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3.04 Declarative Memory System: Amnesia

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3.04.1 Introduction

Memory is not a single entity but is composed of several separate systems (Squire, 1992; Schacter and Tulving, 1994). Long-term memory can be divided into several parallel memory systems. The major distinction is between declarative and nondeclarative memory. Declarative memory refers to conscious knowledge of facts and events. Nondeclarative memory refers to a collection of nonconscious knowledge systems that provide for the capacity of skill learning, habit formation, the phenomenon of priming, and certain other ways of interacting with the world. The terms "explicit memory" and "implicit memory" are sometimes used as well and have approximately the same meanings as declarative and nondeclarative memory, respectively.

The brain is organized such that declarative memory is a distinct and separate cognitive function, which can be studied in isolation from perception and other intellectual abilities. Significant information about how memory is organized has come from the study of patients with memory disorders (amnesia) and from animal models of amnesia. Amnesia (neurological amnesia and functional amnesia) refers to difficulty in learning new information or in remembering the past.

Neurological amnesia is characterized by a loss of declarative memory. It occurs following brain injury or disease that damages the medial temporal lobe or diencephalon. Neurological amnesia causes severe difficulty in learning new facts and events (anterograde amnesia). Patients with neurological amnesia also typically have some difficulty remembering facts and events that were acquired before the onset of amnesia (retrograde amnesia).

Functional amnesia is rarer than neurological amnesia and can occur as the result of an emotional trauma. It presents as a different pattern of anterograde and retrograde memory impairment than neurological amnesia. Functional amnesia is characterized by a profound retrograde amnesia with little or no anterograde amnesia. In some cases, patients fully recover. Functional amnesia is a psychiatric disorder, and no particular brain structure or region is known to be damaged.

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3.04.2 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 of these conditions is the disruption of normal function in one of two areas of the brain – the medial aspects of the temporal lobe and the diencephalic midline. Bilateral damage results in global amnesia, and unilateral damage results in material-specific amnesia. Specifically, left-sided damage affects memory for verbal material, while right-sided damage affects memory for nonverbal material (e.g., memory for faces and spatial layouts).

3.04.3 Anatomy

Well-studied cases of human amnesia and animal models of amnesia provide information about the neural connections and structures that are damaged. In humans, damage limited to the hippocampus itself is sufficient to cause moderately severe amnesia (Smith et al., 2013). 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 (Zola-Morgan et al., 1986). The severity of memory impairment is exacerbated by additional damage outside of the hippocampus. Thus, severe amnesia results when damage extends beyond CA1 to the rest of the hippocampus and to the adjacent cortex. (Animal studies later elucidated the critical anatomical components of this memory system; see following.) One 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.

It is also possible through structural magnetic resonance 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 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 (Rempel-Clower et al., 1996). The amnesic condition is associated with neuronal death and tissue collapse, but the tissue does not disappear altogether because fibers and glia remain. In patients with larger lesions of the medial temporal lobe, volume reduction as measured by MRI is more dramatic. For example, patient E.P., who became amnesic as a result of viral encephalitis, has damage to all of the perirhinal cortex, all of the entorhinal cortex, virtually all of the hippocampus, and most of the parahippocampal cortex (Stefanacci et al., 2000).

As questions about amnesia and the function of medial temporal lobe structures have become more specific, 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 as 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) 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 to address the kinds of questions now being pursued in studies of memory and the brain.

Functional MRI (fMRI) of healthy individuals who are engaged in learning and remembering allows one to ask what brain areas are associated with these memory processes. The same tasks that are administered to amnesic patients can also be administered to healthy individuals while their brain activation is measured. fMRI reveals activation during these tasks of learning and remembering in the same structures that, when damaged, cause amnesia.

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 (Fig. 1) and in the rodent. An animal model of human amnesia was established in the monkey in the early 1980s (Mishkin, 1982; Squire and Zola-Morgan, 1983). 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. The same animals succeed at tasks of motor skill learning. They also do well at learning pattern discriminations, which share with motor skills the factors of incremental learning and repetition over many trials.

