assessment of retrograde amnesia in two groups of amnesic patients. J Neurosci *9:*828, 1989.)

Atypical patterns of amnesic impairment have also been reported. Patients have been described with substantial retrograde impairments together with little or no impairment in new learning ability, a pattern termed *focal retrograde amnesia*. Evidence that focal retrograde amnesia can result from damage to portions of the anterior temporal lobes or possibly other neocortical areas has important implications for specifying the neuroanatomical substrates of memory. A likely explanation is that these neocortical areas comprise memory storage sites responsible for critical aspects of certain memories for facts and events. In some cases, retrograde deficits have been reported to span exceedingly long time periods, perhaps most of a patient's life. It thus appears possible to disrupt memory for events that occurred many years prior to the brain insult while retaining the ability to form memories for new events. The minimal problems with new learning in focal retrograde amnesia presumably relate to continued functioning in hippocampal and diencephalic regions as well as the availability of storage sites in intact parts of the cerebral cortex.

MEMORY SYSTEMS

Many kinds of memory remain intact in amnesia. The kind that is impaired is termed *declarative memory*. Declarative memory makes possible the conscious recollection of facts and events. A deficit in declarative memory presents itself as a global disorder of impaired memory for routes, lists, faces, melodies, objects, and other verbal and nonverbal material, regardless of the sensory modality in which the material is presented. This amnesic impairment typically occurs in conjunction with the preservation of a heterogeneous set of other memory capabilities, collectively termed *nondeclarative memory*. Nondeclarative memory includes skill learning, habit learning, conditioning, and the phenomenon of priming. Ample evidence has shown that, for these types of memory, amnesic patients can perform normally. A variety of skills, including perceptual, perceptuomotor, and cognitive skills, can be acquired by amnesic patients and normal subjects at equivalent rates. For example, amnesic patients can learn to read mirror-reversed text normally, they exhibit the normal facilitation in reading speed with successive readings of normal prose, and they improve as rapidly as normal subjects at speeded reading of repeating nonwords. In addition, amnesic patients can, after seeing strings of letters generated by a finite-state rule system, classify novel strings of letters as rule-based or not rule-based. Classification performance is normal despite the fact that amnesic patients are impaired at remembering the previously studied items or the events of training, which rely on declarative memory. Amnesic patients can also learn about categories by abstracting prototype information, even though they forget the examples from which the category was built.

Priming refers to a facilitation of the ability to detect or identify stimuli based on recent experience with those stimuli. Priming is another type of memory that occurs at full strength in amnesia. In one type of priming test, amnesic patients exhibited the normal tendency to complete three-letter stems with previously encountered words when they were instructed to produce the first word to come to mind (e.g., MOT__ completed to MOTEL). In another test, amnesic patients studied a list of words and then exhibited preserved priming with respect to their accuracy at identifying briefly presented words and with respect to their estimates of how long each word was presented (Fig. 3.4-8). Yet patients' ability to recognize the same words when presented later was severely impaired. Amnesic patients also exhibited priming for object names, novel objects, and novel faces. For example, in one experiment patients named pictures of previously presented objects reliably faster than they named pictures of new objects, even after a delay of a week. This facilitation occurred at normal levels, despite the fact that amnesic patients were markedly impaired at recognizing which pictures had been presented previously.

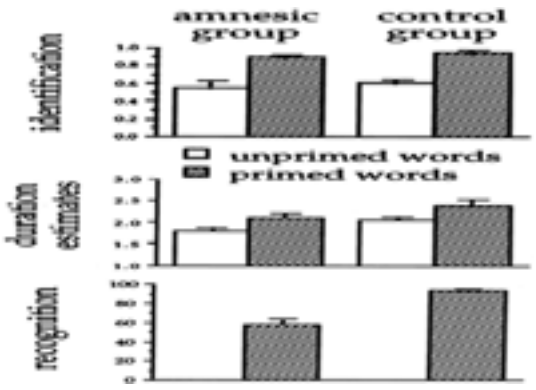


FIGURE 3.4-8 Preserved priming and impaired recognition in amnesic patients. The top graph shows the proportion of briefly presented words identified correctly by a group of amnesic patients and an age-matched control group. The priming effect took the form of more accurate identification for words presented in an earlier study phase (primed words) compared to other words (unprimed words). In the middle panel, both groups showed priming of duration estimations made on an arbitrary four-point scale, in that primed words were rated as having been presented for a longer duration compared to unprimed words. In the bottom panel, recognition performance on a forced-choice, three-alternative recognition test was impaired in the amnesic group (lower percent correct). Values are means plus standard errors of the mean. (Adapted from Paller KA, Mayes AR, McDermott M, Pickering AD, Meudell PR: Indirect measures of memory in a duration-judgment task are normal in amnesic patients. Neuropsychologia *29:*1007, 1991.)

Results from PET studies in normal volunteers suggest that priming reflects changes in early stages of the cortical pathways that participate in perceptual processing (Fig. 3.4-9). With stem-completion priming, both PET and divided visual field studies have implicated visual processing systems in extrastriate cortex, especially in the right hemisphere. In contrast, conscious recollection of remembered words normally engages a larger set of brain areas. Neural correlates of this processing have been observed as blood flow changes in hippocampal, frontal, and other brain areas. This processing simultaneously produces brain electrical activity (event-related potentials) that can be measured at the scalp (Fig. 3.4-10). A role for the frontal lobes in declarative memory has been substantiated both in patients with frontal lesions and in PET studies conducted on normal subjects. Patients with frontal lesions are not globally amnesic but tend to have certain memory problems.

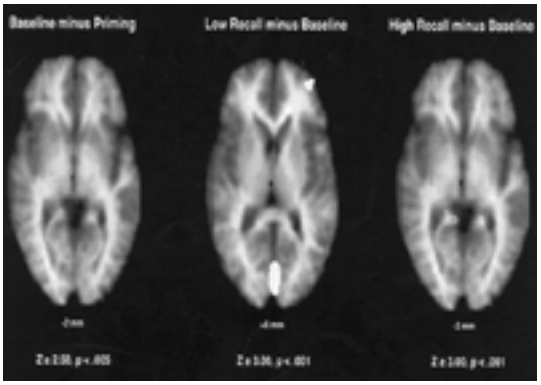


FIGURE 3.4-9 PET activations superimposed over averaged transverse MRI scans with the distance shown representing the distance from the line connecting the anterior and posterior commissure. Words were studied under strong or weak learning conditions (high recall or low recall) and then both declarative memory (cued recall) and nondeclarative memory (priming) were tested. The Baseline minus Priming subtraction showed an area of decreased blood flow (green) in right visual association cortex thought to be related to the greater ease of processing primed words. The Low Recall minus Baseline subtraction showed an area of increased blood flow (yellow) in secondary visual cortex and left prefrontal cortex thought to be related to the effort involved in deliberate, effortful retrieval. The High Recall minus Baseline subtraction showed a region of increased blood flow (red) in bilateral hippocampal regions thought to be related to successful retrieval of recently acquired information. (Reprinted with permission from Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS: Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. Proc Natl Acad Sci USA *93:*321, 1996. ©1996 National Academy of Sciences, U.S.A.)

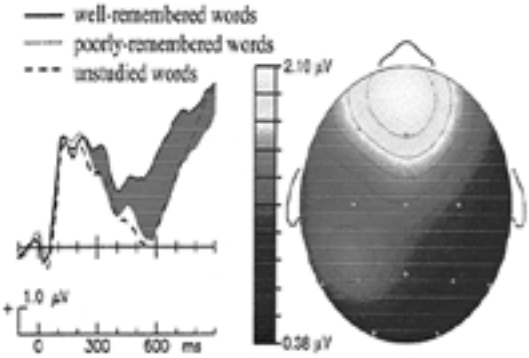


FIGURE 3.4-10 Brain potentials showing a differential response based on the extent to which subjects engaged in recollection following word presentations. Potentials shown at the left were recorded from a frontal scalp electrode. Measurements from multiple electrodes over the 400- to 800-ms latency range were used to generate the topographical map at the right, showing that the neural correlate of recollection was broadly distributed across the scalp, with largest responses over frontal cortex. (Adapted with permission from Paller KA, Kutas M: Brain potentials during memory retrieval provide neurophysiological support for the distinction between conscious recollection and priming. J Cogn Neurosci *4:*375, 1992.) (See Color Plate 6.)

Patient B.G. suffered an infarction restricted to the right frontal lobe, and showed an abnormal tendency towards falsely recognizing as familiar items that had not been presented for study, possibly because of a tendency to rely on a general feeling of familiarity for items rather than specific memories for prior items. By virtue of its connections to posterior neocortical regions, the frontal lobe appears to play a role in the organization of retrieval. In other words, frontal-posterior networks are instrumental both in the on-line processing of information and in the retrieval of declarative memories.

