Amnestic Disorders
Pathophysiology and Patterns of Memory Dysfunction

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A wide variety of conditions seen in medical practice can produce memory impairment (amnesia). Normal aging, depression, and anxiety are commonly associated with memory difficulties, as are many neurologic conditions. Systemic illnesses can impair memory by injuring vulnerable limbic regions sensitive to hypoxia or hypoglycemia. Commonly used over-the-counter and prescription medications can likewise cause amnesia.

These conditions disrupt memory in characteristic ways. Recent studies suggest that immediate, recent, and remote memory functions have different neuroanatomic substrates, as do the processes of registration, retention, and retrieval. New classifications have emerged to explain the evidence for multiple memory subsystems. The neuropharmacology of memory now includes several peptides in addition to cholinergic and noradrenergic pathways. Critical limbic regions have been discovered that mediate memory consolidation, and neuronal mechanisms such as long-term potentiation are being implicated in the unique capacity of these areas to permit new learning to take place.

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Research into human and animal memory has expanded at an enormous rate in recent decades, spanning fields from epidemiology and psychology to single-cell neurophysiology and molecular biology. Once considered a unitary phenomenon, human memory is now thought to involve a number of distinct and interrelated processes. These differ as to their role in information storage and retrieval, neuroanatomic and neurochemical substrates, and vulnerability to various pathologic conditions.

Amnesia refers to a specific deficit in new learning and memory. Retrograde amnesia indicates a loss of memory for events before the onset of the lesion or condition, whereas anterograde amnesia refers to an inability to acquire new information or experiences occurring during the period of the impairment. Amnestic disorders can occur in isolation, but in practice they are most commonly seen within the more global syndromes of delirium or dementia. The cardinal features of delirium include a fluctuating level of consciousness, impaired attention and concentration, disorientation, and frequently hallucinations and delusions. Delirium may develop acutely or subacutely and is a medical emergency, often precipitated by potentially life-threatening conditions. Dementia refers to a chronic—static or progressive—impairment in intellect with a clear sensorium. In addition to memory impairment, the dementia syndrome includes at least one additional area of cognitive dysfunction, such as agnosias, dyspraxia, dysgraphia, dyscalculia, impaired abstraction, impaired judgment, expressive or receptive language deficits, or visuospatial perceptual difficulties. In this review I focus primarily on “pure” amnestic disorders occurring in isolation but will also discuss memory loss associated with dementia.

Terms and Definitions

The classification of memory into its component processes continues to evolve, and the concepts outlined here include only those having a broad consensus in the current literature (Table 1). Information can be viewed as passing through several storage “buffers” of differing capacity and duration. Sensory memory persists for around 250 milliseconds in the visual mode (iconic memory) and 1 to 2 seconds in the auditory mode (echoic memory). For example, the visual icon is responsible for the afterimage one sees after shifting gaze from a picture or item to a blank background. Immediate (short-term, primary) memory has a duration of around half a minute, and extensive studies indicate a limited capacity of seven (plus or minus two) items for this buffer, whether the items be names, numbers, visually presented items, or other “units” of information. This buffer is commonly tested by the digit span (or Corsi blocks for nonverbal span). It is highly vulnerable to distraction, requiring attention and vigilance to maintain the content. As an example, if a person’s attention is distracted while holding a telephone number in immediate memory, the number is usually lost.

Recent (secondary) memory is called “short term” in many clinical studies and “long term” in most studies by cognitive psychologists. This has a duration of minutes to weeks or months and exhibits a much larger storage capacity than immediate memory. Generally, information must have been consciously attended to before it can enter recent...
memory. On entering this buffer, information undergoes a process of consolidation of variable duration. Recent memory is commonly tested by presenting a person with three unrelated words or objects and testing his or her recall for these items after a 2- to 5-minute distraction period. Deficits in the consolidation process that lead to an impairment of recent memory are the cardinal feature of amnestic disorders and occur in a wide range of conditions, which will be discussed further.

The remote (long-term) memory buffer stores information lasting from months to a lifetime and contains a vast array of personal experiences and knowledge about the world. Information passes into this buffer after it has been sufficiently consolidated. Controversy exists as to whether information in remote memory is stored indefinitely or eventually fades or becomes distorted.

