Remembrance of Things Partly

By studying forgetfulness in humans and monkeys, scientists are learning about the anatomy of normal memory. Their findings may help to resolve a fundamental dispute among learning theorists.

The first of two articles on memory and learning.

By WRAY HERBERT

As brain disorders go, amnesia has always been a favorite of storytellers. With a simple blow to the head, it is possible to create a character without a past — and thus a character capable of observing the human condition without bias. As useful as this form of amnesia is as a literary convention, like most literary conventions it is an oversimplification based on an element of truth. While it is true that a severe bruise to the brain can cause "retrograde" amnesia — loss of remote memories — other causes are much more common and memory failure is rarely complete or uncomplicated. Indeed, scientists who have been studying different forms of amnesia are finding that memory collapse occurs in a selective fashion, depending on the cause, and these recent findings are promising new insights into the normal processes of learning and remembrance.

The scientific literature on memory is unique in being dominated by two research subjects, called H.M. and N.A., each of whom suffered a personal tragedy. H.M. suffered a minor head injury when he was seven and began soon after to have seizures. The seizures became progressively worse until, at age 27, he underwent brain surgery. The surgery cured the epilepsy but left H.M. amnestic: Today, as in 1953 when the surgery was performed, he is incapable of laying down new memories.

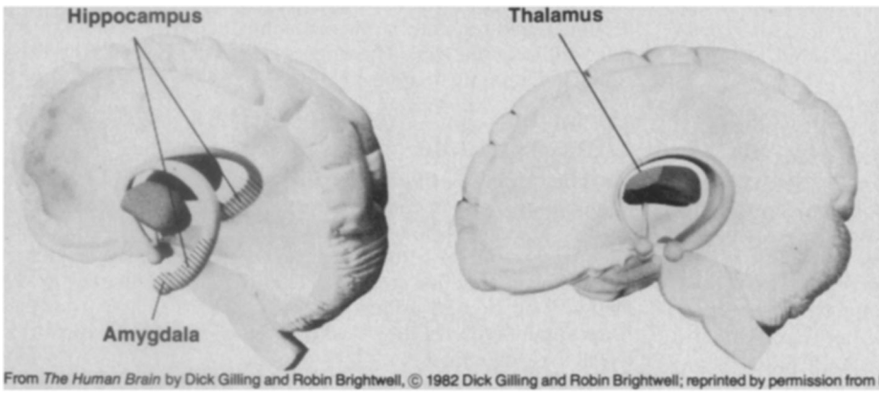
N.A. became amnestic as the result of a freak accident. It was 1960 and he was a young Air Force recruit attending flight school. One day he was in his dormitory room with his roommate, who was fooling around with a miniature fencing foil, thrusting at imaginary foes. N.A. happened to swing around just as his roommate thrust, and the foil entered his right nostril and pierced the middle of his brain.

The misfortunes of H.M. and N.A. have been a boon to memory researchers. Both have been studied for years in memory laboratories, and recently the findings from these two case studies have been integrated with research findings about other kinds of memory failure: amnesia resulting from electroconvulsive therapy (ECT); from chronic alcoholism (known as Korsakoff's syndrome); and from Alzheimer's disease, a form of senility caused by brain atrophy. What these studies are showing is that memory can no longer be viewed as a unitary process: When it fails, it fails in parts, suggesting that it is biologically much more complicated than previously recognized.

Neurology texts have for years described the brain's hippocampus, a small bundle of neurons straddling the middle of the lower brain, as the "gateway to memory." The advantage of studying cases like H.M. and N.A. is that the areas of brain damage, or lesions, are small and can be identified with some precision. Although both suffered cell damage in the brain's limbic system, their lesions are different: In the case of H.M. the surgeon excised most but not all of the hippocampus, the nearby amygdala, and some adjacent neurons; N.A.'s roommate operated with the precision of a surgeon, cutting into the left side of the thalamus.