One organizational scheme for categorizing multiple types of memory appears in Figure 3.4-11. Declarative memory depends on medial temporal and midline diencephalic structures along with extensive portions of the neocortex (see Fig. 3.4-6). This system provides for the rapid learning of facts (*semantic memory*) and events (*episodic memory*). Nondeclarative memory depends on several different brain systems. Habits probably depend on both the neocortex and the neostriatum, the cerebellum is important for conditioning of skeletal musculature, the amygdala for emotional learning, and the neocortex for priming. Declarative and nondeclarative memory differ in important ways; declarative memory is phylogenetically more recent than most types of nondeclarative memory. In addition, declarative memories are available to conscious recollection. The flexibility of declarative memory permits the retrieved information to be available to multiple response systems. Nondeclarative memory is inaccessible to awareness and tends to be inflexible, and it is expressed only by engaging specific processing systems. Nondeclarative memories are stored as changes within these processing systems, changes that are encapsulated such that other processing systems have limited access to the stored information.

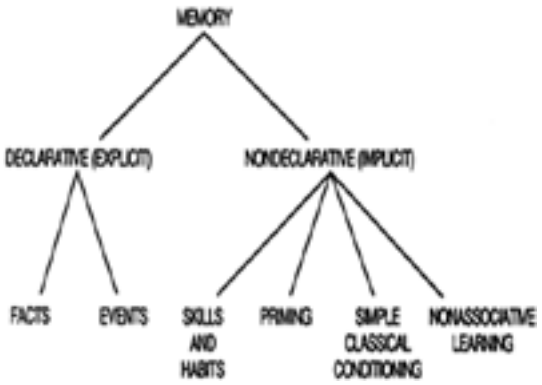


FIGURE 3.4-11 A tentative memory taxonomy. *Declarative memory* refers to conscious recollection of facts and events. *Nondeclarative memory* refers to a collection of abilities wherein performance changes as the result of experience but without affording conscious memory access to the original experience. *Nonassociative learning* includes habituation and sensitization. (Adapted from Squire LR, Zola-Morgan S: The medial temporal lobe memory system. Science *253:*1380, 1991.)

IMPLICATIONS

Current understanding of the biology of memory has significant implications for several fundamental issues in psychiatry. One example is the phenomenon of infantile amnesia, the apparent absence of conscious memory for experiences from approximately the first 3 years of life. Traditional views of infantile amnesia have emphasized repression (psychoanalytic theory) and retrieval failure

(developmental psychology). A common assumption has been that adults retain memories of early events but cannot bring them into consciousness. However, another possibility is that the capacity for classical conditioning and skill learning (i.e., nondeclarative memory) emerges early in infancy, whereas declarative memory does not become available until about the third year; limbic and diencephalic structures essential for declarative memory may not be fully developed until that time. According to this view, infantile amnesia results not from the adult's failure to retrieve early memories but from the child's failure to store them in the first place. This is an intriguing suggestion, but recent evidence has not supported it. First, recall-like memory abilities have been demonstrated in young infants. In addition, it now appears that one of the most commonly employed tests of infant recognition memory, the visual-paired comparison task, depends on declarative memory.

What probably limits the development of declarative memory is not the slow maturation of the limbic-diencephalic structures essential for declarative memory, but rather the gradual development and maturation of the neocortex. As the neocortex develops, memories supported and stored there become more complex. Strategies emerge for organizing incoming information, language develops, and declarative memories become more richly encoded and interconnected, and more persistent. The existence of multiple forms of memory and the gradual maturation of neocortex suggest an alternative to traditional views of infantile amnesia. It is not necessary to suppose that fully formed childhood memories persist but cannot be retrieved. An alternative view is that the capacity to store a viable declarative memory develops only gradually.

The existence of multiple memory systems also has implications for issues in psychoanalytic theory, including the construct of the unconscious. In considering the effects of past experience, it matters what view one takes of the nature of memory. By the traditional view, memory is a unitary faculty, and representations in memory vary mainly in strength and accessibility. According to this view, material that is unconscious is below some threshold of accessibility and could potentially be made available to consciousness. An alternative view begins with the distinction between memory that by its nature can be brought to mind (i.e., declarative memory) and other kinds of memory that are by their nature nonconscious in the sense that the knowledge is expressed through performance without affording any conscious memory content. In this view, early experience might affect later behavior, but the experience can persist to affect behavior without necessarily including a record of the event itself. Behavior can change as experience accumulates in altered dispositions, preferences, conditioned responses, habits, and skills, but these changes do not afford any actual awareness that behavior is being influenced by past experience. Nor is there any necessity that any particular past experience has been recorded. In this sense, the unconscious does not become conscious. Behavioral change can occur when new habits are acquired that supersede old ones or when sufficient awareness of a habit is gained such that it can to some extent be isolated or when the stimuli that elicit it can be processed differently. However, one does not become aware of its content in the same sense that one knows the content of a declarative memory, and one does not become aware of the early experiences that gave rise to the habit.

A better understanding of the biology of memory has also shed light on the imperfect nature of memory retrieval. It is quite possible to remember events that never happened. One way to conceptualize this problem is to consider the phenomenon of source amnesia, which occurs when an individual remembers

some information without being able to remember how, where, or when the information was learned. If an individual imagines a certain event, at some later time it is possible to forget the moment when the scene was imagined while still recalling details as if they really happened. In this way, memory distortions can be caused by misattributions of source. Inferences and other thoughts invoked when recalling an experience can also be incorporated into memory such that a subsequent retrieval mistakenly includes the intervening information. Thus, the reconstructive nature of recollection poses problems for interpreting apparently “recovered” memories of traumatic events and emphasizes the importance of corroboration. As documented by experiments in adults and in children, illusory memories can be created, and children appear to be particularly susceptible to these effects. Several lines of evidence suggest that processing in the frontal lobes is essential for accurate source memory. For example, failures of source memory in the elderly appear to be associated with frontal lobe dysfunction. Patients with frontal lobe damage are highly susceptible to source errors, and they also tend to confabulate, sometimes producing bizarre responses that are inaccurate as well as implausible. Convergent results from PET studies in normal subjects imply that frontal regions, especially in the right hemisphere, play a key role in mediating accurate retrieval.

Finally, the biological understanding of declarative memory developed here is important in relation to the topic of consciousness. Declarative memory entails both a lasting influence of prior experience and an awareness of that remembering. The varieties of nondeclarative memory, such as priming, commonly occur without this awareness of remembering. To the extent that this contrast between memory with awareness versus memory without awareness can be understood at the neural level, a neuroscientific foundation can be developed to explain why certain types of neural processing lead to the subjective experience of remembering. Particular combinations of neocortical processing networks working in concert with the medial temporal lobe appear to come into play during the experience of remembering, whereas altered activity in a localized neocortical area can lead to the phenomenon of priming without explicit remembering. In this way, it may be possible to move from probing the neural substrates of declarative memory to addressing the question of why neural processing engenders consciousness at all, a problem that is central to the study of the neural basis of the mind.

ASSESSMENT OF MEMORY FUNCTIONS

A variety of quantitative methods are available to assess memory functions in neurological and psychiatric patients. Quantitative methods are useful for evaluating and following patients longitudinally as well as for carrying out a one-time examination to determine the status of memory function. If a memory problem is detected, it should be determined whether memory is selectively affected or whether memory problems are occurring against a background of intellectual deficits, as occurs in dementia. Although some widely available tests, such as the Wechsler Memory Scale-Revised, are useful measures of memory, most single tests assess memory rather narrowly, and even general-purpose neuropsychological batteries provide for only limited testing of memory functions. A complete assessment of memory usually involves a number of specialized tests that sample intellectual functions, new learning capacity, remote memory, and memory self-report.

The assessment of general intellectual functions is fundamental to any neuropsychological examination. In the case of memory testing, information about intellectual functions provides both information about a patient's general test-taking ability and a way to assess the selectivity of memory impairment. Useful tests include the Wechsler Adult Intelligence Scale-Revised, a test of object naming such as the Boston Naming Test, a rating scale to assess the possibility of global dementia, a test of word fluency, and specialized tests of frontal lobe function.

New Learning Capacity Memory tests are sensitive to impaired new learning ability when they adhere to either of two important principles. First, tests are sensitive to memory impairment when more information is presented than can be held in immediate memory. For example, one might ask patients to memorize a list of 10 faces, words, sentences, or digits because 10 items is more than can be held in mind. The paired-associated learning task is an especially sensitive test of this kind. In the paired-associate task, the examiner asks the patient to learn a list of unrelated pairs of words (e.g., queen-garden, office-river) and then to respond to the first word in each pair by recalling the second word.

Second, tests are sensitive to memory impairment when a delay, filled with distraction, is interposed between the learning phase and the test phase. In that case, examiners typically ask patients to learn a small amount of information and then distract them for several minutes by conversation, to prevent rehearsal. Recollection is then assessed for the previously presented material. Memory can be tested by unaided recall of previously studied material *(free recall)*, or by presenting a cue for the material to be remembered *(cued recall)*, or by testing recognition memory. In multiple-choice tests of recognition memory, the patient tries to select previously studied items from a group of studied and unstudied items. In yes/no recognition tests, patients see both studied and unstudied items one at a time and are asked to say “yes” if the item was presented previously and “no” if it was not. These various methods for assessing recently learned material can be ranked in terms of their sensitivity for detecting memory impairment (from most sensitive to least sensitive: free recall, cued recall, yes/no recognition, multiple-choice recognition). In practice, a cued-recall test can vary widely in its sensitivity, depending on the effectiveness of the cue.