Three elementary operations govern memory function: registration, storage, and retrieval. Registration refers to the "encoding" or acquisition of information and generally requires intact attentional resources and conscious effort. Retention (storage or consolidation) refers to the ability to store information over time in an intact form. Retrieval (decoding, recall) processes involve the ability to retrieve stored information. As with registration, retrieval generally requires conscious (volitional) processes.6-8

Registration is tested by having the subject repeat or respond to information immediately on its presentation. After a distraction task, the retrieval process is measured by having the subject recall this information. In free recall—the most accurate assessment of the basic retrieval ability—the subject receives no hints or assistance. In cued recall, various types of cues and hints are provided, such as the item's category, function, physical attributes, or other clues. The subject's ability to benefit from such cues partially depends on whether similar cues were identified during the registration of the information. To measure information retention (storage), it is necessary to bypass the retrieval process by the use of recognition tasks, in which the original information is presented along with several other items (multiple choice), one other item (forced choice), or alone (yes or no). In normal and amnestic subjects, recognition tasks typically yield higher scores than free or cued recall, indicating that much information is retained that cannot be readily retrieved.

These processes have been extensively studied in the amnestic disorders and will be frequently referred to below. Free recall, cued recall, and recognition all are examples of explicit memory tasks—that is, they require conscious, volitional processes. Storage can also be assessed by implicit memory tasks, in which more automatic processes are involved. These tasks include priming, in which the speed, accuracy, or type of response to a word is affected by a word presented immediately before it; word-fragment completion, in which the first letter or syllable of a word is presented and the subject asked to complete it; or word-fragment completion, in which parts of a word are presented and the subject asked to complete it. Implicit memory processes are an even more robust measure of storage, and amnestic patients often display intact implicit memory in the face of disrupted explicit memory.6-7

Several broad memory classifications have emerged that deserve mention, as they are frequently used in the literature: “working” versus “reference” memory,9 “episodic” versus “semantic” memory,10 and “declarative” versus “procedural” memory.11-14 Reference memory can be likened to a filing cabinet containing recent and remote information gained from previous experience. Working memory refers to that which is being actively updated by the current experiment or experience (similar to primary memory). This can be likened to a mental desktop. Episodic memory contains information about events occurring in a specific place and time, such as what happened last Christmas, whereas semantic memory houses “eternal” facts, principles, associations, and rules about the world (such as what the meaning of Christmas is, the capital of Russia, the number of hours in a day, and so forth).10 Investigators studying human amnesia argue that little support exists for the above distinctions on physiologic grounds and that a more anatomically robust distinction is that of declarative versus procedural memory systems.11-14 Declarative memory pertains to facts about the world and past personal events that must be consciously retrieved to be remembered. Procedural memory, in contrast, is involved in learning and retaining a skill or procedure, such as how to ride a bicycle, follow the basic rules of a board game like chess, or get dressed. Such abilities become “automatic” and do not require conscious direction. Amnestic patients show an intact ability to acquire new skills at almost normal rates (procedural) but are unable to recall having engaged in the task before (declarative).

A final distinction that should be described is that popularized by Squire, between diencephalic and medial temporal amnesia.14 Diencephalic amnesia occurs in alcoholic patients with Korsakoff's syndrome, who suffer from damage to the mamillary bodies and dorsomedial nucleus of the thalamus (mamillothalamic tract). It is characterized by impaired registration (encoding) and retrieval (decoding), but consolidation or retention is grossly intact. Thus, if given registration or retrieval aids such as the use of an associated word or an item's category, these patients can perform almost as well as normal subjects after hours to weeks. Frontal lobe damage may be present in most of these patients.12 In medial temporal lobe amnesia, registration and retrieval are intact, but
there is a marked deficit in consolidation resulting in an abnormally rapid forgetting rate.1,2,15

Specific Amnestic Disorders

A wide range of psychiatric, neurologic, and systemic conditions can produce amnestic disorders, isolated or in combination with the dementia syndrome.1-3,8,15,16

