

Organic Amnesia

Arthur P. Shimamura

University of California, Berkeley

Organic amnesia is a neurological disorder that affects learning and memory but leaves other mental abilities relatively preserved. One important aim of research on this disorder is to understand how learning and memory are disrupted by brain dysfunction in order to obtain clues to brain organization and normal memory processes.

Much of the current interest in memory and brain function was initiated by Milner and colleagues who studied a now-famous patient with organic amnesia, case H. M., who in 1953 underwent surgery for relief of severe epileptic seizures. The surgery involved bilateral excision of the *medial temporal region*, which reportedly included removal of the uncus (amygdala), anterior two thirds of the hippocampus, and hippocampal gyrus (see Figure 1). Following surgery, H. M.'s seizure activity was attenuated, but he exhibited a profound *anterograde amnesia*—that is, he was unable to remember events and information encountered since his operation. Despite this severe impairment in new learning ability, there was no detectable impairment in intellectual or language abilities. There was some *retrograde amnesia*, which refers to impairment of memory for events that occurred before the onset of amnesia. For example, H. M. could not remember the layout of the hospital ward or recognize members of the medical staff. Moreover, he could not recall the death of a favorite uncle who had died three years previously. Yet, following surgery H.M.'s retrograde amnesia was not severe, as indicated by the fact that he performed as well as control subjects on a test of memory for faces of celebrities who became famous prior to 1950. He was also capable of recalling well-formed autobiographical episodes from his adolescence.

H. M. is still alive, and clinical observations indicate that memory for ongoing events is severely impaired. For example, 30 minutes after eating lunch, H. M. could not recall what he had eaten and could not even recall if he had lunch at all. H. M. is aware of his disorder and has reflected upon his impairment as always "waking from a dream." In other words, he seems to lack continuity in the memory of events across time, even when the events are separated by only a few

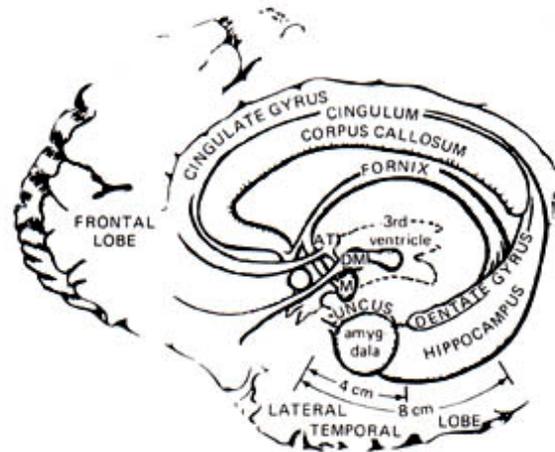


Figure 1. Schematic drawing of the medial surface of the human brain showing structures in the medial temporal lobe (e.g., hippocampus, amygdala) and in the diencephalic midline (e.g., dorsomedial [DM] and anterior [AT] thalamic nuclei, mammillary nucleus [M]). Figure reprinted from Squire (1984).

minutes. Thus, the central feature of H. M.'s memory disorder is anterograde amnesia or new learning impairment. This impairment affects information received from all sensory modalities and includes impairment of both verbal and nonverbal (e.g., spatial) memory. For example, H. M. has failed to acquire new vocabulary words that have been added to the dictionary since his surgery. He also exhibits severe impairment on laboratory tests of word and picture recall, cued-word learning (e.g., learning word pairs), and recognition memory.

Despite the severity of his amnesia, H. M. can think and act normally, as indicated by his preserved I.Q. Indeed, even some memory functions are spared, such as *short-term memory*, which can be measured by intact performance on tests of immediate digit span. Nevertheless, as soon as information is out of conscious experience, it is forgotten. The analysis of H. M.'s amnesia stands as a milestone in our progress to understand memory in the brain. He has provided the crucial evidence for the specific role of the medial temporal region in the process of memory formation and

storage. Indeed, the analysis of H. M. by Milner and colleagues has provided the impetus for many important animal and human studies on the role of the medial temporal region in learning and memory.