The specialization of the cerebral hemispheres means that left and right unilateral damage to limbic-diencephalic structures is associated with different kinds of memory deficits. Accordingly, different kinds of memory tests must be used when unilateral damage is a possibility. Damage to limbic-diencephalic structures in the left cerebral hemisphere results in difficulty remembering verbal material such as word lists and stories. Damage to limbic-diencephalic structures in the right cerebral hemisphere impairs memory for faces, spatial arrangements, and other material that is typically encoded without verbal labels. For example, left medial temporal lobe damage impairs memory for both spoken and written text; right medial temporal lobe damage impairs the learning of spatial arrays, whether the layouts are examined visually or by touch. A useful way to test for anterograde amnesia for nonverbal material, for example, is to ask a patient to copy a complex geometric figure and then, without forewarning, to reproduce it after a delay of several minutes.

Remote Memory Disorders of memory are frequently accompanied by *retrograde amnesia*, that is, memory loss for events that occurred before the amnesia began. Evaluations of retrograde memory loss

should attempt to determine both the severity of the loss and the time period that it covers. Most quantitative tests of remote memory are composed of material in the public domain that can be corroborated. For example, tests have involved questions about former one-season television programs, news events, or photographs of famous persons. An advantage of these methods is that it is possible to sample large numbers of events and target particular time periods. At the least, time periods before which the information could not have been learned can be identified. (For example, knowledge that Sarah Jane Moore tried to assassinate President Ford could not have been acquired prior to the 1970s). However, a disadvantage is that these tests are not particularly useful for detecting memory loss for information learned during the weeks or months immediately prior to the onset of amnesia. Most remote memory tests sample time periods rather coarsely and cannot detect a retrograde memory impairment that covers only a few months.

In contrast, autobiographical memory tests can potentially provide fine-grained information about a patient's retrograde memory. In the word-probe task, first used by Francis Galton in 1879, patients are asked to recollect specific episodes from their past in response to single word cues (e.g., *bird* and *ticket*) and to date the episodes. When normal subjects take the test, the number of episodes recalled is systematically related to the time period from which the episode is taken, and most of the memories come from recent time periods (the past 1 or 2 months). Patients with amnesia often exhibit temporally graded retrograde amnesia, drawing few episodic memories from the recent past, but producing as many remote autobiographical memories as normal subjects (Fig. 3.4-12).

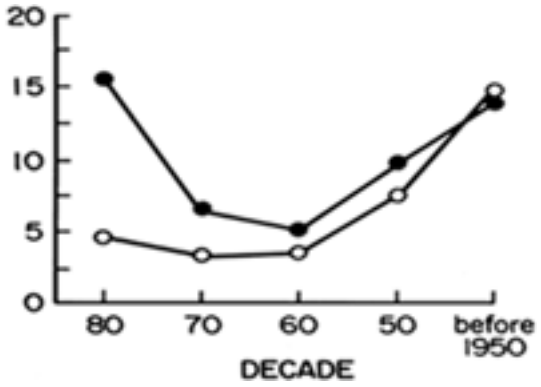


FIGURE 3.4-12 Loss of recent autobiographical memory as measured in five amnesic patients (filled circles) and five normal subjects (open circles). Well-formed memories from specific time periods were recalled in response to 75 single-word cues (e. g., *tree, flag, window*). (Reprinted with permission from MacKinnon D, Squire LR: Autobiographical memory in amnesia. Psychobiology *17:*247, 1989.)

Memory Self-Reports Patients can often supply descriptions of their memory problems that are extremely useful for understanding the nature of their impairment. Tests of the ability to judge one's own memory abilities are called *tests of metamemory*. Self-rating scales are available that yield both quantitative and qualitative information about memory impairment. As a result, it is possible to distinguish memory complaints associated with depression from memory complaints associated with amnesia. Patients with depression tend to rate their memory as poor in a rather undifferentiated way, endorsing equally all the items on a self-rating form. By contrast, patients with amnesia tend to endorse some items more than others; that is, there is a pattern to their memory complaints. Thus, patients with amnesia do not report difficulty in remembering very remote events or in following what is being said to

them, but they do report having difficulty remembering an event a few minutes after it happens. Indeed, the self-reports match rather closely the description of memory dysfunction that emerges from objective tests. Specifically, new learning capacity is affected whereas immediate memory and very remote memory are intact. Some patients with amnesia, however, tend to markedly underestimate their memory impairment. In patients with Korsakoff's syndrome, for example, poor metamemory may stem from frontal lobe dysfunction. In any case, querying patients in some detail about their own sense of impairment and administering self-rating scales are valuable and informative adjuncts to more formal memory testing.

Dissociative Amnesia Differentiating dissociative amnesia from amnestic disorder, which results from neurological injury or disease, is less difficult than might be supposed. The two kinds of amnesia have markedly different characteristics. Dissociative amnesias typically do not affect new learning capacity. Patients enter the hospital able to maintain a continuing record of daily events. By contrast, new learning problems are at the core of amnestic disorder, which is much more common than dissociative amnesia. The main positive symptom in dissociative amnesia is extensive and severe retrograde amnesia. Patients may be unable to recall their own name or to recollect pertinent autobiographical information from childhood. However, patients with amnestic disorder never forget their name, and their remote memory for the events of childhood and adolescence is typically normal unless there is brain damage in the lateral temporal or frontal lobes.

Some patients with dissociative amnesia have circumscribed retrograde memory loss that covers a particular time period or that covers only autobiographical memories. One patient was reported to be able to answer questions about past public events but not questions about past personal events. Another patient scored close to zero on a test of famous photographs, far worse than any patient with neurological amnesia would score, and was also unable to identify proper names, such as *Los Angeles* and *Pontiac*. The challenge for the clinician lies not in distinguishing dissociative amnesia from amnestic disorder, but in distinguishing dissociative amnesia from malingering. Indeed, the diagnosis of dissociative amnesia can be difficult to substantiate and may be met with skepticism by hospital staff. Often, the clinical picture remains unclear until the amnesia clears. In some cases dissociative amnesia has been observed to clear after a period of days, but in other cases it has persisted as a potentially permanent feature of the personality.

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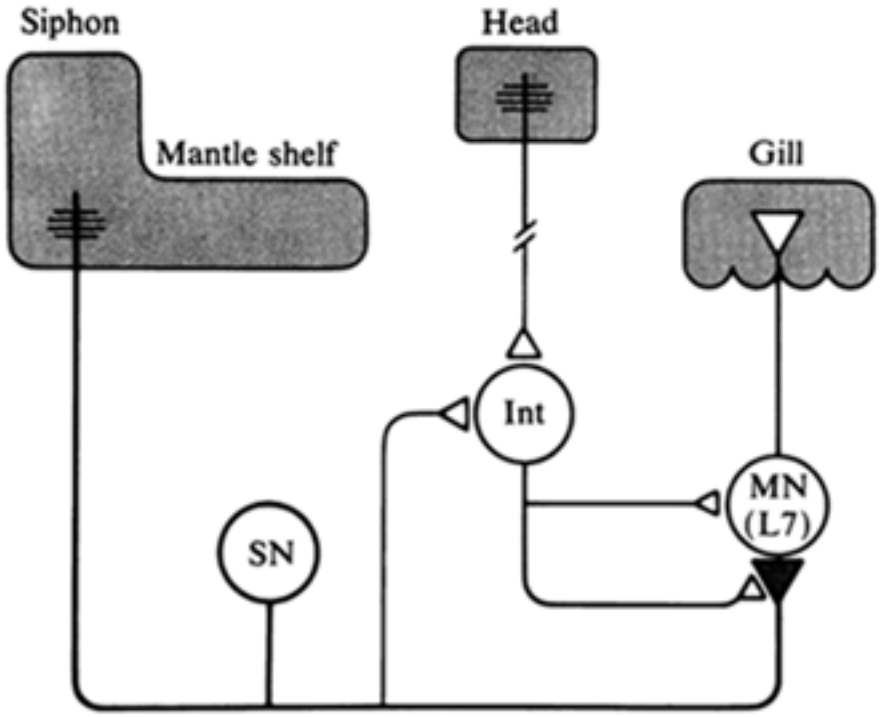

FIGURE 3.4-1 A schematic diagram of the neuronal circuit underlying behavioral habituation and sensitization of the gill-withdrawal reflect in *Aplysia*. The relative simplicity of the nervous system of *Aplysia* makes it a valuable organism for studying cellular and synaptic mechanisms of memory. The synapse between the sensory neuron (SN) and the motor neuron (MN) is an important site of habituation. Sensitization results from activation of the interneuron (Int) pathway. (Reprinted with permission from Kandel ER: *Cellular Basis of Behavior*. Freeman, San Francisco, 1976.)