Age-Related Memory Changes

By the year 2030, the proportion of our population older than 65 years will have increased from its present 11% to 20%. As many as two thirds of older persons experience mild difficulties in recalling names, numbers, and other facts, termed “benign senescent forgetfulness.”17 In fact, a syndrome of age-associated memory impairment has recently been proposed with the following diagnostic criteria: age 50 years or older, memory scores on tests of secondary (recent) memory of at least 1 standard deviation below the mean compared with young adults, an absence of other areas of cognitive decline or of fluctuating levels of consciousness, and the exclusion of causative physical factors.16,18 Most of these cases do not have dementia on five-year follow-up.18

Psychiatric Conditions

Severe anxiety disorders, bipolar manic and depressive episodes, unipolar depression, and schizophrenia can impair memory by causing distractibility, impaired attention and concentration, and inadequate processing of new information.19 The pseudodementia of depression can be difficult to distinguish from organic dementias, as prominent features include variable forgetfulness, a slowing of mental activity, deficits in attention and concentration, and concrete thinking with impaired problem-solving ability.19,20 As these factors clearly affect effortful cognitive processes, it is not surprising that recognition memory, which reflects retention, is less impaired in depression than is free recall, an effortful retrieval process.21,22 Psychogenic amnesia, fugue, and multiple personality disorder are dissociative anxiety states in which a person forgets important personal information (psychogenic amnesia) or adopts an entirely new identity for a period of time (fugue and multiple personality).23 A key feature helping to distinguish these patients from those with organic amnestic disorders is that they are able to learn and acquire new information at a normal rate during an episode—that is, there is no anterograde memory loss.

Neurologic Disorders

Alzheimer’s disease. This disorder affects 4% of persons older than 65 and reaches a 20% prevalence by age 80.24 The most frequent initial complaint is of impaired memory for recent information and events.25,26 The memory disorder of Alzheimer’s disease is complex and varies with the stage of the disease.6,24-31 In the early stages, it can be difficult to distinguish from age-associated memory impairment, and recognition scores may be considerably stronger than free recall scores—indicating retrieval deficits in the face of relatively intact retention of information. Immediate (primary) memory is often normal in the early stages. As the dementia progresses, a more profound amnestic disorder sets in that is unaided by retrieval cues and includes deficits in immediate and remote memory in addition to the severe recent memory impairment. Researchers disagree on the relative contributions of registration, retention, and retrieval deficits to the memory loss seen in these later stages.6,27 There is a growing consensus, however, that a deficit in semantic memory processes (defined earlier) appears early, progresses, and underlies much of the episodic memory failure in patients with Alzheimer’s disease.6,27 Patients show deficits in forming associations to new information (such as providing synonyms, item category, or item function) and show little to no benefit from semantically structured presentation of information (such as listing words by their category groups).

Pick’s disease. In Pick’s disease, which has a prevalence of approximately 2% of cases of Alzheimer’s disease, the frontal and temporal lobes are predominantly affected. In the early stages, memory loss is not as pronounced as in Alzheimer’s disease, whereas personality alterations—due to involvement of the frontal lobes—are more striking.19 As the disease progresses, however, and as medial temporal lobe involvement increases, memory deficits become prominent as well.1

Parkinson’s disease. Several extrapyramidal disorders are associated with memory impairment. Three of these—Parkinson’s disease, Huntington’s disease, and Wilson’s disease—will be discussed. The estimated prevalence of dementia in Parkinson’s disease ranges from 10% to 40%, depending on study design and selection methods.22 The deficits chiefly comprise a slowing of mental activity and difficulty initiating or maintaining effortful processes including memory registration and retrieval.29,33,34 In contrast, retention-consolidation processes may be intact or only mildly impaired, as reflected in superior recognition scores relative to recall scores.29 The degree of cognitive impairment correlates strongly with the extent of motor involvement,33 and in lateralized parkinsonism the neuropsychological deficits—including memory dysfunction—reflect the side of greatest motoric compromise.34 Older patients have a higher prevalence of dementia.32,33 The relative contributions of the dopaminergic nigrostriatal deficits and of Alzheimer-like lesions often found in the brains of demented patients with Parkinson’s disease is currently undergoing debate.32-34

