Amnesia: Declarative and Nondeclarative Memory

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Introduction

Amnesia refers to difficulty in learning new information or in remembering the past. It is important to distinguish the amnesia that occurs following brain injury or disease (neurological amnesia) from the rarer functional (or psychogenic) amnesia that can occur as the result of an emotional trauma. Neurological amnesia has a variety of origins, including prolonged alcoholism, a temporary loss of blood supply or oxygen to the brain, and diseases such as herpes simplex encephalitis. All these conditions preferentially damage the medial temporal lobe or diencephalon. Neurological amnesia causes severe difficulty in learning new facts and events (anterograde amnesia). Amnesic patients also typically have some difficulty remembering facts and events that were acquired before the onset of amnesia (retrograde amnesia). Functional amnesia shows a different pattern of anterograde and retrograde memory impairment. Functional amnesia is characterized by a profound retrograde amnesia that is transient in some cases, and little or no anterograde amnesia is exhibited.

Functional Amnesia

Functional amnesia, also known as dissociative amnesia, is a dissociative psychiatric disorder that involves alterations in consciousness and identity. Although no particular brain structure or brain system is implicated in functional amnesia, the cause of the disorder must be due to abnormal brain function of some kind. Its presentation varies considerably from individual to individual, but in most cases, functional amnesia is preceded by physical or emotional trauma and occurs in association with some prior psychiatric history. Often, the patient is admitted to the hospital in a confused or frightened state. Memory for the past is lost, especially autobiographical memory and even personal identity. Semantic or factual information about the world is often preserved, though factual information about the patient's life may be unavailable. Despite profound impairment in the ability to recall information about the past, the ability to learn new information is usually intact. The disorder often clears, and the lost memories return. Occasionally, the disorder lasts longer, and sizable pieces of the past remain unavailable.

Etiology of Neurological Amnesia

Neurological amnesia results from a number of conditions, including Alzheimer's disease or other dementing illnesses, temporal lobe surgery, chronic alcohol abuse, encephalitis, head injury, anoxia, ischemia, infarction, and the rupture and repair of an anterior communicating artery aneurism. The common factor in all these conditions is that they disrupt normal function in one of two areas of the brain – the medial aspects of the temporal lobe and the diencephalic midline. Global amnesia results from bilateral damage, whereas material-specific amnesia results from unilateral damage. Typically, left-sided damage affects memory for verbal material, and right-sided damage affects memory for nonverbal material (e.g., the recall of faces and spatial layouts).

Anatomy

Well-studied cases of human amnesia and animal models of amnesia provide information about the neural connections and structures that are damaged in neurological amnesia. Damage limited to the hippocampus itself is sufficient to cause amnesia. For example, in one carefully studied case of amnesia (patient R.B.), the only significant damage was a bilateral lesion confined to the CA1 field of the hippocampus. The severity of memory impairment is exacerbated by additional damage outside the hippocampus. Thus, severe amnesia results when damage extends beyond the hippocampus to include adjacent structures in the medial temporal lobe, including the parahippocampal cortex, entorhinal cortex, and perirhinal cortex. Another well-studied case (H.M.) had surgery in 1953 to treat severe epilepsy. Most of the hippocampus and much of the surrounding medial temporal lobe cortices were removed bilaterally (the entorhinal cortex and most of the perirhinal cortex). Although the surgery was successful in reducing the frequency of H.M.'s seizures, it resulted in a severe and persistent amnesia.

Functional magnetic resonance imaging (fMRI) of healthy individuals who are engaged in learning and remembering reveals neural activity in the same structures that, when damaged, cause amnesia. It is also possible through structural imaging (MRI) to detect and quantify the neuropathology in amnesic patients. Many patients with restricted hippocampal damage have an average reduction in hippocampal volume of about 40%. Two such patients whose brains were available for detailed, postmortem neurohistological analysis (patients L.M. and W.H.) proved to have lost virtually all the neurons in the cornu ammonis (CA)

fields of the hippocampus. These observations suggest that a reduction in hippocampal volume of approximately 40%, as estimated from MRI scans, likely indicates the near complete loss of hippocampal neurons. The amnesic condition is associated with neuronal death and tissue collapse, but the tissue does not disappear altogether because fibers and glial cells remain.