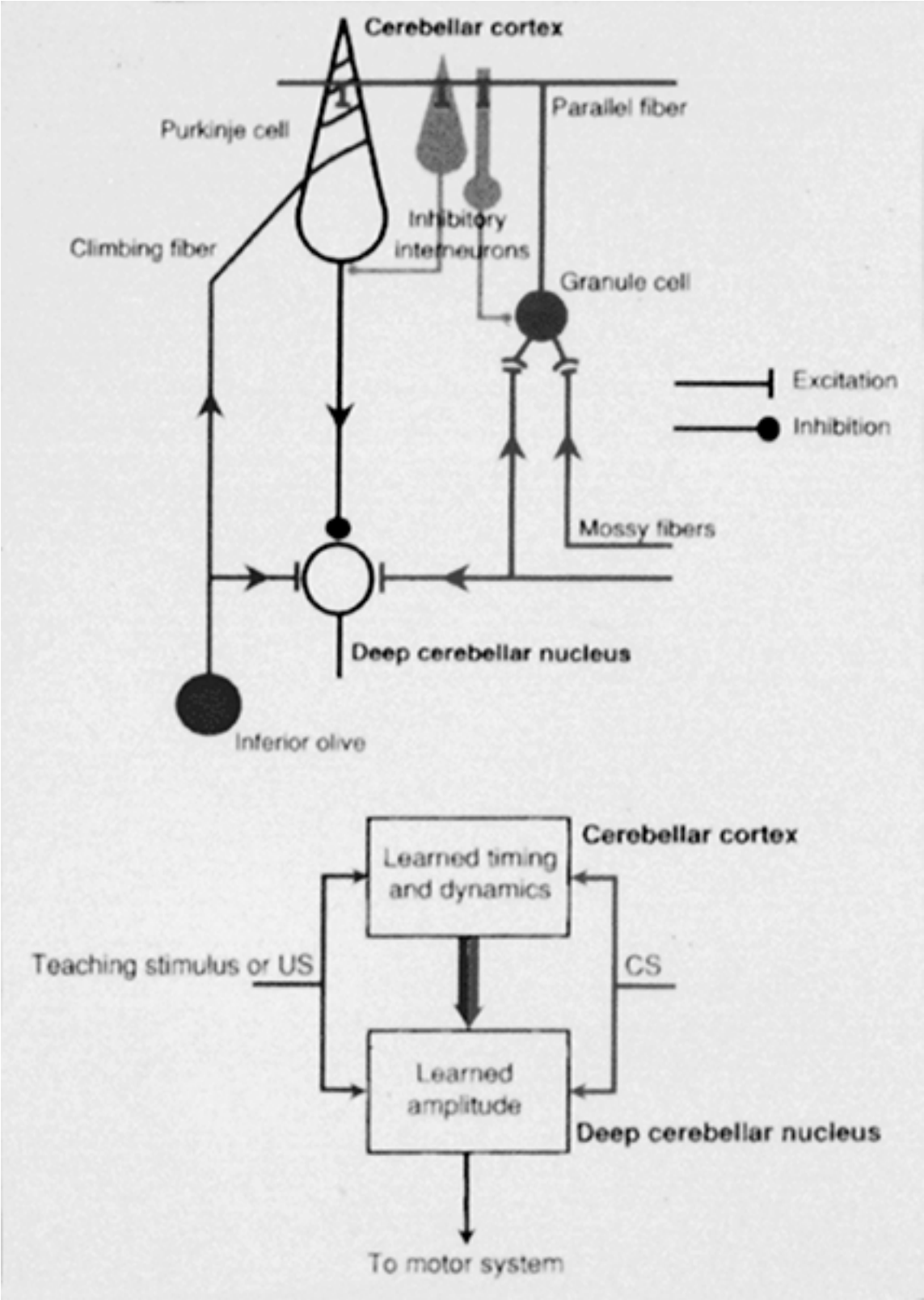

FIGURE 3.4-2 A schematic diagram of the circuitry of the mammalian cerebellum (**top**). In the classically conditioned blink response, input from the air-puff unconditioned stimulus and input from the

auditory conditioned stimulus comes in through parallel pathways to the cerebellar cortex and to the deep cerebellar nucleus, and plasticity occurs in both pathways (**bottom**). (Reprinted with permission from Raymond JL, Lisberger SG, Mauk MD: The cerebellum: A neuronal learning machine? Science *272:*1126, 1996. © 1996 American Association for the Advancement of Science.) (See Color Plate 4.)

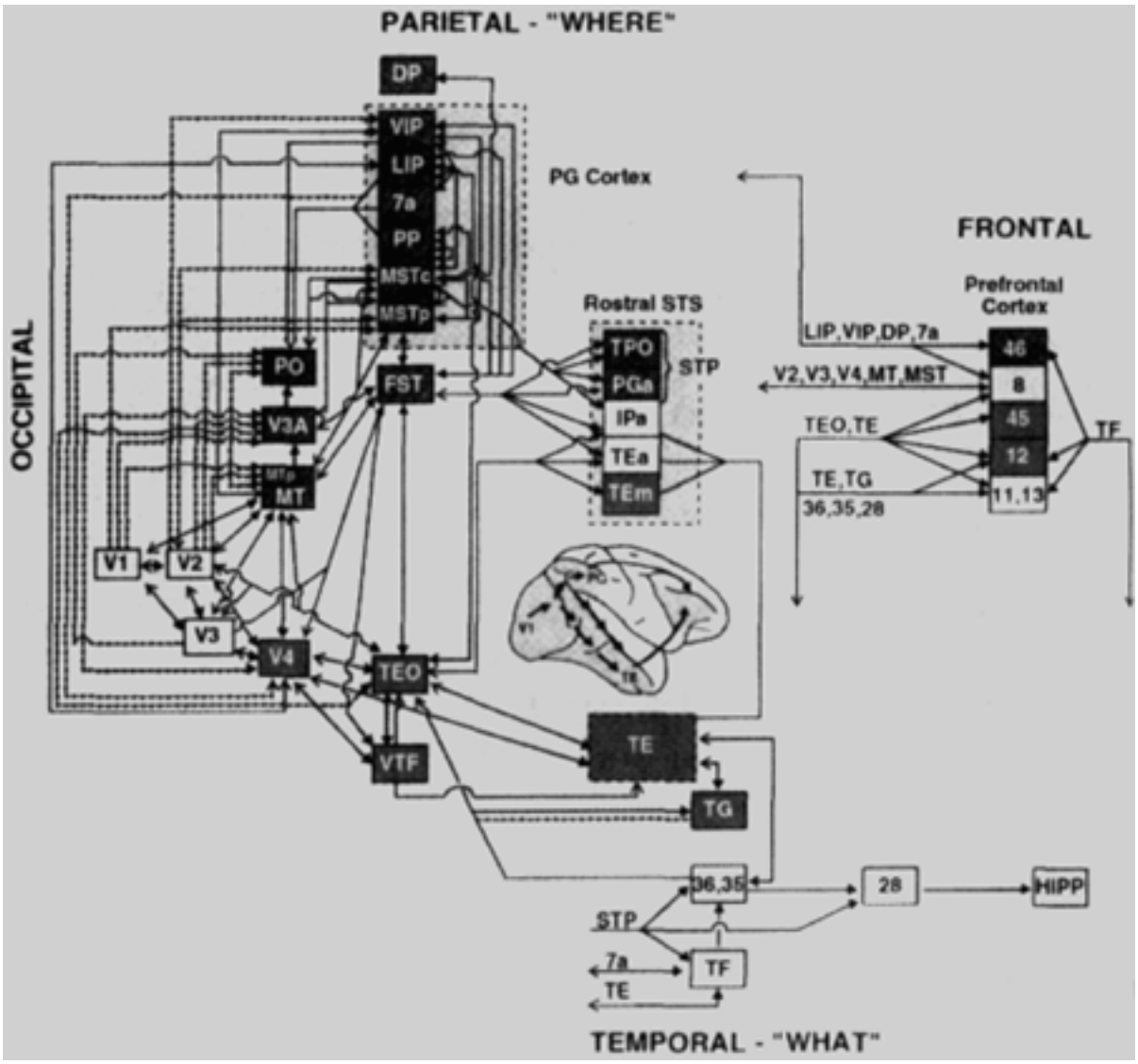

FIGURE 3.4-3 Summary of cortical visual areas and some of their connections. There are two major pathways from striate cortex (V1). The processing stream for object vision follows a ventral route into the temporal lobe via V4 (dark gray boxes) and the processing stream for spatial vision follows a dorsal route into the parietal lobe via MT (light gray boxes). Solid lines indicate connections arising from both central and peripheral visual field representations; dotted lines indicate connection restricted to peripheral field representations. Shaded region on the lateral view of the brain represents the extent of the cortex included in the diagram. Abbreviations: DP, dorsal prelunate area; FST, fundus of superior temporal area; HIPP, hippocampus; LIP, lateral intraparietal area; MSTc, medial superior temporal area, central visual field representation; MSTp, medial superior temporal area, peripheral visual field representation; MT, middle temporal area, MTp, middle temporal area, peripheral visual field representation; PO, parieto-occipital area; PP, posterior parietal sulcal zone; STP, superior temporal polysensory area; VIP, ventral intraparietal area; STS, rostral superior temporal sulcus; and VTF, visual responsive portion of area TF. (Reprinted with permission from Ungerleider LG: Functional brain

imaging studies of cortical mechanisms for memory. Science *270:*769, 1995. © 1995 American Association for the Advancement of Science.)