Huntington’s disease. Patients with Huntington’s disease may exhibit clear neuropsychological impairment several years before overt motor manifestations develop,35 and several well-controlled studies indicate that memory is the first area to be affected.36 Here, as in Parkinson’s disease, the greatest deficits occur in the registration and retrieval processes, while milder compromises are seen in consolidation. In contrast with those with Parkinson’s disease, however, patients with Huntington’s disease appear much less able to benefit from memory cues, apparently because of profound deficits in registration (acquisition, or encoding).36 Also, a large study of immediate memory using verbal (digit span) and nonverbal (Corsi block) measures showed that patients with Huntington’s chorea scored considerably lower than patients with either Parkinson’s disease or progressive supranuclear palsy.37

Other extrapyramidal disorders. Mild to moderate memory deficits with little to no associated cognitive impairment have been recently described in two other disorders that can present with extrapyramidal features: Wilson’s disease (hepatolenticular degeneration)38 and olivopontocerebellar atrophy.39 Medalia and co-workers and Kish and associates did not attempt to distinguish the roles played by registration, consolidation, or retrieval processes, however.38,39

Cerebrovascular disease. This disorder can produce a
variety of amnestic syndromes, depending on which central nervous system structures are affected. The posterior cerebral artery supplies the occipital lobe and medial temporal lobe, and infarctions in this distribution produce homonymous hemianopsia along with an anterograde and retrograde amnesia, impairing memory consolidation processes. The amnesia is particularly severe when bilateral infarctions occur.\(^1\) The confusional state resulting is largely based on the anterograde memory loss, but deficits in focal attention and loss of linguistically organized memory (when the dominant lobe is affected) have also been reported.\(^{40}\) In the thalamus, infarctions in two locations can lead to anterograde amnesia, which is frequently coupled with confusion and confabulation, particularly when the infarcts are bilateral. The first involves the paramedian area, including the dorsomedial thalamic nucleus and internal medullary lamina.\(^{41-43}\) The second affects the anterior thalamic nucleus and the mamillothalamic tract that reciprocally connects it with the mamilary bodies.\(^{44}\) This latter area is precisely where the lesions of Korsakoff’s syndrome occur, and it is significant that confabulation is also prominent in patients with this condition (to be discussed further).

Infarctions in the subthalamic and mesencephalic regions frequently induce impaired attention and mental control, with slowing of verbal and motor responsiveness. These deficits are probably due to a complex mixture of damage to fibers of the ascending reticular activating system traveling through the medial thalamus and of damage to specific ascending monoaminergic pathways arising in the medial brain-stem tegmentum.\(^{45}\) The result is prominent deficits in concentration, registration, and retrieval. One noteworthy case of combined anterograde and retrograde amnesia was recently reported in a 39-year-old man following hemorrhage from an arteriovenous malformation into the splenium of the corpus callosum.\(^{46}\) Although this lesion spared important memory structures (hippocampus, thalamus, basal forebrain, and fornix), it effectively dislocated the anterior thalamus from the hippocampus by involving interconnecting projection fibers between these two key limbic structures.

Transient global amnesia, while not associated with an increased risk of infarctions, may be due to transient ischemia in the posterior cerebral artery distribution. The condition occurs in middle-aged or older patients of both sexes and is characterized by a suddenly impaired memory without associated neurologic findings. Recovery is complete within 24 hours, but during the episode the patient displays a profound anterograde and retrograde amnesia in a clear sensorium. Immediate memory is normal (repetition of verbal and nonverbal material is intact), but the patient may appear confused owing to the loss of secondary (recent) memory function, as recall for material after a several-minute delay is absent. The retrograde amnesia extends to events and memories anywhere from hours to years before the episode. After the episode resolves, permanent amnesia for the episode itself remains.\(^{45-47}\)

**Epilepsy.** Studies of patients with intractable epilepsy show that those with complex partial seizures (also called “temporal lobe” or “psychomotor” seizures) have deficits in memory, learning, and attention.\(^{48}\) Material-specific memory deficits have been described—that is, verbal memory is particularly impaired when the dominant medial temporal lobe is involved, and nonverbal memory when the nondominant side contains the primary seizure activity.\(^{49}\) Registration processes appear intact, as does immediate memory. The primary deficit appears to occur in the retention or consolidation phase of memory, as shown by impaired performance on recognition as well as recall tasks and by rapid rates of forgetting.\(^{48}\)