The Anatomy of Memory

There are other neurological disorders that damage the medial temporal region and thus produce an amnesic syndrome similar to that seen in H. M. For example, tumors, head injuries, or vascular disorders (e.g., strokes) in this region can cause organic amnesia. Also, some neurological disorders—such as viral infection, ischemia (i.e., loss of blood flow to the brain), or hypoxia (i.e., loss of oxygen to the brain), particularly damage the medial temporal region. In these disorders, anterograde amnesia is often the outstanding cognitive impairment, though retrograde amnesia can also occur. General intellectual abilities and short-term memory are generally intact.

An amnesic patient studied by Zola-Morgan et al. has provided additional clues concerning the prominent role of the hippocampus in memory. Patient R. B. became amnesic in 1978, when he experienced an ischemic episode that occurred during open-heart surgery. R. B. was given extensive neuropsychological assessment and was found to exhibit anterograde amnesia but little if any retrograde amnesia. In 1983, R. B. suffered a fatal cardiac arrest, and, with the encouragement of his family, a comprehensive examination of his brain was performed. This examination revealed a discrete bilateral lesion restricted to a portion of the hippocampus called the CA1 subfield. R. B. represents the first extensively studied case of amnesia that occurred as a result of damage restricted to the hippocampus.

Another area of the brain, the *diencephalic midline*, can also produce organic amnesia (see figure 1). This area includes various midline thalamic nuclei (nuclei are bundles of neurons) as well as subthalamic nuclei. These nuclei receive and send projections to various areas in the brain, including the medial temporal region. Patients with neurological damage due to cerebrovascular stroke or head injury in this area often exhibit organic amnesia.

The best-studied cases of amnesia resulting from damage to the diencephalic midline are patients with *Korsakoff's syndrome*. As reviewed by Butters and Cermak, Korsakoff's syndrome is an amnesic disorder that develops after many years of chronic alcohol abuse and nutritional deficiency. Studies by Victor et al. of postmortem brain tissue

show bilateral damage along the diencephalic midline, typically involving the dorsomedial thalamic nuclei and a subthalamic nuclei called the mammillary bodies. In addition, cortical atrophy and cerebellar damage are often observed.

Patients with Korsakoff's syndrome exhibit severe anterograde amnesia and often extensive retrograde amnesia. The severity of retrograde amnesia, however, is variable among these patients, with some showing extensive retrograde amnesia and others showing little. One factor that complicates the characterization of the memory impairment in Korsakoff's syndrome is widespread cortical atrophy, which is presumed to be a consequence of chronic alcohol abuse. Indeed, some mental functions, such as stimulus encoding, attention, and problem solving are impaired in patients with Korsakoff's syndrome but not in other amnesic patients. Moreover, patients with Korsakoff's syndrome are often emotionally flat, apathetic, and without insight about their deficit. These additional cognitive and personality disorders may occur as a result of extensive cortical damage, in particular damage to the prefrontal cortex.

Not all amnesic syndromes are permanent. For example, head injury can cause a transient and selective memory impairment. Following initial stages of unconsciousness or confusion, anterograde and retrograde amnesia occurs, and the severity of anterograde amnesia is often correlated with the temporal extent of retrograde amnesia. Retrograde amnesia tends to follow *Ribot's Law*, which states that memory for the recent past is affected more severely than memory for the distant past. Amnesia following head trauma can last for minutes, days, or even weeks. In mild trauma cases, new learning ability recovers to premorbid levels. In more severe cases, both amnesia and other cognitive impairment can be long-lasting and sometimes permanent.