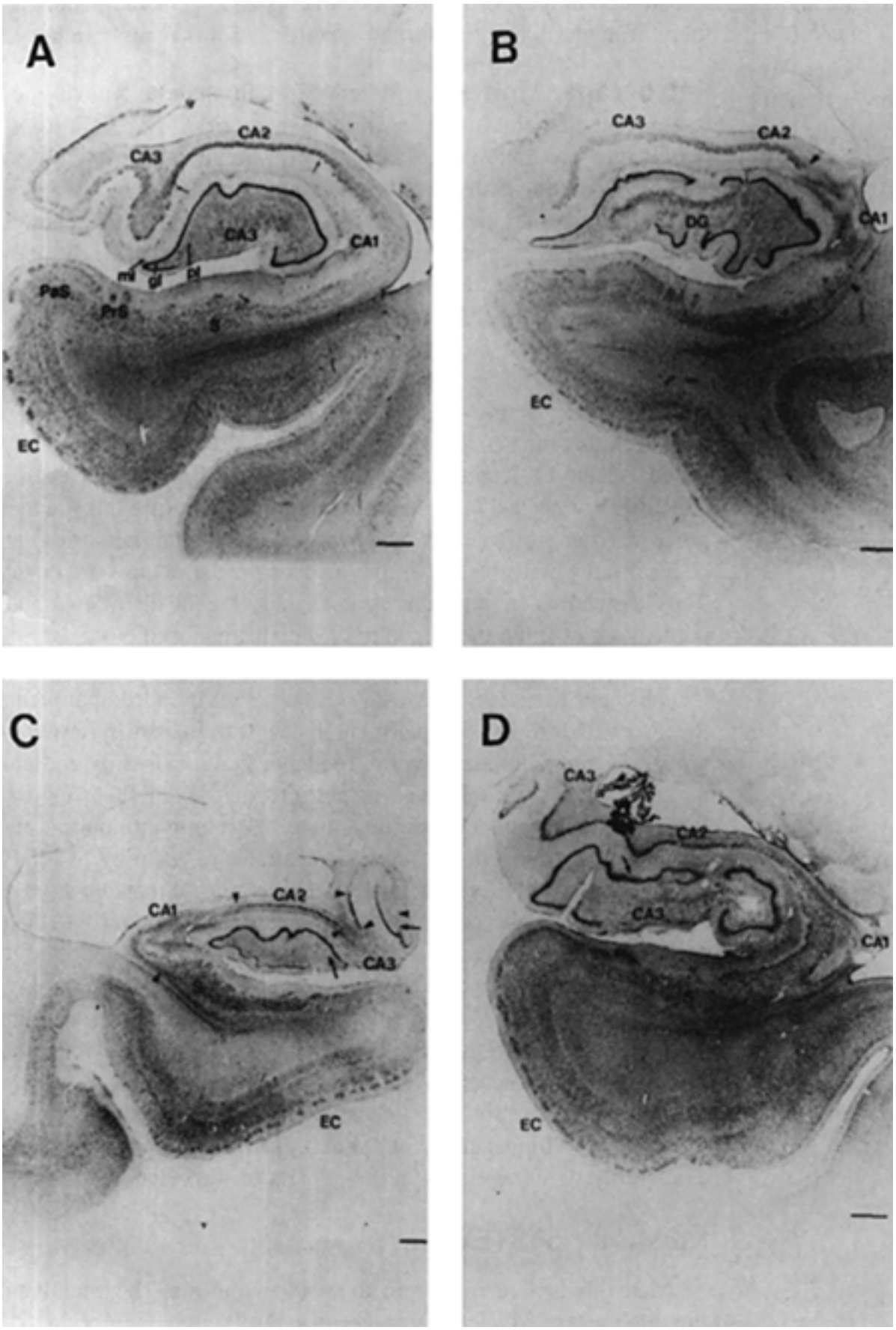
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FIGURE 3.4-4 Coronal sections through the hippocampal region stained with thionin in a normal subject (**A**) and three amnesic patients with bilateral damage to the hippocampal formation (**B-D**). The hippocampus proper can be divided into three distinct fields, designated *CA1*, *CA2*, and *CA3*. The CA1 field extends to the subiculum (*S*). Other structures include the dentate gyrus (*DG*), presubiculum (*PrS*), parasubiculum (*PaS*), and entorhinal cortex (*EC*). In patient GD (**B**), damage included CA1; in patient LM (**C**), damage included CA1, CA2, CA3, DG, and EC; in patient WH (**D**), damage included CA1, CA2, CA3, DG, S, and EC. For additional details, see Rempel-Clower N, Zola SM, Squire LR, Amaral DG: Three cases of enduring memory impairment following bilateral damage limited to the hippocampal formation. J Neurosci *16:*5233, 1996. (Reprinted with permission from Squire LR, Zola SM: Memory, memory impairment, and the medial temporal lobe. In *Cold Spring Harbor Symposia on Quantitative Biology*, vol 61. Cold Spring Harbor Laboratory Press, Plainview, New York, 1996.)

Table 3.4-1 Associated and Dissociated Deficits in Amnesia

Test	Amnesia	Korsakoff's Syndrome	Frontal Lobe Damage
Delayed recall	+	+	−
Dementia rating scale: memory index	+	+	−
Dementia rating scale initiation/ perseveration index	−	+	+
Wisconsin Card-Sorting Test	−	+	+
Temporal order memory	+	+ +	+ +
Metamemory	−	+	+
Release from proactive interference	−	+	−

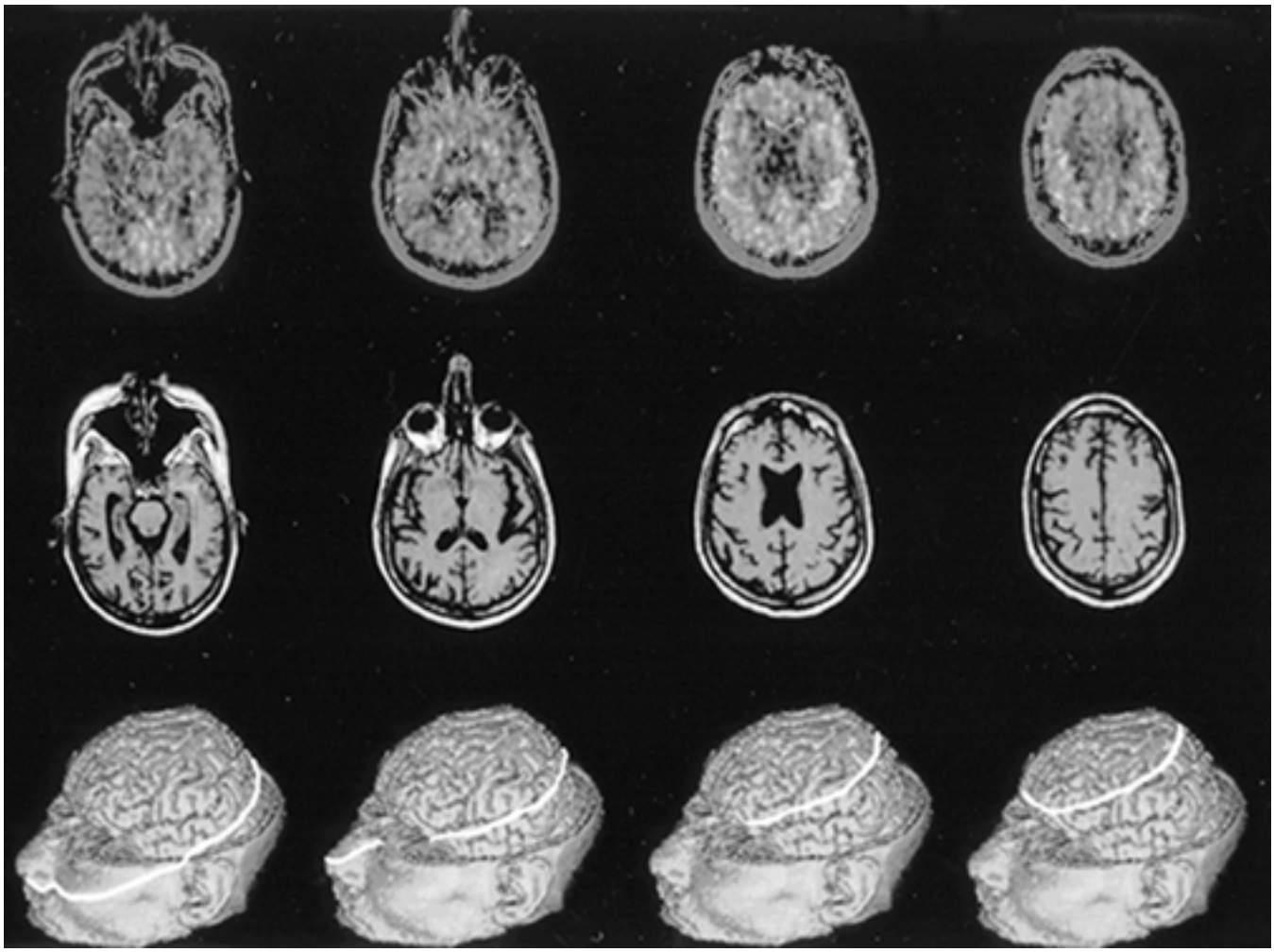


FIGURE 3.4-5 PET and MRI scans in a patient with Korsakoff's syndrome. Neural dysfunction was evident as reduced glucose utilization in multiple cortical regions in the frontal and parietal lobes, and in the cingulate. Functional neuroimaging can reveal brain dysfunction that might otherwise not be evident if limited to structural neuroimaging results. In Korsakoff's syndrome, the memory impairment probably reflects a disruption of thalamocortical circuitry. (Reprinted with permission from Paller KA, Acharya A, Richardson BC, Plaisant O, Shimamura AP, Reed BR, Jagust WJ: Functional neuroimaging of cortical dysfunction in alcoholic Korsakoff's syndrome. J Cogn Neurosci *9:*277, 1997.) (See Color Plate 5.)