The placement of these lesions is interesting to memory researchers because, although both men suffer profound amnesia, their disorders are not identical. The most apparent difference is that N.A.'s lesion, confined to the left side of his brain, wiped out his ability to form verbal memories while sparing much of his memory for imagery. H.M., in contrast, suffered damage to both sides of his brain, and his amnesia is much more extensive. According to Massachusetts Institute of Technology psychologist Suzanne Corkin, H.M. has a few "islands of remembering" — he appears to know what an astronaut is, for example, and he knows that someone named Kennedy was assassinated — but these memories are very sparse and thin; she attributes them to the small bit of hippocampus H.M. has remaining. With these rare exceptions, she says, H.M. has global "anterograde" amnesia: Unable to form new memories, he gets by with whatever he learned before 1953.

H.M. and N.A. differ in other respects as well. In fact, according to Larry R. Squire, a neuroscientist at the University of California at San Diego, they may represent two fundamentally different forms of amnesia, one having to do with initial encoding of memories at the time of learning and the other with the consolidation and elaboration of memories for a period of time after



Clinical studies of two severely amnestic men have revealed two fundamentally different kinds of memory failure. One, involving damage to the brain's thalamus, results from an inability to create new memory traces. The other, which involves damage to the hippocampus and amygdala, is an impaired ability to elaborate and consolidate memories during the months following the experience.

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learning takes place. To test this idea, Squire and his co-workers had H.M., N.A. and normal controls study a collection of colored slides for as long as it took for them to learn them; although the amnestics took much longer to memorize the images, they were able to reach a point where, after a ten-minute delay, they demonstrated normal retention. Then the researchers tested the subjects over the next week to see how quickly they forgot their new learning: N.A., they found, forgot at a normal rate, whereas H.M. lost the new memories very rapidly. In addition, Squire conducted the same experiment on Korsakoff patients and patients undergoing ECT, and he found that the Korsakoff patients, like N.A., had normal retention; the ECT patients had rapid rates of forgetting.

Although it is not known for certain which brain regions are affected by ECT, the hippocampal formation is a good candidate because it is known to be sensitive to seizures, Squire says. ECT patients, it appears, experience a temporary version of H.M.'s hippocampal lesion, and they suffer the same (though temporary) form of amnesia — suggesting that the hippocampal region probably plays a role in the fixing of memories during the hours and days following learning. N.A. and Korsakoff patients, in contrast, have intact hippocampal areas but damaged thalamic regions: Because the thalamus is thought to be responsible for giving the original "print" order for a memory, it follows that the amnesia of these patients is related to their impaired ability to form a memory initially.

These findings might also help explain another interesting difference between H.M. and N.A.: N.A.'s remote memory—for learning that took place before his accident—is unimpaired; but H.M. appears to have lost some of his remote memories as well, particularly those from the few years just prior to the surgery. Brenda Milner of McGill University in Montreal, the scientist who originally studied H.M., has speculated that this brief retrograde amnesia was the result of a problem with consolidation of memories due to the hippocampal damage. In order to investigate this hypothesis, Squire recently tested ECT patients — those with the analagous brain disruption—on their memories for television programs that were cancelled after one season: Although their remote memories were intact before the ECT treatments, the shock to the hippocampal region dislodged only memories for programs that had run during the past few years. What this suggests, Squire says, is that the consolidation of memories—presumably involving the hippocampal region—can continue for a few years. This evidence suggests an answer to a long-standing question in memory research: Is amnesia a memory storage or a memory retrieval problem? If it were a retrieval problem, Squire says, then amnestic patients should be equally poor at remembering old and very old memories. They are not, suggesting that the age of the memories themselves at the time of brain damage determines whether they are lost or retained.

The idea that different anatomical structures in the limbic system have different memory functions is receiving support from animal studies. National Institute of Mental Health (NIMH) psychologist Mortimer Mishkin has been working with monkeys, selectively cutting either the hippocampus or the amygdala, and he has found that the two regions are involved in parallel but distinct memory circuits. In the first, he explains, the neocortex (the higher part of the brain where perception takes place) signals the hippocampus, which in turn stimulates the thalamus, which orders the print: This circuit, Mishkin believes, is involved in the processing of spatial memories. It stores the information necessary to give an image a geographical context.