Amnesia can also occur after *electroconvulsive therapy* (ECT), which is sometimes prescribed for severe depressive illness. Anterograde amnesia can be quite severe, particularly in patients who receive bilateral ECT. Retrograde amnesia is often temporally-graded, following Ribot's Law. By several months after ECT treatment, there is extensive recovery of new learning capacity. Retrograde amnesia also resolves considerably when testing occurs 6-9 months after ECT. Although the biological factors that cause the transient amnesic disorder following ECT are not well understood, it is known that the hippocampus has one of the lowest seizure thresholds of all brain structures.

Thus, hippocampal functioning may be particularly compromised following ECT.

Advances in neuroimaging techniques, such as *computed tomography (CT)*, *magnetic resonance (MR) imaging* and *positron emission tomography (PET)*, have allowed more detailed analysis of the brain areas that are damaged in neurological patients. For example, analyses of computed tomography (CT) brain scans of patients with Korsakoff's syndrome corroborated postmortem findings by identifying signs of increased fluid and low neural density in the midline diencephalic region. A new technique by Press et al. has been developed for MR imaging of the hippocampus. This technique produces a clear cross-sectional image of the hippocampal formation and has already provided remarkable images of the extent of hippocampal damage in amnesic patients. For example, it was shown that, compared to control subjects, amnesic patients exhibited an average loss of 49% of tissue in the area of the hippocampal formation. Despite this tissue loss in the hippocampal area, the average area of the temporal lobe in these patients was nearly identical to that of control subjects. Although PET analyses of amnesic patients have not been thoroughly studied, they offer another approach to the physiological dysfunction associated with organic amnesia.

Preserved Memory Functions in Amnesia

One of the most striking findings is that amnesic patients can perform in an entirely normal fashion on certain "implicit" or "nondeclarative" memory tests. These tests involve habit or automatic learning, such as the kind of memory expressed on tests of skill learning, classical conditioning, and "priming." For example, H. M. showed considerable retention of perceptual-motor skill on a mirror drawing task in which he was required to trace the outline of a star while viewing the star in a mirror. The task is difficult at first but then becomes easier and easier with practice. H. M. also exhibited skill learning on a pursuit-rotor task in which a stylus must be kept on a rotating target. In these tests, H. M. performed as a skilled individual but did not have conscious knowledge of having performed the task before. Preserved skill learning has been observed in other cases of amnesia as well. For example, normal pursuit-rotor skill learning and one-week retention in three patients with Korsakoff's syndrome and two patients with amnesia due to viral encephalitis. Also, in a jig-saw puzzle assembly task, these amnesic patients exhibited faster completion times across six

trials and good retention when the same puzzle was given 1 week later.

Cohen and Squire observed preserved skill learning by amnesic patients on a mirror reading task. In this task, subjects were asked to read mirror-reversed words. Patients with Korsakoff's syndrome, patients prescribed ECT, and patient N. A. improved their reading speed of mirror-reversed words across training sessions to the same extent as control subjects. Moreover, amnesic patients exhibited normal retention of the mirror-reading skill even when they were tested one month after learning. Despite this intact skill learning performance, patients failed to recognize the words used in the task. Moreover, the patients often did not even recognize the testing apparatus nor did they have conscious recollection of having engaged in the task before. Performance by amnesic patients in these tasks indicates that skill learning can be preserved even when the patient has little or no recollection of having acquired the skill. These findings suggest that amnesic patients can exhibit a certain "unconscious" form of knowledge ("knowing how") in the absence of explicit or declarative knowledge ("knowing that").

There are several other forms of preserved memory function in amnesia. One form is illustrated by an early anecdote of "unconscious" memory that was reported by Claparede. During an interview with an amnesic patient, Claparede hid a pin between his fingers and surreptitiously pricked the patient on the hand. At a later time during the interview, he once again reached for the patient's hand, but the patient quickly withdrew her hand. The patient did not acknowledge the previous incident, and, when asked why she withdrew her hand, she simply stated, "...sometimes pins are hidden in people's hands." This anecdote is an example of stimulus-response learning without awareness. Another form of such learning was demonstrated by Weiskrantz & Warrington, who assessed Pavlovian classical conditioning of the eyeblink response in two amnesic patients. These patients retained the eyeblink response for as long as 24 hours, even though they did not recognize the test apparatus.