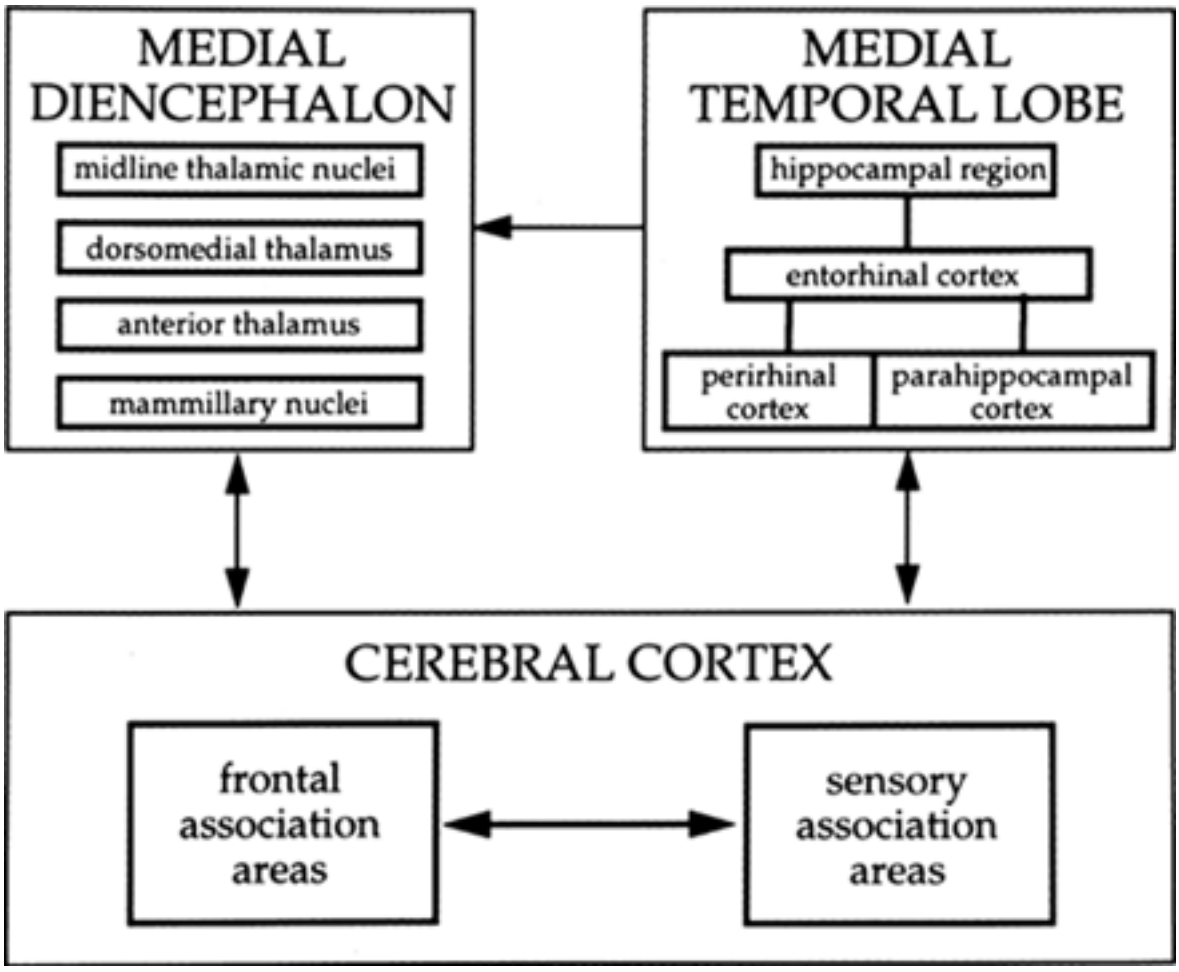
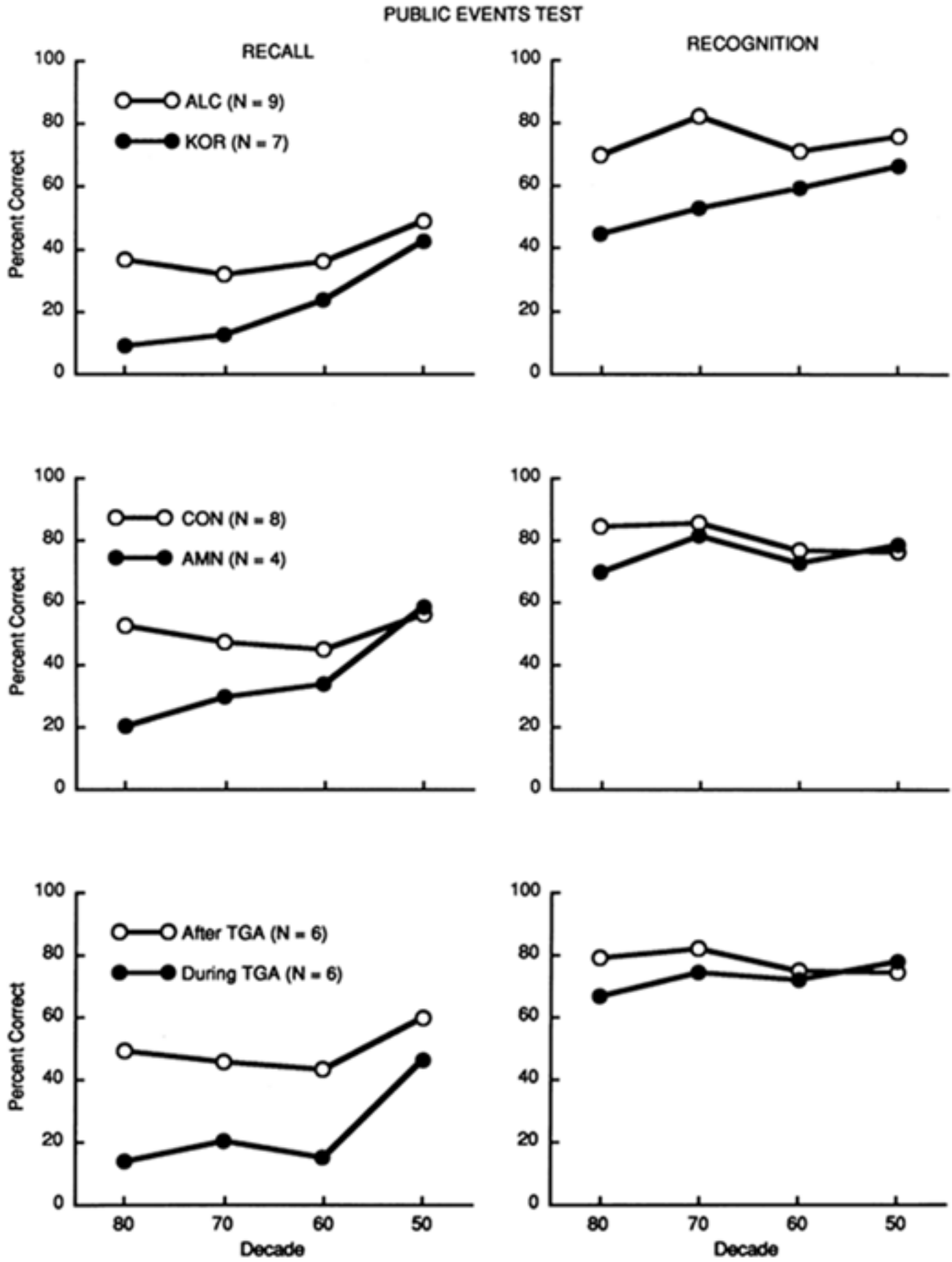


FIGURE 3.4-6 A schematic view of some of the chief brain regions critical for declarative memory. The entorhinal cortex is the major source of projections to the hippocampus, and nearly two thirds of the cortical input to the entorhinal cortex originates in the perirhinal and parahippocampal cortex. Entorhinal cortex also receives direct connections from cingulate, insula, orbitofrontal, and superior temporal cortex.