Patients with Korsakoff’s syndrome from alcohol-associated thiamine deficiency experience anterograde and retrograde amnesia. The critical underlying lesion appears to be damage to the mamillothalamic tract and dorsomedial thalamic nucleus. The retrograde amnesia extends backward 3 to 20 years before the amnesia began.\(^{45}\) The condition is distinct from alcoholic dementia in which deficits in attention, word-list generation, abstraction, and constructions accompany the memory impairment.\(^{15}\) In patients with Korsakoff’s syndrome, the anterograde amnesia results primarily from an acquisition (registration) disorder, rather than a failure of retention.\(^{14,31}\) Of interest, these patients frequently exhibit confabulation (memory falsifications) thought to be associated with injury to the medial frontal lobes and mamillothalamic tract.\(^{50}\)

**Multiple sclerosis.** Memory is one of the most consistently impaired cognitive functions in patients with multiple sclerosis. Immediate (short-term) memory capacity as measured by digit span appears grossly intact, but retrieval of verbal information from secondary (long-term) memory is impaired, as measured on tests such as paired-associate word recall and logical memory for paragraphs.\(^{51}\) This may be due to impaired working memory—specifically, to a defect in what Baddeley calls the “articulatory loop,” the speech-based temporary store that allows short-term retention through subvocal rehearsal.\(^1\) In addition, patients exhibit slowed information processing on tests that require encoding of complex information under speeded conditions.\(^{52}\) These observations, coupled with normal forgetting rates, suggest that the predominant memory function affected is that of acquisition (registration). Patients with the chronic progressive form of multiple sclerosis may have relatively greater deficits in recognition tasks than other patients with multiple sclerosis, but even here the evidence points largely to an impairment of acquisition (registration) processes rather than to retention (consolidation) dysfunction.\(^{53}\)

**Head injury.** The most frequently reported cognitive complaint following head injury is memory impairment. At one-year follow-up of 102 patients with head injury in a large longitudinal study,\(^{54}\) the measures least affected were those assessing concentration (mental control), orientation, and immediate memory (digit span forward). Most affected were tasks requiring recent memory (logical memory for paragraphs, delayed recall, and difficult pairs of word associates). Indices of recognition were the most robust, and retrieval was the most vulnerable.

According to a survey study of 1,088 male college students,\(^{55}\) the extent to which retrograde amnesia persists following head injury appears related to the duration of the posttraumatic period of anterograde amnesia. In cases where the posttraumatic amnesia lasts over an hour, more than 50 % of subjects exhibit long-lasting retrograde amnesia. During the period of posttraumatic amnesia, subjects matched to controls on the acquisition of information (by providing them with longer stimulus exposure times) showed accelerated rates of forgetting over 32 hours.\(^{56}\) This impairment in memory consolidation is not surprising, as the brain regions most susceptible to contusion are the temporal poles and the
orbitofrontal surface, as well as long fiber bundles such as the fornix. Therefore, limbic and paralimbic areas are especially vulnerable to head trauma.1

Other conditions. Herpes simplex encephalitis often damages limbic structures to the exclusion of other areas of the central nervous system (CNS). With its predilection for the medial temporal lobe (amygdala, hippocampus, and parahippocampal gyrus) and orbitofrontal structures, the virus causes an anterograde amnesia characterized by intact immediate memory and registration processes but impaired recent memory or consolidation function.1,15 Compared to patients with Korsakoff's psychosis, patients with herpes simplex encephalitis have less confabulation, more awareness of their deficits, and less improvement with memory cues.57

Space-occupying CNS lesions such as tumors and abscesses can produce amnesia in a variety of ways. They act both through their local effects on various parts of the limbic system—basal forebrain, mamillary hypothalamic tract, and medial temporal lobe—and by exerting pressure on distant structures through increased intracranial pressure and edema. Tumors in the walls and floors of the third ventricle are most likely to cause an amnestic syndrome, being immediately adjacent to the thalamus.1,15

Obstructive hydrocephalus can either be noncommunicating—owing to blocked flow from the ventricular system into the subarachnoid space—or communicating—from impaired absorption of cerebrospinal fluid by the pacchionian villi of the subarachnoid space. In either case, clinical characteristics include dementia, gait disturbance, and incontinence. The dementia features include slowed mentation and a decreased capacity for effortful memory functions such as registration and retrieval.15 Table 2 provides a summary of some of the disorders just described and their known pathophysiology.