As questions about amnesia and the function of medial temporal lobe structures have become more sophisticated, it has become vital to obtain detailed, quantitative information about the damage in the patients being studied. In addition, single-case studies are not nearly so useful as group studies involving well-characterized patients. In the case of patients with restricted hippocampal damage, one can calculate the volume of the hippocampus itself as a proportion of total intracranial volume. One can also calculate the volumes of the adjacent medial temporal lobe structures (the perirhinal, entorhinal, and parahippocampal cortices), again in proportion to intracranial volume. Last, when there is extensive damage to the medial temporal lobe, it is important to calculate the volumes of lateral temporal cortex and other regions that might be affected. It is important to characterize patients in this way in order to address the kinds of questions now being pursued in memory research.

To understand the anatomy of human amnesia, and ultimately the anatomy of normal memory, animal models of human amnesia have been established in the monkey and in the rodent. In the monkey, following lesions of the bilateral medial temporal lobe or diencephalon, memory impairment is exhibited on the same kinds of tasks of new learning ability that human amnesic patients fail. Cumulative work with animal models suggests that the full medial temporal lobe memory system consists of the hippocampus and adjacent, anatomically related structures, including the entorhinal cortex, parahippocampal cortex, and perirhinal cortex (see Figure 1). When these adjacent structures are damaged, the severity of amnesia is greater than when only the hippocampus itself is damaged.

The important structures in the diencephalon are the mediodorsal thalamic nucleus, the anterior thalamic nucleus, the internal medullary lamina, the mammillary nuclei, and the mammillo-thalamic tract. Because diencephalic amnesia resembles medial temporal lobe amnesia in the pattern of sparing and loss, these two regions likely form an anatomically linked, functional system.

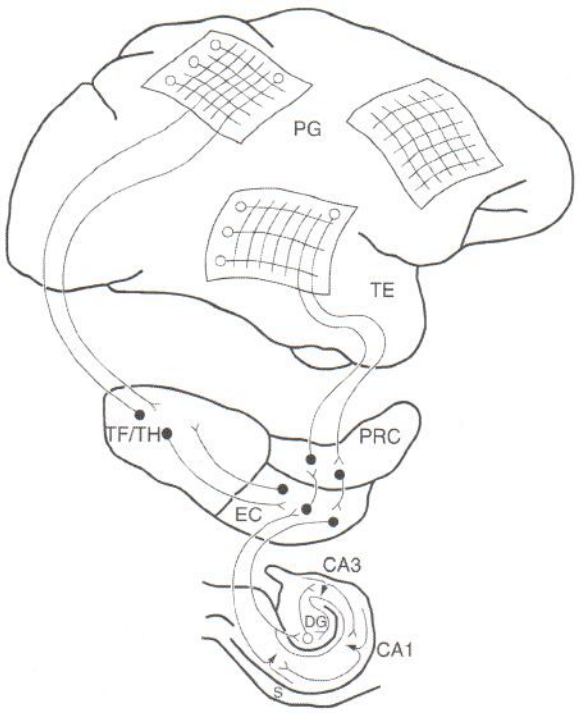

Figure 1 Schematic drawing of primate neocortex together with the structures and connections in the medial temporal region important for establishing long-term memory. The networks in the cortex show putative representations concerning visual object quality (in area TE) and object location (in area PG). If this disparate neural activity is to cohere into a stable long-term memory, convergent activity must occur along projections from these regions to the medial temporal lobe. Projections from neocortex arrive initially at the parahippocampal gyrus (TF/TH) and perirhinal cortex (PRC) and then at entorhinal cortex (EC), the gateway to the hippocampus. Further processing of information occurs in the several stages of the hippocampus, first in the dentate gyrus (DG) and then in the CA3 and CA1 regions. The fully processed input eventually exits this circuit via the subiculum (S) and the EC, where widespread efferent projections return to neocortex. The hippocampus and adjacent structures are thought to support the stabilization of representations in distributed regions of neocortex (e.g., TE and PG) and to support the strengthening of connections between these regions. Subsequently, memory for a whole event (for example, a memory that depends on representations in both TE and PG) can be revivified even when a partial cue is presented. Damage to the medial temporal lobe system causes anterograde and retrograde amnesia. The severity of the deficit increases as damage involves more components of the system. Once sufficient time has passed, the distributed representations in neocortex can operate independent of the medial temporal lobe. (This diagram is a simplification and does not show diencephalic structures involved in memory function.)