PUBLIC EVENTS TEST
RECALL
RECOGNITION
ALC (N = 9)
KOR (N = 7)
CON (N = 8)
AMN (N = 4)
After TGA (N = 6)
During TGA (N = 6)
Percent Correct
100
80
60
40
20
0
80
70
60
50
Decade

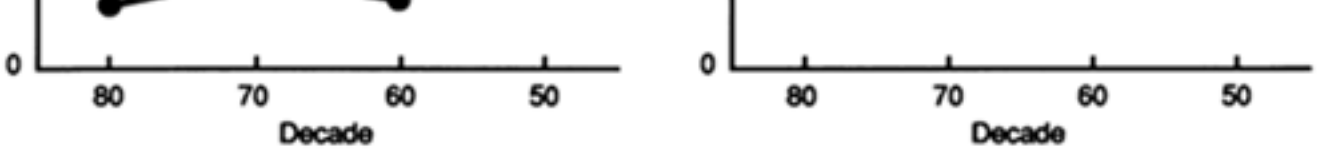


FIGURE 3.4-7 Remote memory performance of amnesic patients with Korsakoff's syndrome (KOR), alcoholic control subjects (ALC), amnesic patients with confirmed or suspected damage to the hippocampal formation (AMN), healthy control subjects (CON), and patients with transient global amnesia (TGA). The left column shows recall scores for past public events that had occurred in one of the four decades from 1950 to 1985. The right column shows performance on a multiple-choice test (four alternatives) involving the same public events. (Reprinted with permission from Kritchevsky M, Squire LR: Transient global ischemia: Evidence for extensive, temporally graded retrograde amnesia. Neurology *39:*213, 1989 and Squire LR, Haist F, Shimamura AP: The neurology of memory: Quantitative assessment of retrograde amnesia in two groups of amnesic patients. J Neurosci *9:*828, 1989.)

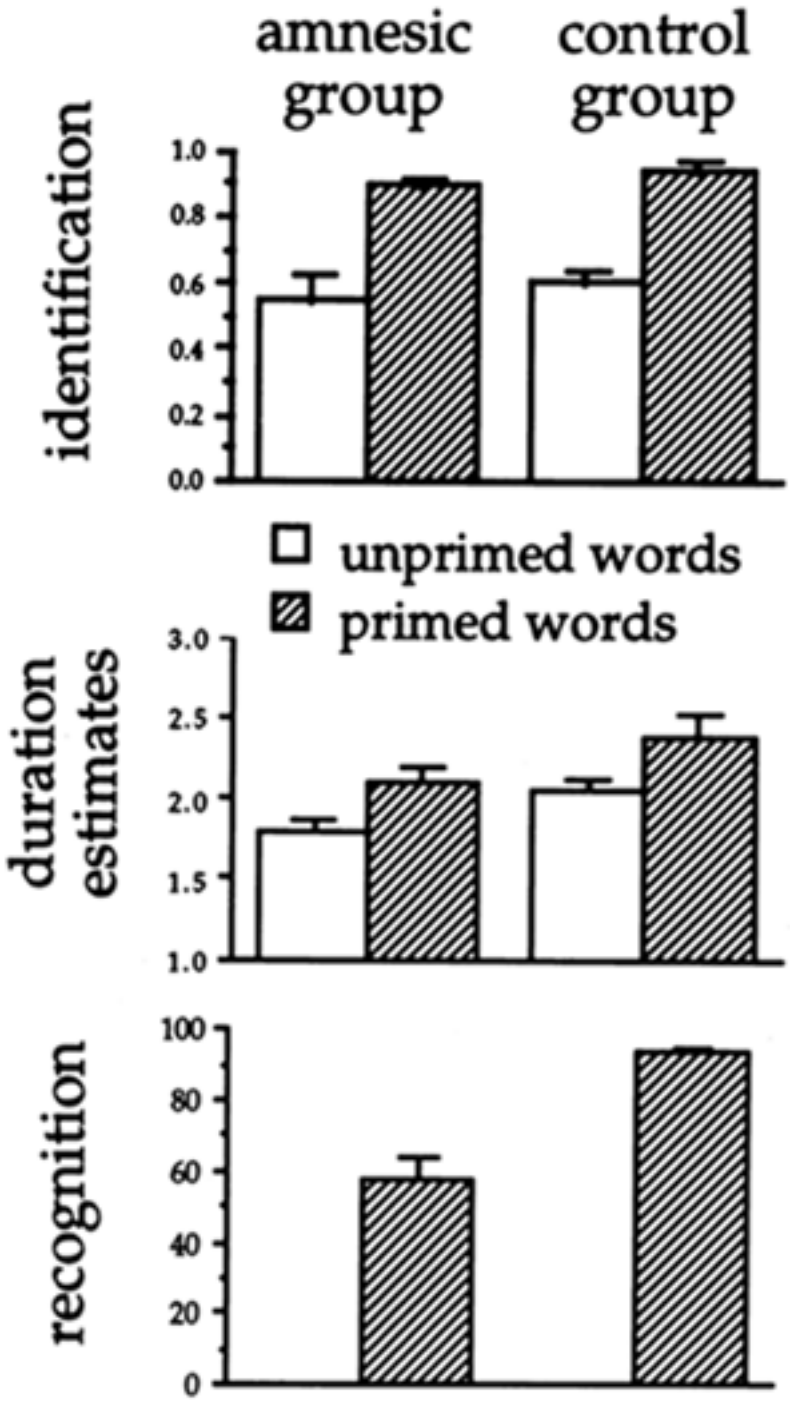


FIGURE 3.4-8 Preserved priming and impaired recognition in amnesic patients. The top graph shows the proportion of briefly presented words identified correctly by a group of amnesic patients and an age-matched control group. The priming effect took the form of more accurate identification for words presented in an earlier study phase (primed words) compared to other words (unprimed words). In the middle panel, both groups showed priming of duration estimations made on an arbitrary four-point scale, in that primed words were rated as having been presented for a longer duration compared to unprimed words. In the bottom panel, recognition performance on a forced-choice, three-alternative recognition

test was impaired in the amnesic group (lower percent correct). Values are means plus standard errors of the mean. (Adapted from Paller KA, Mayes AR, McDermott M, Pickering AD, Meudell PR: Indirect measures of memory in a duration-judgment task are normal in amnesic patients. Neuropsychologia *29:*1007, 1991.)