Systemic Conditions

Memory impairment is seen in association with a host of systemic diseases. Most often, it is accompanied by the broader syndromes of delirium or dementia. Relatively isolated memory loss, however, can occur from medical disease through one of two mechanisms: impaired memory consolidation from medial temporal lobe dysfunction, or in deficits in registration and retrieval processes through effects on the thalamus or frontal lobes.

Hypoxia can cause either type of deficit. When it is severe and short-lived, only those areas of the brain most vulnerable to an acute lack of oxygen are permanently affected. Thus, damage is often greatest to the hippocampus, and a permanent defect in new learning and memory consolidation (anterograde amnesia) results.58 Cardiopulmonary arrest, acute respiratory failure, anesthetic accidents, carbon monoxide poisoning, drowning, strangulation, and other conditions that induce acute hypoxemia can produce this type of memory loss.1,15 If the hypoxia is severe or prolonged, more widespread neuropsychological deficits occur, including apathy, attentional difficulties, and a dementia syndrome.1,15

Chronic or recurrent hypoxia of moderate severity resulting in this more widespread impairment is seen in many patients with chronic obstructive pulmonary disease.59 Acute hypoglycemia also has its greatest impact on hippocampal function, and subacute or recurrent episodes of acute hypoglycemia—such as may occur in poorly controlled insulin-dependent diabetes mellitus—can produce a relatively "pure" amnestic syndrome.60

| TABLE 2.—Selected Amnestic Disorders and Their Pathophysiology |
|-----------------------|---------------------------------------------------------------|
| Disorder              | Physiologic Substrate for Amnesia                             |
| Alzheimer’s disease   | Neuronal loss in nucleus basalis of Meynert                   |
|                       | Loss of acetylcholine and choline acetyltransferase activity in septohippocampal pathway |
|                       | Neurofibrillary tangles in CA1 and CA3 pyramidal cell regions of hippocampus |
|                       | Neuritic plaques in dentate gyrus                            |
|                       | Neuronal loss in entorhinal cortex, layers II and IV          |
| Korsakoff’s syndrome  | Thiamine deficiency-induced lesions in dorso medial nucleus of the thalamus, mamillary bodies, mamillothalamic tract |
| Transient global amnesia | Transient ischemia to hippocampus and other medial temporal lobe regions |
| Head trauma           | Injury to hippocampus and other medial temporal lobe regions |
| Herpes simplex encephalitis | Viral attack on limbic regions including medial temporal lobe and cingulate gyrus |
| Partial complex epilepsy | Possible damage to CA3 region                                |
| Infarction, anoxia    | Damage to medial temporal lobes or thalamus                   |

Neurochemistry and Neuropharmacology of Memory

In normal subjects, anticholinergic agents—particularly muscarinic blockers such as scopolamine—appear to mimic the type of learning and memory deficits seen in Alzheimer’s disease.61,62 The majority of cholinergic fibers supplying the cortex and hippocampus emanate from cells in the nucleus basalis of Meynert. Cell loss in this region and profound reductions in choline acetyltransferase activity in the septo-hippocampal pathway have been found in brains from patients with Alzheimer’s disease.63,64 The aspects of learning and memory affected by cholinergic pathways appear to be somewhat controversial. They include memory consolidation,61,63,65,66 registration, and retrieval processes67 as well as attentional processes.68 Atropine, scopolamine, belladonna, and the antihistamines are active ingredients in many over-the-counter and prescription sleeping agents, antiparkinsonian medications, and a number of antidepressant and antipsychotic medications.69 Thus it is not surprising that such agents are often noted to impair memory and concentration, particularly in the elderly or demented.