The Nature of Amnesia

It is important to appreciate that amnesic patients are not impaired at all kinds of memory. The major distinction is between declarative and nondeclarative memory. Only declarative memory is affected in amnesia. Declarative memory refers to the capacity to remember the facts and events of everyday life. It is the kind of memory that is meant when the term 'memory' is used in ordinary language. A declarative memory can be brought to mind as a conscious recol-

lection. Declarative memory provides a way to model the external world, and in this sense it is either true or false. The stored representations are flexible and can guide successful performance under a wide range of test conditions. Finally, declarative memory is especially suited for rapid learning and for forming and maintaining associations between arbitrarily different kinds of material (e.g., learning to associate two different words).

Anterograde Amnesia

Amnesia is characterized especially by profound difficulty in new learning. This impairment is referred to as anterograde amnesia. Amnesia can occur as part of a more global dementing disorder that includes other cognitive deficits, including impairments in language, attention, visuospatial abilities, and general intellectual capacity. However, amnesia can also occur in the absence of other cognitive deficits and without any change in personality or social skills. In this more circumscribed form of amnesia, patients have intact intellectual functions and intact perceptual functions, even on difficult tests that require the ability to discriminate between similar images containing overlapping features. Patients also have intact immediate memory (as measured, for example, by the ability to repeat a short string of digits). Their intact immediate memory explains why amnesic patients can carry on a conversation and appear quite normal to the casual observer. Indeed, if the amount of material to be remembered is not too large (e.g., a three-digit number), then patients can remember the material for minutes, or as long as they can hold it in mind by rehearsal. One would say in this case that the patients have carried the contents of immediate memory forward by engaging in explicit rehearsal. This rehearsal-based activity is referred to as working memory. The difficulty for amnesic patients arises when an amount of information must be recalled that exceeds immediate memory capacity (typically, when a list of eight or more items must be remembered) or when information must be recalled after a distraction-filled interval or after a long delay. In these situations, patients will remember fewer items than will their healthy counterparts.

Amnesic patients are impaired on tasks of new learning, regardless of whether memory is tested by free recall, recognition (e.g., presenting an item and asking whether it was previously encountered), or cued recall (e.g., asking for recall of an item when a hint is provided). In addition, the memory impairment involves not just difficulty in learning about specific episodes and events that occurred in a certain time and place (episodic memory), but also difficulty in learning factual information (semantic memory). Finally, the memory deficit is present regardless of the sensory modality in which information is presented (visual, auditory, olfactory, and so on).

Retrograde Amnesia

In addition to impaired new learning, amnesia also impairs memories that were acquired before the onset of amnesia. This type of memory loss is referred to as retrograde amnesia. Retrograde amnesia is usually temporally graded. That is, information acquired in the distant past (remote memory) is spared relative to more recent memory. The extent of retrograde amnesia can be relatively short and encompass only 1–2 years, or it can be more extensive and cover a much longer time. For example, an amnesic patient can have retrograde amnesia covering the previous one or two decades. In contrast, memories for the facts and events of childhood and adolescence can be intact. The severity and extent of retrograde amnesia is determined by the locus and extent of damage. Patients with restricted hippocampal damage have a limited retrograde amnesia covering a few years prior to the onset of amnesia. Patients with large medial temporal lobe damage have extensive retrograde amnesia covering decades.

The sparing of remote memory relative to more recent memory illustrates that the brain regions damaged in amnesia are not the permanent repositories of long-term memory. Instead, memories undergo a process of reorganization and consolidation after learning, during which time the neocortex becomes more important. During the process of consolidation, memories are vulnerable if there is damage to the medial temporal lobe or diencephalon. After sufficient time has passed, storage and retrieval of memory no longer require the participation of these brain structures. Memory is at that point supported by neocortex. The areas of neocortex important for long-term memory are thought to be the same regions that were initially involved in the processing and analysis of what was to be learned. Thus, the neocortex is always important, but the structures of the medial temporal lobe and diencephalon are also important during initial learning and during consolidation.