The second circuit, operating from the cortex through the amygdala to the thalamus, is involved in the storage of emotional memories. If a face, for example, is perceived as joyful or fearful, that aspect of the memory is processed through the amygdala. Mishkin speculates that there may be dozens of parallel memory pathways, each involved in transmitting and fixing a different aspect of an experience—texture, color, size, time. Brain damage, then, could be expected to impair different aspects of memory: These findings might help explain an unusual case, reported in the literature, where a woman lost all memories of former acquaintances, but continued to respond with appropriate emotions to those she had liked and those she had not.

H.M., of course, had his entire amygdala and most of his hippocampal region excised, which would explain why his amnesia is so extensive. But the finding from recent research that is perhaps most intriguing is that even H.M., with his severe impairment, appears capable of certain kinds of new learning. Experiments by Corkin and her colleagues have shown that he is perfectly capable of learning new skills; his "procedural" memory, as opposed to his "declarative" memory, is intact. Moreover, the skills that H.M. has mastered are not merely motor skills, Corkin says; he can learn motor skills, such as hitting a tennis ball, but he has also proven himself capable of perceptual skills—mirror reading, for example—and intellectual skills—such as puzzle solving. And he acquires these skills while forgetting the training sessions themselves. Squire, too, has found skill learning preserved in N.A. and in Korsakoff patients, and both researchers have come to the same conclusion: The brain makes a fundamental distinction between knowledge and skill.

The implication of this finding, should it hold up, is stunning. The most divisive issue in modern psychology has been human learning: Do people acquire and store knowledge and then act on the basis of ideas, as cognitive psychologists argue? Or, as behaviorists believe, are humans merely conditioned by their interactions with the environment, forming innumerable stimulus-response bonds that guide behavior? Mishkin suggests that both kinds of learning—memories and "habits"—are involved in laying down the effects of experience, and he has demonstrated the distinction in animal experiments. Monkeys with limbic lesions are incapable of putting down associative memories—an object and food, for example—but with repeated trials over a long period of time they are able to learn the habit of approaching a particular object, when approaching is continually rewarded with food. The monkeys are not intellectually processing and storing information, Mishkin says; indeed, they cannot store information. Yet they were equal to the normal control monkeys in learning, suggesting to

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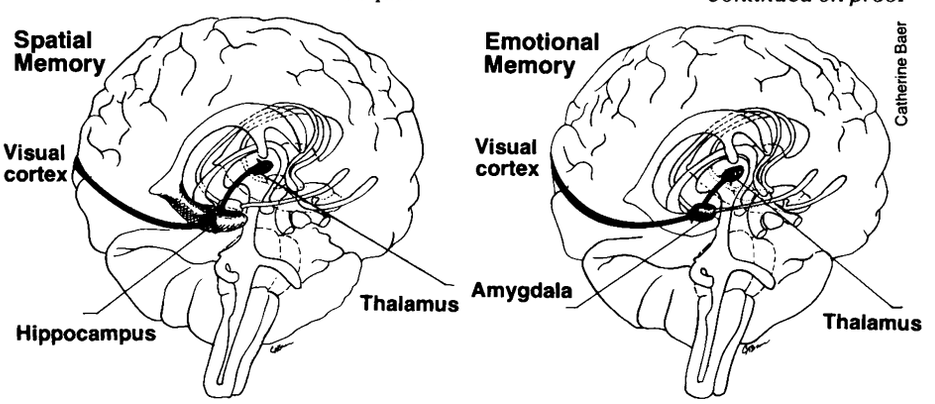


Scientists think that different aspects of an experience may be memorized using different brain pathways. When spatial memories are laid down, the brain's visual cortex, which perceives the image, signals the hippocampus, which in turn tells the thalamus to "print" (left). But if the significant content of the experience is emotional in nature, the cortex signals the amygdala instead, which relays the storage command to the thalamus (right). Other still unknown pathways may be involved in storing other aspects of an experience.