Systematic and cumulative work in monkeys succeeded in identifying the system of structures in the medial temporal lobe essential for memory (Squire and Zola-Morgan, 1991). The important structures are the hippocampal region (hippocampus proper, dentate gyrus, and subiculum) and adjacent, anatomically related structures (entorhinal cortex, perirhinal cortex, and parahippocampal cortex). The amygdala, although critical for aspects of emotional learning (Davis, 1994; LeDoux, 1996) and for the enhancement of declarative memory by emotion (Adolphs et al., 1997), is not a part of the declarative memory system itself. The consistency between the available neuroanatomical information from humans and the findings from monkeys have considerably illuminated the description of memory impairment and its anatomical basis. These lines of work have also made it possible to pursue parallel studies in experimental animals such as rats and mice. As a result, one can now study memory in rodents and have some confidence that what one learns will be relevant to the human condition.

Anatomical connections from different parts of the neocortex enter the medial temporal lobe at different points (Suzuki and Amaral, 1994a, b), which raises the question of whether these medial temporal lobe structures play different roles in declarative
memory. For example, visual association cortex projects more strongly to the perirhinal cortex than to the parahippocampal cortex, whereas the parietal cortex projects to the parahippocampal cortex but not to the perirhinal cortex. Further, the hippocampus lies at the end of the medial temporal lobe system and is a recipient of convergent projections from each of the structures that precedes it in the hierarchy. The possibility that different medial temporal lobe structures make different contributions to memory has been addressed in a number of studies in monkeys, comparing performance on memory tasks following damage to different components of the medial temporal lobe. This work has shown that the severity of memory impairment depends on the locus and extent of damage within the medial temporal lobe memory system. Damage limited to the hippocampal region causes significant memory impairment, but damage to the adjacent cortex increases the severity of memory impairment. It is also important to note that the discovery that larger medial temporal lobe lesions produce more severe amnesia than smaller lesions is compatible with the idea that structures within the medial temporal lobe might make qualitatively different contributions to memory function. Indeed, damage to the perirhinal cortex especially impairs object recognition, whereas damage to the parahippocampal cortex especially impairs spatial memory.

Another important brain area for memory is the diencephalon. The important structures include the mediodorsal thalamic nucleus, the anterior thalamic nucleus, the internal medullary lamina, the mamillary nuclei, and the mammillo-thalamic tract. Monkeys with medial thalamic lesions exhibit an amnesic disorder, and monkeys with mamillary nuclei lesions exhibit a modest impairment. 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.

### 3.04.4 The Nature of Amnesia

Amnesic individuals exhibit significant memory impairment. Yet, despite their memory deficit, patients have intact ability for some forms of new learning and memory (see section Nondeclarative Memory). Also, they have intact immediate memory and memory...
for a great deal of information from the past, especially childhood. In addition, patients with neurological amnesia can have intact intelligence test scores, intact language and social skills, and intact perceptual abilities. In fact, amnesic patients can appear quite normal on casual observation. It is only when one interrogates their capacity for new learning of conscious knowledge that the impairment becomes evident.

3.04.4.1 Impairment in Declarative Memory

It is important to appreciate that amnesic patients are not impaired at all kinds of long-term memory. The major distinction is between declarative and nondeclarative memory. Declarative memory is the kind of memory impaired in amnesia. Declarative memory refers to the capacity to remember the facts and events of everyday life and is the kind of memory that is meant when the term “memory” is used in ordinary language. Declarative memory can be brought to mind as a conscious recollection. 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 in that they are accessible to multiple response systems and can guide successful performance under a wide range of test conditions. Last, 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).

3.04.4.2 Anterograde Amnesia

Amnesia is characterized especially by profound difficulty in new learning, and this impairment is referred to as anterograde amnesia. Amnesia can occur as part of a more global dementia disorder that includes other cognitive deficits such as impairments in language, attention, visuospatial abilities, and general intellectual capacity. However, when damage is restricted to the medial temporal lobe or midline diencephalon, 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 and perceptual functions, even on difficult tests that require the ability to discriminate between highly similar images containing overlapping features (Levy et al., 2005; Shrager et al., 2006). In some patients with memory impairment, visual perceptual deficits have been described (Lee et al., 2005a, 2005b). In these cases, damage might extend laterally, beyond the medial temporal lobe, and quantitative brain measurements are needed to understand what underlies these deficits. Thus, present data support the idea that declarative memory is separable from other brain functions.