Spatial Memory

Discussions of amnesia have focused especially on the status of spatial memory because of the discovery of 'place cells' in the rodent hippocampus and the possible importance of the hippocampus in forming spatial maps. In human amnesia, spatial memory is impaired along with other forms of declarative memory. Patients have difficulty acquiring new spatial knowledge, and they are impaired in remembering recently acquired spatial knowledge. However, as is the case with other forms of declarative memory, remote spa-

tial knowledge is intact. One well-studied patient with large medial temporal lobe lesions and severe amnesia (E.P.) was able to mentally navigate his childhood neighborhood, use alternate and novel routes to describe how to travel from one place to another, and point correctly to locations in the neighborhood while imagining himself oriented at some other location. These findings show that the medial temporal lobe is not needed for the long-term storage of spatial knowledge and does not maintain a spatial layout of learned environments that is necessary for successful navigation. Accordingly, the available data support the view that the hippocampus and related medial temporal lobe structures are involved in learning new facts and events, both spatial and nonspatial. Further, these structures are not repositories of long-term memory, either spatial or nonspatial.

Nondeclarative Memory

It is a striking feature of amnesia that many kinds of learning and memory are spared. Memory is not a unitary faculty of the mind but is composed of many parts that depend on different brain systems. Amnesia impairs only declarative memory and spares nondeclarative memory. Nondeclarative memory refers to a heterogeneous collection of abilities, all of which afford the capacity to acquire knowledge nonconsciously. Nondeclarative memory includes motor skills, perceptual and cognitive skills, priming, adaptation-level effects, simple classical conditioning, and habits, as well as phylogenetically early forms of experience-dependent behavior such as habituation and sensitization. In these cases, memory is expressed through performance rather than recollection, and performance does not require reflection on the past or even the knowledge that memory is being influenced by past events. For example, in the case of motor skills, one can learn how to ride a bicycle but be unable to describe what has been learned, at least not in the same sense that one might recall riding a bicycle on a particular day with a friend. Perceptual skills include such things as reading mirror-reversed print and searching a display quickly to find a hidden letter. In formal experiments, amnesic patients acquire perceptual skills at the same rate as individuals with intact memory, even though the patients may not remember performing the task.

Priming refers to an improved ability to identify a word or other item as a result of its prior presentation. For example, suppose that a line drawing of a dog, hammer, and airplane are presented in succession, with the instruction to name each item as quickly as possible. Typically, about 800 ms are needed to produce each name aloud. If in a later test these same pictures are presented intermixed with new drawings, the new drawings will still require about 800 ms to name, but now the dog, hammer, and airplane are named about 100 ms more quickly. The improved naming time occurs independent of whether one remembers having seen the items earlier. Furthermore, amnesic patients exhibit this effect at full strength, despite having a poor memory of seeing the items earlier. Priming effects of this kind can persist across intervals as long as several weeks. In formal experiments, severely amnesic patients had intact priming for recently presented words, even when the patients performed at guessing levels (50% correct) on tests that asked them to recognize which words were presented previously and which were not. This result shows that priming is fully independent of declarative memory.

Adaptation-level effects refer to changes in judgments about stimuli (e.g., their heaviness or size) that are caused by recent experience. For example, experience with light-weighted objects subsequently causes other objects to be judged heavier than they would be if the light-weighted objects had not been presented. Amnesic patients show this effect to the same degree as healthy individuals, though they have difficulty remembering what they have done.

Classical conditioning refers to the development of an association between a previously neutral stimulus and an unconditioned stimulus. One of the best-studied examples of classical conditioning in humans is eyeblink conditioning. In a typical conditioning procedure, a tone repeatedly precedes a mild air puff directed to the eye. After a number of pairings, the tone comes to elicit an eyeblink in anticipation of the air puff. Amnesic patients acquire the tone-air puff association at the same rate as healthy individuals do. In both groups, awareness of the temporal contingency between the tone and the air puff is unrelated to successful conditioning. Simple classical conditioning, where the tone overlaps with the air puff and terminates with it, is dependent on the cerebellum.