One Archive of Memory

A rabbit hears a tone and shortly thereafter feels an unpleasant puff of air on its eyeball. It doesn't take many repetitions of this incident before the rabbit closes its eyelid when it hears the tone. The memory of the link between tone and air puff is stored in the rabbit's brain, and scientists now report they are determining precisely where that memory trace, as they call it, is.

The nature and location of memories has been one of the most baffling problems in biology. Psychologist Karl Lashley remarked, after almost 25 years of fruitless searching, that memory should not be possible. He had done experiments removing different regions of rat cerebral cortex, but he could not find the rat's mechanism for storing information nor locate the storage area. This sort of experiment led to the concept that memories are somehow widely distributed, like holograms, in the brain. But psychologist Richard F. Thompson of Stanford University now presents evidence to the contrary.

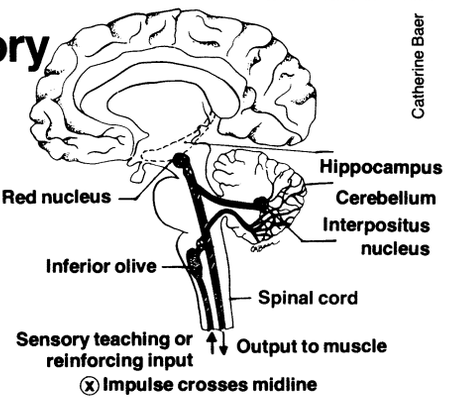
"We have been the first to demonstrate unequivocably in a mammalian brain a memory trace circuit that is highly localized," Thompson said at the recent meeting in Boston of the Society for Neuroscience. "Loss of cellular tissue no greater than 1 cubic millimeter can destroy the memory for a specific learned response," he reports.

Thompson and David A. McCormick, also at Stanford, have worked out the brain circuits involved in a rabbit's learning to close the lid of one eye in response to a tone. They surgically or chemically destroy brain cells on one side of the brain in specific locations deep in the structure called the cerebellum, which is known to be involved in controlling motor activities. After treatment, the rabbit no longer responds to a tone by closing the trained eye nor can it be retrained to close that eye in response to the tone. "There is no recovery and no back-up," Thompson says.

The loss is specific to the learned association. The animal still can close its eyelid—it will do so as a reflex. And the rabbit can still hear the tone. The opposite eye can still be trained to close in response to a puff of air.

Cellular activity provides another indication that the cerebellum is involved in the learning process. When the scientists record the electrical activity of cells within certain areas of the cerebellum, they observe a characteristic pattern that develops during training and precedes the learned response in a test situation.

Thompson and colleagues find that the simple eyeblink learning task also requires both a bundle of nerve fibers, called the superior cerebellar peduncle, that carry signals from the cerebellum and, on the opposite side of the brain, the mid-brain area called the red nucleus.



Catherine Baer

Tracing a memory: A simple learned motor response involves nerve cells in the lower regions of the brain. Information of sensory stimuli is carried by fibers of the spinal cord to the inferior olive, and the training aspect of this information then goes to the cerebellum, where it is processed in the interpositus nucleus, Thompson proposes. This memory is converted to action by a pathway that carries signals to the red nucleus on the opposite side of the brain. Then the path crosses back and descends to act on the nerve cells that go to muscles. Slightly more complex learning situations also employ the hippocampus, which lies deep in this view of the midline plane of the brain.

The circuitry necessary for the eyeblink learned response is not specific just for that one task. A similar learning situation also seems to depend on the same brain structures, called the interpositus nuclei of the cerebellum. Thompson and N. H. Donegan have taught rabbits to associate a tone with an electric shock to one hindpaw, and therefore to withdraw the leg when they hear the tone. Surgical lesions of the cerebellum abolish this learned response. These results indicate that the lesion effects of McCormick, Thompson and colleagues are not peculiar to the eyeblink system. Thompson and Donegan propose from the leg withdrawal work that the cerebellum is an essential part of the circuitry for classical conditioning of discrete voluntary muscle response, at least with aversive training stimuli.