Amnesic patients are impaired on tasks of new learning, regardless of whether memory is tested by free (unaided) 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). For instance, in a standard test of free recall, participants are read a short prose passage containing 21 segments. They are then asked to recall the passage immediately and after a 12-min delay. Amnesic patients with damage to the medial temporal lobe do well at immediate recall but are impaired at the delay, usually recalling zero segments (Squire and Shimamura, 1986). Amnesic patients are also impaired on recognition memory tests, where a list of words is presented and participants try to decide (yes or no) if each word had been presented in a recent study list (Squire and Shimamura, 1986). Last, in a cued recall task, individuals study a list of word pairs, such as ARMY–TABLE. During test, they are presented with one word from each pair (ARMY), and they are asked to recall the word that was paired with it (TABLE). Amnesic patients are impaired on this task as well.

The memory impairment in amnesia involves both difficulty in learning factual information (semantic memory) as well as difficulty in learning about specific episodes and events that occurred in a certain time and place (episodic memory). The term “semantic memory” is often used to describe declarative memory for organized world knowledge (Tulving, 1983). In recalling this type of information, one need not remember any particular past event. One needs only to know about certain facts. Episodic memory, in contrast, is autobiographical memory for the events of one’s life (Tulving, 1983). Unlike semantic memory, episodic memory stores spatial and temporal landmarks that identify the particular time and place when an event occurred. Both episodic memory and semantic memory are declarative.

Formal experiments have compared directly the ability to accomplish fact learning (or semantic memory ability) and event learning (or episodic memory ability). In one experiment, amnesic patients were taught new factual knowledge in the form of three-word sentences (e.g., MEDICINE cured HICCUP). Then, during testing, sentence fragments were presented with the instruction to complete each fragment with a word that had been studied (e.g., MEDICINE cured ______). The amnesic patients were similarly impaired on tests of fact memory (what word completed the sentence fragment) and on tests of event memory (what specific events occurred during the testing session) (Hamann and Squire, 1995). Taken together, the data favor the view that episodic memory and semantic memory are similarly impaired in amnesia (Squire and Zola, 1998). Semantic knowledge is thought to accumulate in cortical storage sites as a consequence of experience and with support from the medial temporal lobe. Episodic memory requires similar interactions between the medial temporal lobes and cortical storage sites, yet additionally requires involvement of the prefrontal cortex to attribute the new information to the particular time and place in which it was learned (Janowsky et al., 1989).

Last, the memory deficit in amnesia is global and encompasses all sensory modalities (e.g., visual, auditory, olfactory). That is, memory is impaired regardless of the kind of material that is presented and the sensory modality in which information is presented. For example, recognition memory of amnesic patients was assessed for line drawings of objects (visual), designs (visual), and odors (olfactory) (Levy et al., 2004). The patients were impaired on all three tasks, showing that their impairment spans the visual and olfactory domains. Formal experiments have also demonstrated recognition memory impairment for auditory stimuli.
3.04.4.3 Remembering Versus Knowing and Recollection Versus Familiarity

Remembering (R) is meant to refer to the circumstance when an item elicits a conscious recollection that includes information about the context in which the item was learned. Knowing (K) is meant to refer to a circumstance when an item appears familiar, but memory for the original learning context is not available (Tulving, 1985). Thorough studies of healthy individuals indicate that in practice, remembering and knowing responses are closely related to the strength of a memory and that items given K responses are often items for which information is also available about the original learning context (Wixted and Stretch, 2004). In any case, formal studies show that both R and K responses are impaired in amnesia. In one such experiment, amnesic patients and control participants were given a recognition memory test 10 min after studying words. For each word, participants indicated whether they remembered it (R) or whether they knew that the word was presented but had no recollection about it (K). The patients were impaired for both R and K responses, and they performed like a control group that was tested after 1 week. That is, the patients were similarly impaired for R and K responses (Knowlton and Squire, 1995; also see Manns et al., 2003). Accordingly, the evidence suggests that remembering and knowing are two different expressions of declarative memory.

A distinction closely related to remembering and knowing is recollection and familiarity. Recollection involves remembering the contextual associations of the original learning experience, whereas familiarity does not require any recollection of the original experience. It has sometimes been proposed that recollection relies on the hippocampus, while familiarity can be supported by the adjacent cortex within the medial temporal lobe. In this view, patients with damage limited to the hippocampus should be selectively, or disproportionately, impaired at recollecting information and less impaired at recognizing material when it can be supported by familiarity.