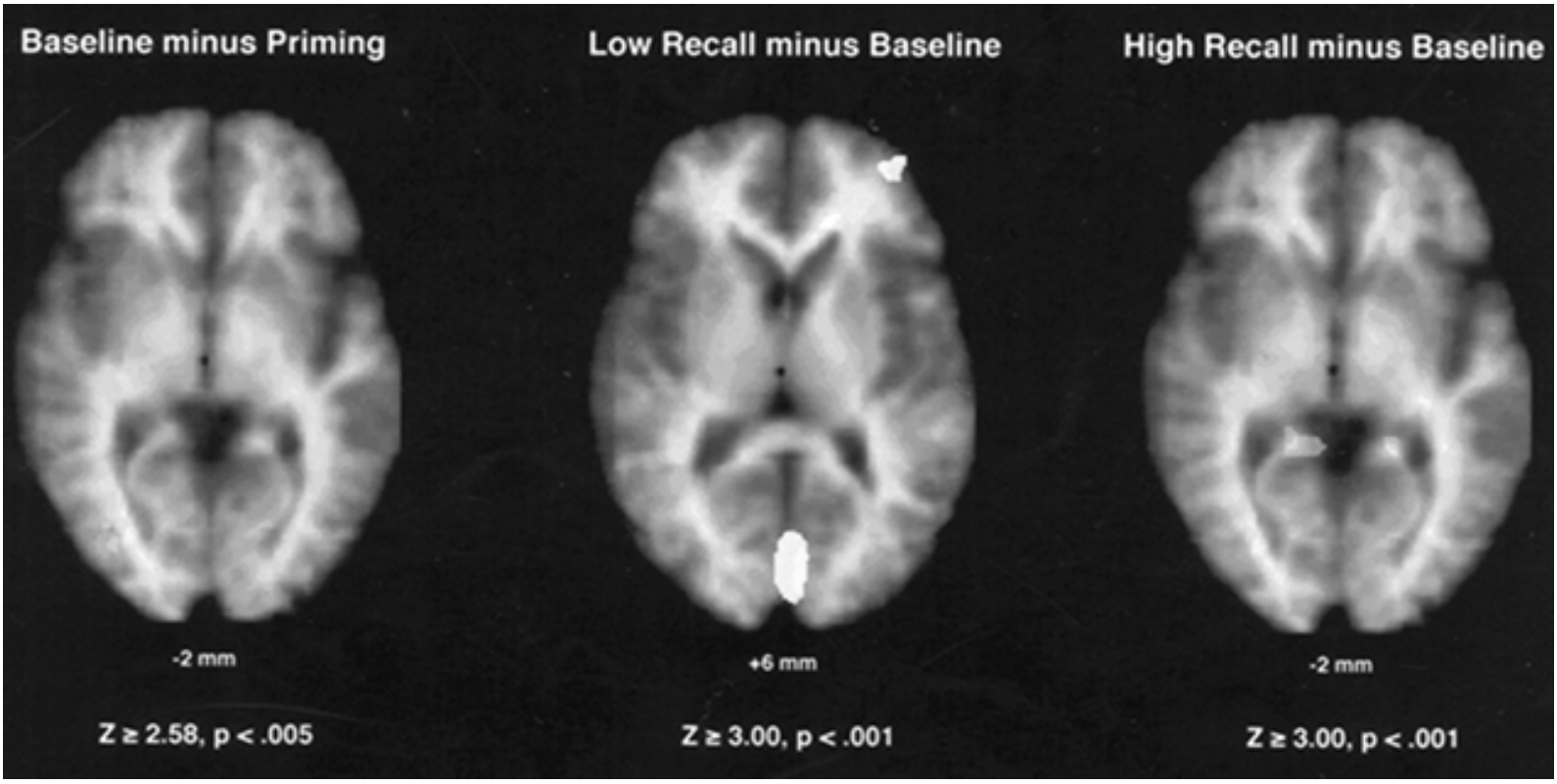


FIGURE 3.4-9 PET activations superimposed over averaged transverse MRI scans with the distance shown representing the distance from the line connecting the anterior and posterior commissure. Words were studied under strong or weak learning conditions (high recall or low recall) and then both declarative memory (cued recall) and nondeclarative memory (priming) were tested. The Baseline minus Priming subtraction showed an area of decreased blood flow (green) in right visual association cortex thought to be related to the greater ease of processing primed words. The Low Recall minus Baseline subtraction showed an area of increased blood flow (yellow) in secondary visual cortex and left prefrontal cortex thought to be related to the effort involved in deliberate, effortful retrieval. The High Recall minus Baseline subtraction showed a region of increased blood flow (red) in bilateral hippocampal regions thought to be related to successful retrieval of recently acquired information. (Reprinted with permission from Schacter DL, Alpert NM, Savage CR, Rauch SL, Albert MS: Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. Proc Natl Acad Sci USA *93:*321, 1996. ©1996 National Academy of Sciences, U.S.A.) (See Color Plate 5.)

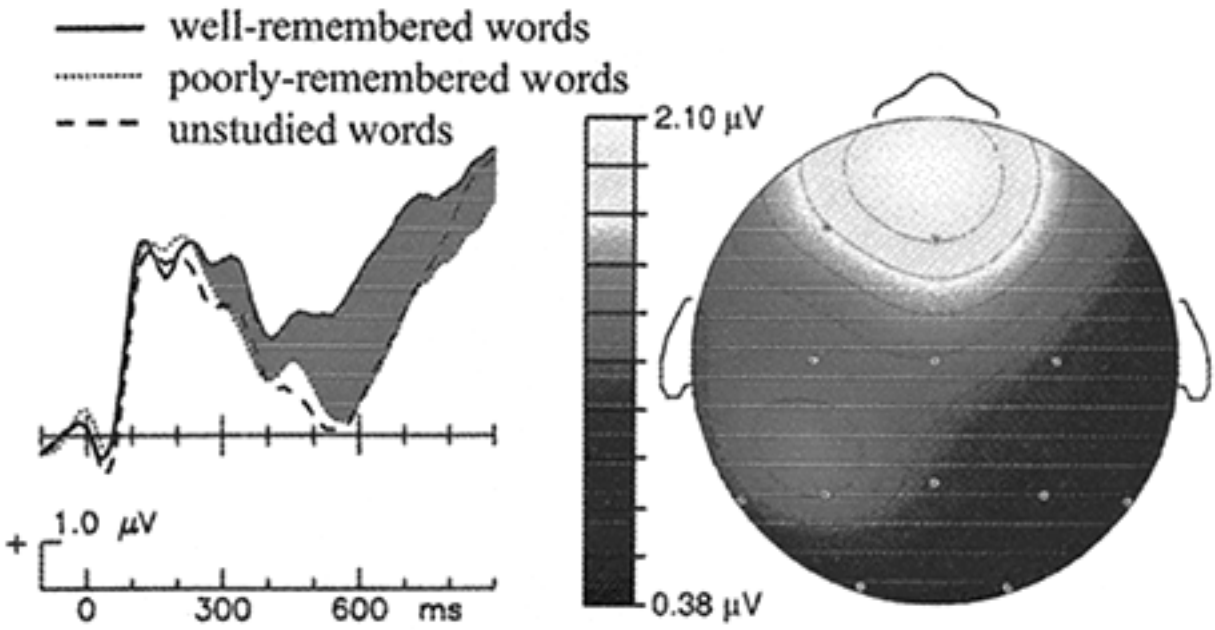


FIGURE 3.4-10 Brain potentials showing a differential response based on the extent to which subjects engaged in recollection following word presentations. Potentials shown at the left were recorded from a frontal scalp electrode. Measurements from multiple electrodes over the 400- to 800-ms latency range were used to generate the topographical map at the right, showing that the neural correlate of recollection was broadly distributed across the scalp, with largest responses over frontal cortex. (Adapted with permission from Paller KA, Kutas M: Brain potentials during memory retrieval provide neurophysiological support for the distinction between conscious recollection and priming. J Cogn Neurosci *4:*375, 1992.) (See Color Plate 6.)

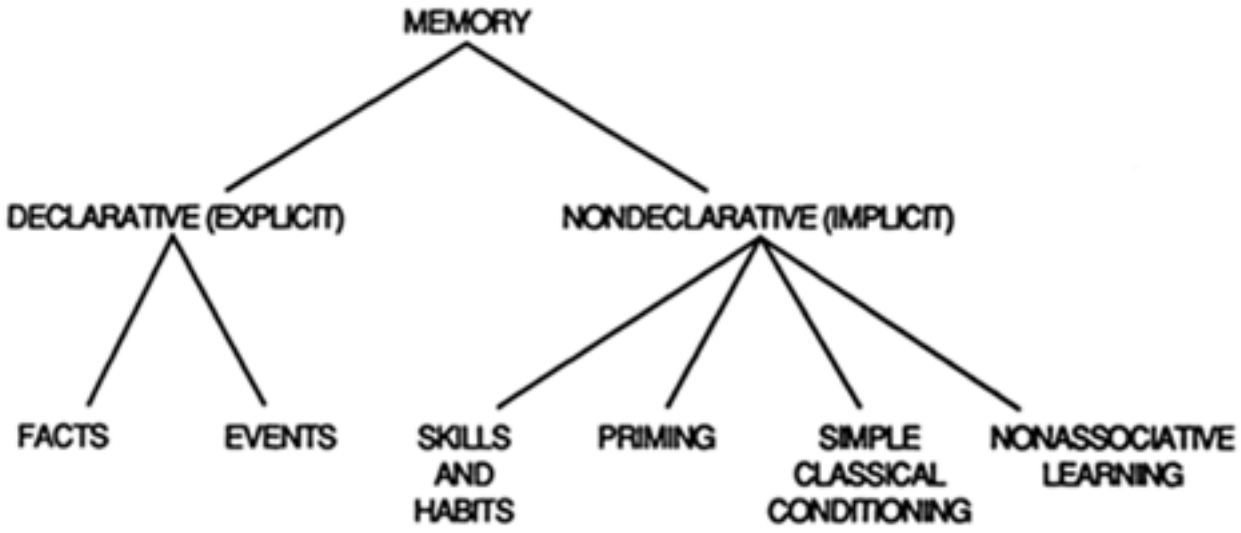


FIGURE 3.4-11 A tentative memory taxonomy. *Declarative memory* refers to conscious recollection of facts and events. *Nondeclarative memory* refers to a collection of abilities wherein performance changes as the result of experience but without affording conscious memory access to the original experience. *Nonassociative learning* includes habituation and sensitization. (Adapted from Squire LR, Zola-Morgan S: The medial temporal lobe memory system. Science *253:*1380, 1991.)

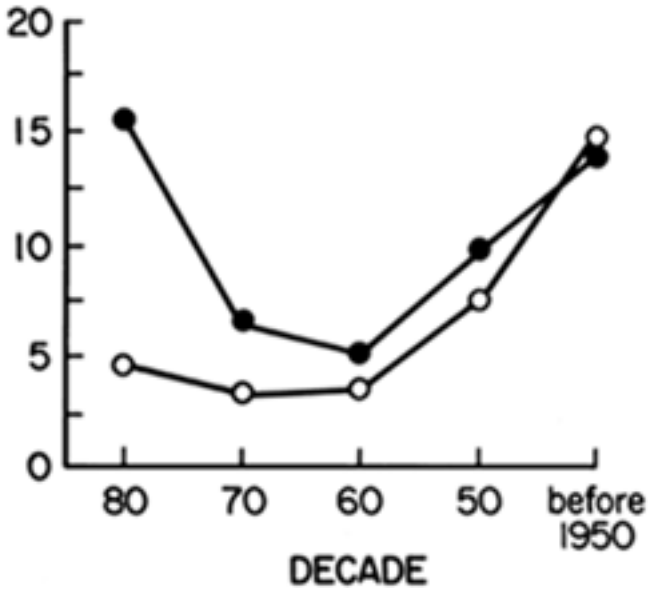


FIGURE 3.4-12 Loss of recent autobiographical memory as measured in five amnesic patients (filled circles) and five normal subjects (open circles). Well-formed memories from specific time periods were recalled in response to 75 single-word cues (e.g., *tree, flag, window*). (Reprinted with permission from MacKinnon D, Squire LR: Autobiographical memory in amnesia. Psychobiology *17:*247, 1989.)