The exact position of the cerebellar lesion that disrupts the hindlimb learned response is nearer the midline of the brain than the lesion that disrupts the eyeblink response. Thompson says that these positions agree exactly with the representation of the body on the interpositus nucleus just reported at the Boston meeting by James Houk of Northwestern University in Chicago. "It's a beautiful, beautiful fit," Thompson says.

The cerebellum is certainly not the sole seat of memory, according to Thompson. Some forms of learning clearly do not employ the brain circuits used in the eyeblink and leg withdrawal tasks. Such distinct forms of learning include the increase in heart rate known as learned fear and also human language learning. Thompson expects these and other types of learning to use different, but specific, pathways in the brain, like those described by Mishkin and Squires but not yet analyzed in fine detail (see p. 379).

Higher regions of the brain are not essential for the simple learning tasks of eyeblink and leg withdrawal. But Thompson has demonstrated that a slight change in the task, making greater demands on the animal, can call higher systems into play. Suppose in the rabbit eyeblink training, there is a pause of a half second between the end of the tone and the start of the air puff. In this case, when parts of the brain structure called the hippocampus have been destroyed an animal will not learn to close its eye. Also, scientists find that neuronal activity in the hippocampus reflects learning of the task. The hippocampus has already been shown essential in certain forms of monkey and human memory.

Clues about the cellular basis for simple learning have come out of Thompson's experiments. Work with Jack D. Barchus of Stanford has demonstrated that certain chemicals that interfere with signal transmission (via the inhibitory neurotransmitter GABA) between nerve cells can selectively and reversibly wipe out the memory trace. Another chemical, in contrast, strengthens the learned response, Thompson says. The findings suggest that a critical aspect of the memory trace system involves removing inhibitory control of specific neurons, rather than just increasing excitation.

But where is a memory? At what point is a sensory cue linked to a specific motor program? Thompson expects it to be in the region demarcated by the circuitry, although it might be in one of the few areas that feed into this circuitry. "We don't know now just where the trace is stored, but it is just a matter of time," he says.

The problem of locating memories has been a barrier to analyzing cellular mechanisms of information storage and retrieval in mammals. "No one has known where to look," Thompson says. "Now these seemingly impossible problems are beginning to be solved." He predicts the solutions will provide a whole range of new ideas about the brain and about information processing.

—Julie Ann Miller

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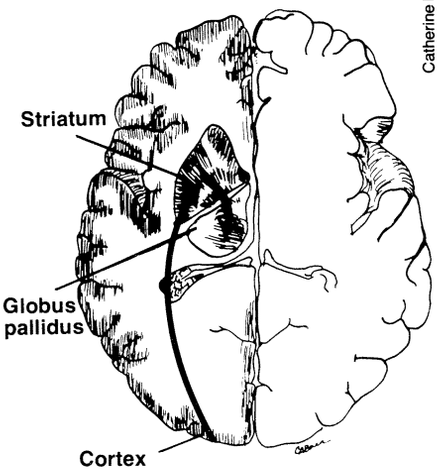
Mishkin that they have gradually acquired a long list of stimulus-response bonds. Where memorizing seems to be quick and effortful, habitual learning is automatic, building up slowly as the result of continuous reinforcement.

This distinction might help explain the finding of another NIMH psychologist, Herbert Weingartner, that normal human subjects learn in two ways — with and without effort. With work, people can store a long list of words, but even while doing so they are also noticing and storing the wallpaper design, the furniture, faces of strangers. And Weingartner has found that when effortful memory is impaired — in patients with Parkinsonism, for example — automatic memory is spared. In addition, Weingartner notes, effortful memory can be enhanced with certain drugs; automatic memory cannot.