An alternative view is that recognition memory decisions are based on a unidimensional strength-of-memory variable that combines estimates of recollection and familiarity. Thus, as in the case of remembering and knowing, a capacity for recollection is likely to be associated with strong memories and familiarity with weaker memories (Wixted, 2007). In one study, patients with hippocampal damage were impaired on a recognition memory test, where they gave confidence judgments (scale of 1–6). The results indicated that both processes, recollection and familiarity, were operative in the absence of the hippocampus (Wais et al., 2006). Last, electrophysiological recordings from patients being evaluated for epilepsy surgery found neurons in the hippocampus that responded to familiar images during a recognition test. These familiarity signals were present even when recollection failed (i.e., there was a familiarity signal in the hippocampus regardless of whether any recollection had occurred) (Rutishauser et al., 2006).

3.04.4.4 Retrograde Amnesia

In addition to impaired new learning, damage to the medial temporal lobe 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 (Ribot, 1881). The extent of retrograde amnesia can be relatively short and encompass only 1 or 2 years, or it can be more extensive and cover decades. Even then, memories for the facts and events of childhood and adolescence are typically intact. Indeed, severely amnesic patients can produce detailed autobiographical narratives of their early life. These memories were indistinguishable from the memories of healthy individuals with respect to the number of details, the duration of the narratives, the number of prompts needed to begin a narrative, and the reported vividness of the memories (Bayley et al., 2003, 2005b; Kirwan et al., 2008).

The severity and extent of retrograde amnesia is determined by the locus and extent of damage. Patients with restricted hippocampal damage have 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. Moreover, the number of premorbid years impacted by retrograde amnesia is strongly correlated with the severity of anterograde amnesia across patients (Smith et al., 2013). This close relationship indicates that medial temporal lobe regions are similarly important for acquisition and provisional storage of declarative memories. When damage occurs beyond the brain system that supports declarative memory, which can result from conditions such as encephalitis and head trauma, retrograde amnesia sometimes can be ungraded and extensive and include the facts and events of early life.

Because the study of human retrograde amnesia is based almost entirely on findings from retrospective tests, the clearest data about retrograde amnesia gradients come from studies using experimental animals, where the delay between initial learning and a lesion can be manipulated directly. Findings from such studies make three important points. First, temporal gradients of retrograde amnesia can occur within long-term memory. That is, retrograde amnesia does not reflect simply the vulnerability of a short-term memory that has not yet been converted into a long-term memory. Second, after a lesion, remote memory can be even better than recent memory. Third, lesions can spare old weak memories while disrupting strong recent ones, showing that it is the age of the memory that is critical.

These same points can be illustrated by a study of rabbits given trace eyeblink conditioning. Trace conditioning is a variant of classical conditioning in which the conditioned stimulus (CS), such as a tone, is presented and terminated, and then a short interval (e.g., 500 ms) is imposed before the presentation of the unconditioned stimulus (US). In normal rabbits, forgetting occurs gradually after training, and retention of the conditioned response is much poorer 30 days after training than after only 1 day. Nevertheless, complete aspiration of the hippocampus 1 day after training abolished the strong 1-day-old memory, whereas the same lesion made 30 days after training had no effect on the weaker 30-day-old memory (Kim et al., 1995).
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.

3.04.4.5 Spatial Memory

Since the early discovery of place cells (O’Keefe and Dostrovsky, 1971) and, more recently, grid cells (Hafting et al., 2005) in the rat hippocampus and entorhinal cortex, respectively, an influential idea has been that the hippocampus creates and uses spatial maps and that its predominant function is to support spatial memory (O’Keefe and Nadel, 1978). Discussions of amnesia have therefore focused especially on the status of spatial memory. It is clear that spatial memory is impaired in human amnesia. Amnesic patients are impaired on tests that assess their knowledge of the spatial layout of an environment, and they are also impaired when asked to navigate to a destination in a virtual environment (Maguire et al., 1996; Spiers et al., 2001). Similarly, the noted patient H.M. was impaired at recalling object locations (Smith, 1988). It is also clear, though, that amnesic patients are impaired on memory tests that have no obvious spatial component, such as recall or recognition of items (Squire and Shimamura, 1986). Furthermore, formal experiments that directly compared spatial and nonspatial memory in amnesic patients showed that the patients were similarly impaired on tests of spatial memory and tests of nonspatial memory. There was no special difficulty with the test of spatial memory (Cave and Squire, 1991).