Habit learning refers to the gradual acquisition of associations between stimuli and responses, such as learning to make one choice rather than another. Habit learning depends on the neostriatum (basal ganglia). Many tasks can be acquired either declaratively, through memorization, or nondeclaratively, as a habit. For example, healthy individuals will solve many trial and error learning tasks quickly by simply engaging declarative memory and memorizing which responses are correct. In this circumstance, amnesic patients are disadvantaged. However, tasks can also be constructed that defeat memorization strategies, for example, by making the outcomes on each trial probabilistic. In such a case, amnesic patients and healthy individuals learn at the same

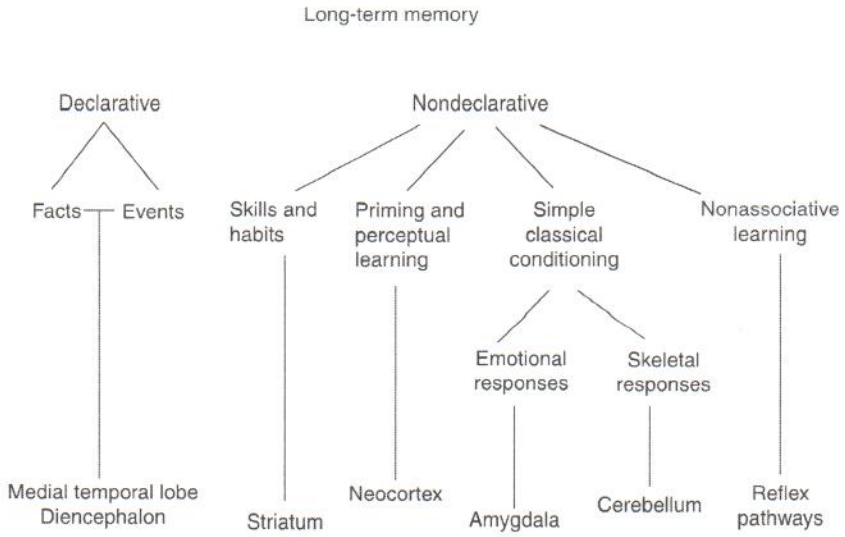

Figure 2 Classification of mammalian long-term memory systems. The taxonomy lists the brain structures thought to be especially important for each form of declarative and nondeclarative memory. In addition to the central role of the amygdala in emotional learning, it is able to modulate the strength of both declarative and nondeclarative learning.

gradual rate. It is also true that severely amnesic patients who have no capacity for declarative memory can gradually acquire trial-and-error tasks, even when the task can be learned declaratively by healthy individuals. In this case they succeed by engaging habit memory.

This situation is nicely illustrated by the eight-pair concurrent discrimination task, which requires individuals to learn the correct object for each of eight object pairs. Healthy individuals learn all eight pairs in a single test session. Severely amnesic patients acquire this same task over many weeks, even though at the start of each session they cannot describe the task, the instructions, or the objects. It is known that this task is acquired at a normal (slow) rate by monkeys with medial temporal lobe lesions and that monkeys with lesions of the neostriatum (basal ganglia) are impaired. Thus, humans appear to have a robust capacity for habit learning that operates outside awareness and independent of the medial temporal lobe structures that are damaged in amnesia.

These examples illustrate that nondeclarative memory is distinct from declarative memory. It is spared in amnesia, and it operates outside awareness. Nondeclarative forms of memory depend variously on the neostriatum, the amygdala, the cerebellum, and on processes intrinsic to neocortex (Figure 2).

Summary

The study of amnesia has illuminated the nature of memory disorders and has also led to a better understanding of the neurological foundations of memory. Experimental studies in patients, neuroimaging studies of healthy volunteers, and related studies in experimental animals continue to reveal insights about what memory is and how it is organized in the brain. As more is learned about the neuroscience of memory, about how memory works, more opportunities will arise for achieving better diagnosis, treatment, and prevention of diseases and disorders that affect memory.

See also: Animal Models of Amnesia; Episodic Memory; Functional Amnesia; Hippocampus: Computational Models; Memory Disorders; Recognition Memory; Semantic Memory.

Further Reading

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Relevant Websites

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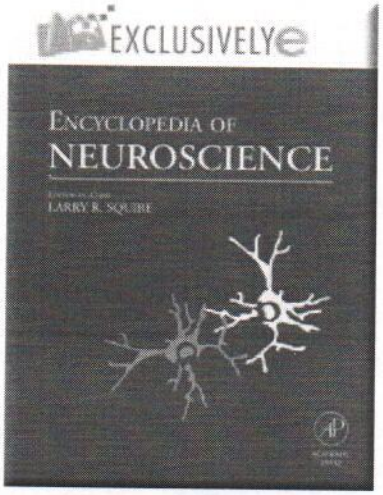
http://whoville.ucsd.edu – Home page of Larry R. Squire.
http://www.nia.nih.gov – National Institute on Aging, Alzheimer's Disease Centers.



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