A memory phenomenon known as *priming* is also preserved in amnesia. Priming is an automatic facilitation or bias in performance as a result of recently encountered information. The seminal evidence for preservation of priming in amnesia came from Warrington and Weiskrantz. Amnesic patients were asked to identify words or pictures that were presented in a degraded form. If the subject could not identify the stimulus, a succes-

sion of less degraded versions of the stimulus were shown until identification was successful. When amnesic patients were asked to identify the same degraded words or pictures at a later time, their performance was facilitated by the previous experience; that is, they were able to identify the stimuli more quickly. This priming effect occurred despite failure to discriminate previously presented stimuli from new ones in a recognition memory test.

Graf et al. used a word completion task to study priming effects. In this task, words are presented (e.g., MOTEL) to the subject and later cued by three-letter word stems (e.g., MOT). Subjects are asked to say the first word that comes to mind for each word stem. In both amnesic patients and control subjects, the tendency to use previously presented words in the word completion test was increased by 100-200% over baseline levels. In this test, words appear to "pop" into mind, and amnesic patients exhibited this effect to the same level as control subjects. However, when subjects were asked to use the same word stems as aids to recollect words from the study session, the control subjects exhibited better performance than amnesic patients.

A variety of priming paradigms have since been used to demonstrate preserved priming in amnesia. For example, in one task subjects were presented words (e.g., BABY) and later asked to "free associate" to related words (e.g., CHILD). Amnesic patients exhibited a normal bias to use recently presented words in this word association task. This finding suggests that semantic associations can also be used to prime information in memory. This priming effect, as well as others, are short-lasting, and decline to baseline levels after a 2-hour delay. Although patients with circumscribed diencephalic or medial temporal lesions exhibit normal priming effects, patients with the clinical diagnosis of Alzheimer's disease do not. For example, impaired word completion and word association priming has been observed in patients with senile dementia of the Alzheimer type. These findings suggest that priming effects may depend critically on neocortical areas that are damaged in Alzheimer's disease.

Demonstrations of preserved memory functions in amnesic patients suggest that some memory processes can be dissociated from the brain regions that are damaged in organic amnesia. As reviewed by Squire, various taxonomies have been used to distinguish the memory forms that are impaired in amnesia from those that are preserved. For example, many distinguish between "con-

scious" recollection from unconscious or automatic memory. Squire and colleagues suggested that amnesia impairs *declarative* memory and spares *procedural* or *nondeclarative* memory. Others have used related terms such as *explicit* and *implicit* memory or *memory* and *habit*. Such descriptions provide a framework for theoretical views about the organization of memory in the brain.

Memory Systems in the Brain

Findings from amnesic patients have led to the conclusion that there are multiple memory systems in the brain, such that some forms exist entirely outside the brain regions that are damaged in organic amnesia. Amnesic patients apparently cannot explicitly or consciously recollect information learned since the onset of amnesia. The impairment is often thought to affect the ability to store and also to retrieve newly learned information. Amnesic patients, however, can often perform in a normal fashion on certain "indirect" tests of memory—tests that do not require conscious recollection of past learning sessions. Tests of skill learning, classical conditioning, and priming can be characterized as indirect or implicit tests.

Various theories have been proposed to describe the amnesic disorder. Squire and colleagues have specified a neurological basis for declarative memory—the form of memory that is impaired in amnesia. It is hypothesized that declarative memory involves a storage or consolidation process that depends critically on the interaction of the hippocampus with areas in neocortex. The hippocampal "system" receives projections from many neocortical areas. Thus this region may be involved in relating or connecting information between various neocortical areas so that memory storage and retrieval can be accomplished quickly and efficiently. Warrington and Weiskrantz have suggested that amnesia is due to a disruption of diencephalic midline projections that connect the medial temporal region to the prefrontal cortex. Similarly, Mishkin has suggested that amnesia is caused by disruption of the interaction of the hippocampus and amygdala with structures in neocortex and in the diencephalic midline (mediodorsal and anterior nuclei of the thalamus).