As is the case with nonspatial memory, remote spatial 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 (Teng and Squire, 1999). 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.

3.04.4.6 Amnesia Is a Memory Disorder

Data from patients with brain damage restricted to the medial temporal lobe have indicated that the impairment of declarative memory in amnesia is pervasive yet circumscribed. Their impairment in declarative memory is broad. It does not spare semantic memory, recognition memory, or nonspatial memory. However, impairment is nevertheless specific to declarative memory. It does not normally extend to performance on other types of tasks except by indirect effects of the memory impairment.

One instance in which amnesic patients can be disadvantaged is when the task instructions create a memory burden. Memory-impaired individuals will perform poorly on nonmemory tasks if they have forgotten what they have been asked to do. Furthermore, the task procedure itself can create a memory burden. For example, some tasks that are intended to assess visual perception can nevertheless handicap amnesic patients by asking them to process more information than they can maintain in working memory. In one study, amnesic patients were impaired relative to healthy participants when they were asked to identify visually an oddball item among up to eight other very similar items (Knutson et al., 2013). Without further data, one might conclude that the patients exhibited a deficit in visual perception. However, in the same study (Knutson et al., 2013), the participants were subsequently offered a pencil as a memory aid to keep track on each trial of which items had been ruled out as the potential oddball. In this condition, when the memory burden was removed, but the visual perceptual demands were unchanged, the amnesic patients performed as well as healthy participants, even on the most difficult perceptual discriminations.

Spatial navigation tasks can similarly create a declarative memory burden if participants are asked to retrace long routes from memory. However, if the memory load is kept to a minimum by using short routes, amnesic patients can perform similarly to healthy individuals (Kim et al., 2013). Thus, online perceptual or spatial processing abilities tend to be intact in amnesic patients with damage limited to the medial temporal lobe, so long as the task procedure does not additionally tax declarative memory.

Another instance in which amnesic patients can be disadvantaged is when they are asked to imagine novel scenes or scenarios, including possible future scenarios. Healthy individuals will call on remembered stories from the past to construct hypothetical stories about the future. When amnesic patients have intact autobiographical memory, at least for the remote past, they can construct imagined future events as well as healthy individuals, as measured by the number of details produced (Squire et al., 2010). However, in other studies, memory-impaired patients have exhibited impoverished autobiographical memories from all periods of their life, including the remote past. In some patients, impairments in imagining the future have also been described (Hassabis et al., 2007). One concern is that the finding of retrograde amnesia for very remote events raises the possibility that brain regions outside the medial temporal lobe may have been damaged (Bayley et al., 2005b). Another concern is that the reduced capacity to imagine the future may be secondary to a reduced capacity to remember any part of the past. Without coherent narratives
of the past to serve as templates, it is perhaps not surprising that patients can perform poorly at generating coherent narratives of the future. Even amnesic patients with damage restricted to the medial temporal lobe, and whose remote autobiographical memory is spared, might still be penalized by some mental imagery tasks. Remembering yesterday benefits imagining tomorrow more than remembering one’s childhood does. In any case, when task instructions are made available to all participants at the start of the trial and can be maintained in working memory, amnesic patients can perform imagery tasks as well as healthy individuals even with difficult tasks such as mental rotation (Kim et al., 2013) or scene construction (Kim et al., 2015). These results emphasize the importance of disentangling specific memory impairments from nonspecific impairments in performance (Cahill et al., 2001).

3.04.5 Spared Learning and Memory Abilities

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 long-term declarative memory and spares immediate and working memory, as well as nondeclarative memory. Immediate memory and working memory can be viewed as a collection of temporary memory capacities that operate shortly after material is presented. 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, habits, and phylogenetically early forms of experience-dependent behavior such as habituation and sensitization. In these cases, memory is expressed through performance rather than remembrance.