The distinction between habits and memories may also help explain another phenomenon that has long puzzled memory researchers — so-called childhood amnesia. Human infants are obviously learning, yet adults rarely have memories from early childhood. Freud suggested that, for emotional reasons, childhood memories were repressed; indeed, the practice of psychoanalysis is founded on the belief that the memories are there, just difficult to get at. But Mishkin believes that the answer is simpler: The memory system of the brain develops later than the habit system.

In order to test this theory, Mishkin tested monkeys of different ages on both a memory task and habit acquisition task.

Habit System



Catherine Baer

Clinical studies suggest that some kinds of learning — specifically skill learning — may not involve memory at all. One theory is that the cortex signals a brain region called the striatum, completely bypassing the memory system. The striatum might then stimulate the adjacent globus pallidus, a sub-cortical motor area, thus forming a bond between a perceived stimulus and a motor response.

The memory task is a very simple association task that adult monkeys mastered very quickly, Mishkin notes, but the young monkeys were unable to succeed until they were close to six months old; and they did not reach adult proficiency until they were close to two years old. In contrast, even the three-month-old monkeys were as proficient as adults on the conditioning task.

Just where the habit system is located in the brain remains unclear, but Mishkin speculates that it is another sub-cortical region known as the striatal complex. From an evolutionary perspective, the striatal area is older than the limbic system and the cortex, and so is present in the brains of lower animals that are capable of rudimentary learning; and there is some evidence, Mishkin says, that it precedes the limbic system in normal development. In addition, it is positioned in such a way that it can easily receive sensory information from the cortex and, in turn, signal the motor areas of the brain — thus creating the stimulus-response bonds that show up as habits.

What does all this mean to those suffering from amnesia? Storybook amnesia is cured as simply as it is caused — with a blow to the head — but unfortunately science is far from providing any such solution. Indeed, the lives of H.M. and N.A. stand as dramatic testimony to the importance of memory in every aspect of human behavior. Neither can work, and both live lives of isolation. N.A., less impaired, can find his way home sometimes, although as Squire describes it, it is like he is finding his way around a town he hasn't been to in 20 years. H.M. spends his days watching TV and doing crossword puzzles — with the vocabulary he had at age 27. Although he is 55 now, he is the same good-natured and polite young man who entered the operating room in 1953 seeking a cure for epilepsy. He has described his perspective to Corkin: Every minute, he says, is like waking from a dream. □

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Enjoy Old Age: A Program of Self-Management — B.F. Skinner and M.E. Vaughan. This book is based on a paper delivered at the American Psychological Association meeting in August 1982 (SN: 8/28/82, p. 141). Skinner, at 79, shares what he has learned about aging from experience, training and research. Vaughan, an expert in the field, has distilled information and practical suggestions from the literature on aging. Norton, 1983, 157 p., $11.95.

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The Guinness Book of Astronomy: Facts & Feats — Patrick Moore. Completely updated, this second edition includes new sections on Venus and Mars and new information about Jupiter and Saturn. The star catalogue has been amended to the year 2000. Guinness (Sterling), 2nd ed., 1983, 289 p., color/b&w illus., $19.95, paper, $12.95.

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The Illustrated Dinosaur Dictionary — Helen Roney Sattler, foreword by John H. Ostrom. Dinosaurs have been known to the world for only a little more than a century and a half. Of the approximately 300 kinds included here almost 100 were discovered and named in the last 20 years. This book is an alphabetical guide to dinosaurs and some other prehistoric animals with descriptions of the animals in simple language together with line drawings of many of these fascinating creatures. Lothrop, 1983, 315 p., color/b&w illus., $17.50.

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The Tangled Wing: Biological Constraints on the Human Spirit — Melvin Konner. A well-written, well-balanced synthesis of human nature that includes the latest research findings. Originally published in hardback by Holt, Rinehart & Winston in 1982. Har-Row, 1983, 543 p., paper $8.95.