In summary, neuropsychological studies of memory functions in amnesic patients have provided useful information about the organization of memory systems in the brain. Damage to the medial temporal region or diencephalic midline causes an amnesic syndrome in which conscious or declarative memory is severely impaired. Interestingly, other implicit or procedural functions

(e.g., skills, habits) are entirely preserved. These findings suggest that there are multiple memory systems in the brain and that one system can be dissociated from other memory and cognitive systems. These findings may offer important avenues for both rehabilitative and pharmacological interventions. That is, it may be possible to develop more efficient and more specific diagnoses and therapies for neurological patients as well as for individuals with more subtle forms of memory dysfunction, such as that observed in aging.

Bibliography

- Andreason NC: Brain imaging: Applications in psychiatry. *Science*: 239: 1381-1388, 1988.
- Butters N, Cermak LS: *Alcoholic Korsakoff's Syndrome: An Information Processing Approach*. New York: Academic Press, 1980
- Cohen NJ, Squire LR: Preserved learning and retention of pattern analyzing skill in amnesia: Association of knowing how and knowing that. *Science*. 210: 207-209, 1980
- Corkin S: Lasting consequences of bilateral medial temporal lobectomy: Clinical course and experimental findings in H. M. *Sem Neurol* 4: 249-259, 1984
- Graf P, Squire LR, Mandler G: The information that amnesic patients do not forget. *J Exper Psychol: Learn Mem Cognit* 10: 164-178, 1984
- Graff-Radford NR, Tranel D, VanHoesen GW, Brandt J.P: Diencephalic amnesia, *Brain*, 113, 1-25, 1990
- Milner B, Corkin S, Teuber H: Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia* 6: 215-234, 1968
- Mishkin, M. A memory system in the monkey. In D. E. Broadbent, & L. Weiskrantz, Eds., *The Neuropsychology of Cognitive Function*, pp. 85-95 London: The Royal Society, 1982
- Press, GA, Amaral DG, Squire LR: Hippocampal abnormalities in amnesic patients revealed by high-resolution magnetic resonance imaging. *Nature* 341: 54-57, 1989
- Schacter DL: Implicit memory: History and current status. *J Exper Psychol: Learn Mem Cognit* 13: 501-518, 1987
- Shimamura AP: Disorders of memory: The cognitive science perspective. Boller F Grafman J. *Handbook of Neuropsychology* Amsterdam, The Netherlands: Elsevier Sciences Publishers, 1989: 35-73
- Shimamura AP: Priming in amnesia: Evidence for a dissociable memory function. *Q J Exper Psychol* 38, A: 619-644, 1986
- Squire LR: The neuropsychology of memory. In Marler P, Terrace H (Editors), *The Biology of Learning, Dahlem Konferenzen*, Berlin: Springer-Verlag, 1984.
- Squire LR: *Memory and Brain*. New York: Oxford University Press, 1987
- Victor M, Adams R.D, Collins GH: *The Wernicke-Korsakoff Syndrome*. Philadelphia: Davis Company, 1971
- Warrington EK, Weiskrantz L: Amnesia: A disconnection syndrome? *Neuropsychologia* 20: 233-248, 1982
- Warrington EK, Weiskrantz L: New method of testing long-term retention with special reference to amnesic patients. *Nature* 217: 972-974, 1968
- Weiskrantz L, Warrington EK: Conditioning in amnesic patients. *Neuropsychologia* 17: 187-194, 1979
- Zola-Morgan S, Squire LR, Amaral DG: Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J Neurosci* 6: 2950-2967, 1986