3.04.5.1 Immediate and Working Memory

Amnesic patients have intact immediate memory. Immediate memory refers to what can be held actively in mind beginning the moment that information is received. It is the information that forms the focus of current attention and that occupies the current stream of thought. The capacity of immediate memory is quite limited. This type of memory is reflected, for example, in the ability to repeat back a short string of digits. 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 threedigit 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, and it is independent of the medial temporal lobe system. 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, when the capacity of working memory is exceeded, patients will remember fewer items than their healthy counterparts.

The intact capacity for immediate and working memory was well illustrated by patient H.M. when he was asked to remember the number 584. H.M. was left to himself for several minutes, and he was able to retain this information by working out mnemonic schemes and holding the information continuously in mind. Yet, only a minute or two later, after his attention had been directed to another task, he could not remember the number or any of his mnemonic schemes for holding the number in mind.

3.04.5.2 Nondeclarative Memory

Nondeclarative memory refers to a collection of nonconscious knowledge systems, but it is not itself a brain systems construct. Rather, the term encompasses several different kinds of memory. Nondeclarative forms of memory have in common the feature that memory is nonconscious. Nondeclarative memory is expressed through performance and does not require reflection on the past or even the knowledge that memory is being influenced by past events.

The following examples illustrate that nondeclarative memory is distinct from declarative memory. It is spared in amnesia, and it operates outside of awareness. Nondeclarative forms of memory depend variously on the striatum, the amygdala, and the cerebellum and on processes intrinsic to neocortex (Fig. 2). Learning changes behavior, and nondeclarative memory reflects refinements within the circuitry needed to support particular behavioral adaptations.

3.04.5.2.1 Motor Skills and Perceptual 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. This is because the learning of motor skills is largely nondeclarative, and amnesic patients can learn these skills at a normal rate. In one experiment, amnesic patients and control participants performed a serial reaction-time task in which they responded successively to a sequence of four illuminated spatial locations. The task was to press one of four keys as rapidly as possible as soon as the location above each key was illuminated. The amnesic patients learned the sequence, as did the normal participants, as measured by their decreased reaction times for pressing a key when it was illuminated. When the sequence was changed, the reaction times increased for both groups. Strikingly, the amnesic patients had little or no declarative knowledge of the sequence, though they had learned it normally (Reber and Squire, 1994).
Perceptual skills are also often intact in amnesic patients. These include such skills as reading mirror-reversed print and searching a display quickly to find a hidden letter. In formal experiments, amnesic patients acquired perceptual skills at the same rate as individuals with intact memory, even though the patients did not remember what items were encountered during the task and sometimes did not remember the task itself. For example, amnesic patients learned to read mirror-reversed words at a normal rate and then retained the skill for months. Yet, after they had finished the mirror-reading task, they could not remember the words that they had read, and in some cases they could not remember that they had ever practiced the mirror-reading skill on a previous occasion (Cohen and Squire, 1980).

3.04.5.2.2 Artificial Grammar Learning

Another kind of learning that is intact in amnesia is the learning of artificial grammars. In an artificial grammar-learning task, participants are presented with a series of letter strings that are generated according to a rule system that specifies what letter sequences are permissible. After viewing these letter strings, participants are told for the first time that the letter strings were formed according to a set of rules and that their task is to decide for a new set of letter strings whether each one is formed by the same set of rules as the set they had just studied. Even though individuals often report that they are simply guessing, they are able to classify new letter strings as grammatical or nongrammatical. Amnesic patients classify items as grammatical or nongrammatical as well as healthy individuals, despite being impaired at recognizing the letter strings that were used during the initial training (Knowlton et al., 1992; Knowlton and Squire, 1994, 1996).

3.04.5.2.3 Priming

Priming refers to an improved ability to identify or produce a word or other stimulus as a result of its prior presentation. The first encounter with an item results in a representation of that item, and that representation then allows it to be processed more efficiently than items that were not encountered recently. For example, suppose that line drawings 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 independently of whether one remembers having seen the items earlier. Amnesic patients exhibit this effect at full strength, despite having poor memory of seeing the items earlier.