Numerous studies of animals have implicated catecholaminergic systems in learning and memory processes.63,70 Drugs disrupting these systems disrupt memory storage, whereas agonists produce dose-dependent facilitation at a restricted range (window) of dosages.71-73 Although numerous changes in catecholamine systems occur in humans with age, their relationship to age-associated memory impairments has not been established. In particular, the use of adrenergic stimulants such as methylphenidate hydrochloride (Ritalin) has not been shown to improve memory performance in the aged.63

Benzodiazepines can exert a direct amnestic effect in an otherwise clear sensorium.63 Lorazepam is particularly implicated in this regard.74 A study of diazepam use found that the major memory subsystem impaired by benzodiazepines
is the declarative memory system and that the procedural memory system is spared. The neuroanatomic sites of action of the benzodiazepines are heterogeneous, and binding sites have been shown to exist in several limbic regions.

In recent years, neuropeptides of hypothalamic and pituitary origin have been increasingly implicated in learning and memory processes. Adrenocorticotropic hormone (ACTH) and vasopressin analogues improve memory and learning performance in animals and humans. It has been suggested that ACTH affects motivation and attention and that vasopressin is more directly related to memory processes. Elderly patients given lysine vasopressin in nasal spray form did better than those given placebo on tests of attention, concentration, and memory. Mildly demented aged subjects likewise seem to show benefit from the use of desmopressin acetate (1-deamino-8-D-arginine vasopressin; DDAVP), whereas more severely demented patients show no benefit. The administration of ACTH does not reduce the memory impairment seen in aged subjects; it may instead exert its effects on mood and attentional processes. Neuropeptide Y, a 36-amino-acid peptide occurring in highest concentrations in the hippocampus and amygdala, has recently been reported to alleviate amnesia induced by scopolamine and by protein-synthesis inhibitors in mice.

**Neuroanatomy and Neurophysiology of Memory**

The role of the hippocampus, thalamic nuclei, and mamillary bodies in providing the neural substrate necessary for acquiring and retaining new information has been alluded to (Figure 1). It is unlikely that these structures in themselves contain specific memories, but in some way they provide a means to store and to retrieve memories, particularly those that are undergoing consolidation. The most extensively studied of these limbic regions is the hippocampus. Since the famous case of H.M., a patient who showed severe anterograde amnesia following bilateral amygdalohippocampectomies for seizure control in 1956, a huge volume of research in humans and animals has sought to define the hippocampal role in memory.

A critical pathway by which information from the cortical association areas reaches the hippocampus is through the entorhinal cortex located at the anterior pole of the parahippocampal gyrus. Moreover, the amygdala, which receives impulses from large cortical, hypothalamic, and basal forebrain areas, has extensive projections to the entorhinal cortex. Cell bodies in layers II and III of the entorhinal cortex receive the majority of these projections and send fibers through the perforant pathway to the dentate gyrus of the hippocampus. The dentate granule cells, in turn, send mossy fibers that synapse on apical dendrites of the CA3 cells of the hippocampus. Cells of the dentate gyrus appear capable of integrating recently acquired information. Interestingly, in patients with Alzheimer’s disease, neurofibrillary tangles develop in the cells of origin of the perforant pathway (layers II and III of entorhinal cortex), and neuritic plaques develop in the outer layer of the dentate gyrus, effectively disconnecting the hippocampus from the association and limbic cortices. Further, CA1 pyramidal cells, which receive fibers from the CA3 cells and serve as the major output from the hippocampus, are themselves extensively affected by neurofibrillary tangles. Layer IV of the entorhinal cortex, which receives a strong projection from the hippocampus and projects to widespread cortical regions, is also damaged. The hippocampus is thus effectively disconnected from its major incoming and outgoing pathways in Alzheimer’s disease (Figure 2). These observations, coupled with the profound reductions in choline acetyltransferase activity in the septohippocampal pathway and the extensive loss of cholinergic neurons in the nucleus basalis of Meynert, may serve to explain why the most common and predominant complaint in patients with Alzheimer’s disease is of an anterograde amnesia for new information and recent events.