The dissociation between intact priming and impaired recognition memory in amnesic patients can be particularly compelling. One study investigated priming in patient E.P., who is so severely amnesic that he exhibits no detectable declarative memory (Hamann and Squire, 1997). E.P. sustained complete bilateral damage to the medial temporal lobe as the result of herpes simplex encephalitis. Two tests of priming were given. In one of the priming tests, word stem completion, participants were shown a short word list, which included, for example, the words MOTEL and ABSENT. Then, they were shown the fragments MOT___ and ABS___, with instructions to form the first word that comes to mind. Participants had a strong tendency (30%–50%) to produce the words that were recently presented. (The probability was about 10% that participants would produce these words if they had not been presented recently.) In addition, two parallel tests of recognition memory for words were given: alternative forced choice and yes–no recognition. E.P. performed entirely normally on the two priming tests but performed at chance (50%) on the recognition tests.

In another experiment, participants saw words slowly clearing from a mask. They tried to identify each word as quickly as possible and then make a recognition judgment (old/new) about whether the word had been presented in a preceding study phase.
Amnesic patients exhibited intact fluency (the tendency to label those words that were identified more quickly as old) and intact priming, but their recognition was impaired (Conroy et al., 2005). These results support the idea that priming depends on brain structures independent of the medial temporal lobe, and they show that the combined effects of priming and fluency are not sufficient to increase recognition performance.

### 3.04.5.2.4 Adaptation-Level Effects

Adaptation-level effects refer to the finding that experience with one set of stimuli influences how a second set of stimuli is perceived (e.g., their heaviness or size). For example, experience with light-weighted objects subsequently causes other objects to be judged as 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, even when they experience the first set of objects with one hand and then make judgments with the other hand. However, they have difficulty remembering their prior experience accurately (Benzing and Squire, 1989).

### 3.04.5.2.5 Classical Eyeblink Conditioning

Classical conditioning refers to the development of an association between a previously neutral stimulus (CS) and a US, and is a quintessential example of nondeclarative memory. One of the best-studied examples of classical conditioning in humans is delay conditioning of the eyeblink response. It is reflexive and automatic and depends solely on structures below the forebrain, including the cerebellum and associated brainstem circuitry (Thompson and Krupa, 1994). In a typical conditioning procedure, a tone repeatedly precedes a mild airpuff directed to the eye. After a number of pairings, the tone comes to elicit an eyeblink in anticipation of the airpuff. Amnesic patients acquire and retain the tone–airpuff association at the same rate as healthy individuals. In both groups, awareness of the temporal contingency between the tone and the airpuff is unrelated to successful conditioning.

In trace conditioning, a brief interval of 500–1000 ms is interposed between the CS and the US. This form of conditioning requires the hippocampus (McGlinchey-Berroth et al., 1997). Formal experiments suggest that trace conditioning is hippocampus dependent because it requires the acquisition and retention of conscious knowledge during the course of the conditioning session (Clark and Squire, 1998). Only those who became aware of the CS–US relationship acquired differential trace conditioning. There was a correlation between measures of awareness taken after the conditioning and trace conditioning performance itself, whereas there was no correlation between awareness and conditioning performance on a delay conditioning task.

### 3.04.5.2.6 Habit Learning

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 striatum. 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 gradual rate (Knowlton et al., 1992).

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 in each of eight object pairs. Healthy individuals can learn all eight pairs in one or two test sessions. 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 striatum are impaired. Thus, humans appear to have a robust capacity for habit learning that operates outside of awareness and independently of the medial temporal lobe structures that are damaged in amnesia (Bayley et al., 2005a).

### 3.04.6 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. Sometimes, the disorder lasts longer, and sizable pieces of the past remain unavailable.
3.04.7 Summary

The study of amnesia has helped to understand the nature of memory disorders and has 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, and about how memory works, more opportunities will arise for achieving better diagnosis, treatment, and prevention of diseases and disorders that affect memory.

See also: 1.02 A Typology of Memory Terms. 2.07 Autobiographical Memory. 2.09 Working Memory: The Information You Are Now Thinking of. 2.19 Spatial Memory and Navigation. 3.02 Interactions Among Multiple Parallel Learning and Memory Systems in the Mammalian Brain. 3.10 Animal Models of Amnesia. 3.11 Neurobiology of Recognition Memory. 3.13 Spatial Memory. 3.15 Short-Term and Working Memory. 3.26 Episodic Memory Decline and Healthy Aging.

References


Zola-Morgan, S., Squire, L.R., Amaral, D.G., 1986. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J. Neurosci. 6, 2960–2967.