A candidate physiologic mechanism for the consolidation of new memories within the hippocampus is that of long-term potentiation. This refers to a stable, relatively long-lasting increase in the magnitude of a postsynaptic response to a constant afferent volley, following brief tetanic (high-frequency) stimulation of those afferents. While long-term potentiation has only been elicited by electrical stimulation and not by natural phenomena, several features suggest that it may represent a model for, or use the same underlying neuronal apparatus as, learning and memory. Parallel between learning-induced increases in hippocampal neuronal

Figure 2.—The critical hippocampal memory pathways are shown: (1) The cell body in layer II of the entorhinal cortex (EC) projects through the perforant pathway to the outer layer of the dentate gyrus (DG); (2) a dentate granule cell sends mossy fibers to synapse on a CA3 pyramidal cell; (3) the CA3 cell sends an axon to synapse with a CA1 pyramidal cell; (4) the CA1 pyramidal cell sends an axon to synapse on a cell in the subiculum; and (5) the subiculum cell sends a projection to layer IV of the entorhinal cortex. The dots (stippled area) indicate regions of cell bodies.

**Figure 1.**—The drawing shows the limbic areas involved in memory: A, amygdala; a, anterior thalamic nucleus; CG, cingulate gyrus; dm, dorsomedial thalamic nucleus; EC, entorhinal cortex; F, fornix; H, hippocampus; Hy, hypothalamus; M, mamillary body; Th, thalamus.
activity and long-term potentiation include the observations that both

- Are exhibited by pyramidal neurons in the hippocampus;
- Require only a small number of stimuli (electrical pulses or stimulus presentations) for induction;
- Develop over a similar time course (hours to days);
- Exhibit a similar magnitude of increase over baseline;
- Depend on a specific range of stimulus frequencies; and
- Persist for long periods of time.

The induction of long-term potentiation requires nearly simultaneous activation of the presynaptic membrane and postsynaptic depolarization (Figure 3). This coincident activity results in an influx of calcium ions into the postsynaptic dendritic spine. This influx is mediated by voltage-dependent N-methyl-D-aspartate receptors, which at the resting membrane potential are blocked by magnesium. Sufficient depolarization of the membrane—which is provided by the combined presynaptic activation and postsynaptic depolarization from earlier tetanic stimulation—removes this voltage-dependent block. The necessity for near-simultaneous activation of presynaptic and postsynaptic elements accounts for the associative (learning) nature of long-term potentiation.

Declarative and procedural memory are two broad subdi-

visions of recent (secondary) memory processes. Most scientific investigation has been directed at the limbic structures necessary for declarative memory. Their integrity is best measured by using explicit memory tasks. Recent studies, however, have begun to focus on the neural substrates for procedural memory. While this form of memory is complex and likely to involve multiple CNS sites including motor and method-specific sensory cortex, evidence is mounting for a critical role for the cerebellum in helping to mediate many types of procedural (implicit) memory tasks.9

Immediate (primary) memory has been found to require a region distinctly removed from the limbic structures that mediate recent memory. This is the perisylvian cortex surrounding the sylvian fissure, an area also essential for language (digit) repetition. Evidence seems to indicate that remote memories are stored diffusely in multiple brain sites, possibly including secondary and tertiary association cortex.8

Conclusion

The field of memory research has now reached the point at which tasks that index selective memory processes are being combined with sophisticated techniques to elucidate the brain anatomy, chemistry, and physiology that underlie these.92–97 Clinical studies of memory disorders are likewise making use of more precise conceptualizations of what stage of information acquisition, storage, and retrieval is affected by the disease in question.98–100 It is hoped these advances will provide a basis for improved treatments of amnestic disorders in the future.

REFERENCES


Figure 3.—This diagram of long-term potentiation and N-methyl-D-aspartate (NMDA) receptors shows two separate mossy fibers (presynaptic membranes), each synapsing onto a different dendritic spine of a CA3 pyramidal cell: (1) The time record of presynaptic stimulation shows a constant-amplitude pulse of invariate frequency in A, contrasted with a brief period of rapid tetanic stimulation in B; (2) the constant, low-frequency stimulation in A opens non-NMDA receptors through the binding of transmitter (clear rectangles), allowing a small, transient depolarization. In B, the tetanic (high-frequency) stimulation permits summation of each new depolarizing event with the previous one. This greater degree of depolarization removes the voltage-dependent blockade of NMDA receptors (black rectangles) by magnesium, so that each new incoming pulse triggers calcium influx through NMDA as well as non-NMDA receptors; (3) the postsynaptic potential spike is shown as fixed in amplitude for A, but in B it increases its amplitude markedly during tetanic stimulation and sustains this increase following resuming the normal stimulus train, presumably due to continued opening of the NMDA receptors.