Remembering

Larry R. Squire & John T. Wixted

Abstract: A major development in understanding the structure and organization of memory was the identification of the medial temporal lobe memory system as one of the brain systems that support memory. Work on this topic began in the 1950s with the study of the noted amnesic patient H.M. and culminated in studies of an animal model of human memory impairment in the nonhuman primate. These discoveries opened new frontiers of research concerned with the functional specialization of structures within the medial temporal lobe, the existence of multiple memory systems, the process of memory consolidation, and the role of neural replay and sleep in the consolidation process. This work also led to new insights about how and where memories are ultimately stored in the brain. All of this research has improved our understanding of how memory is affected by normal aging and why it is so profoundly impaired by the pathological processes associated with dementia.

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Memory is a large topic, growing out of the fundamental fact that the experiences we have can modify the nervous system such that our mental life and our behavior can be different than they were in the past. The study of memory ranges widely – from cellular and molecular questions about the nature of synaptic change to questions about what memory is, whether it is one thing or many, which brain systems support memory, and how those systems operate. We will consider in particular the structure and organization of memory with a focus on brain systems.

The idea that functions of the nervous system can be localized was well accepted by the end of the nineteenth century. Yet these ideas concerned mainly sensory-motor functions and language and did not speak to the topic of memory itself. In the early twentieth century, an influential program of research in the rat concluded that memory is not localized but is distributed through the neocortex (the outer layer of the cerebral hemispheres of the brain of mammals in-

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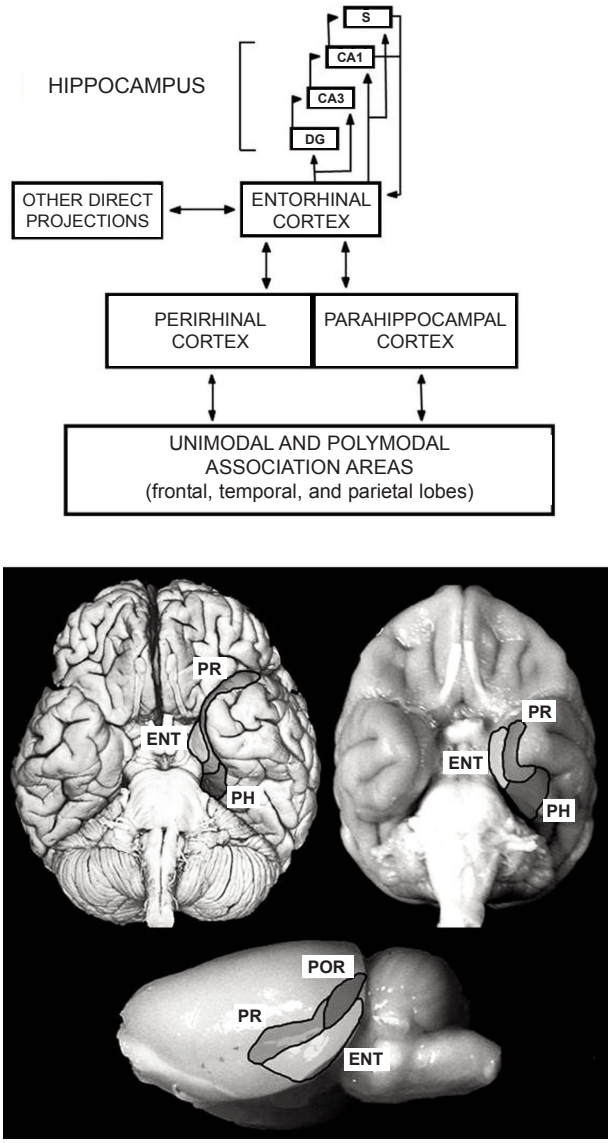
volved in higher functions such as sensory perception, attention, memory, and action), such that each region contributes equivalently to the whole.[1] Memory was thought to be distributed and well integrated with intellectual and perceptual functions, and no particular brain region was thought to be dedicated to memory function.

All of this changed in the 1950s when profound effects on memory were reported following a bilateral medial temporal lobe resection (the removal of the inner structures of the temporal lobe) carried out in the patient known as H.M.[2] This experimental surgery successfully relieved H.M.'s severe epilepsy, as was intended, but it also resulted in severe and debilitating forgetfulness, which occurred against a background of apparently intact intellectual and perceptual functions. For example, the patient could copy a complex drawing as well as controls, suggesting that his ability to perceive visual information was intact; and he could continuously rehearse (and then repeat back) a string of five or six digits as well as controls, suggesting that his "working memory" was also intact. But when his attention was diverted, he soon forgot the drawing and the digits. Early descriptions of H.M. can be said to have inaugurated the modern era of memory research and strongly influenced the direction of subsequent work. Most significantly, this work identified for the first time a particular area of the brain as important for memory.

H.M.'s bilateral lesion included the hippocampus, amygdala, and the adjacent parahippocampal gyrus. The immediate question was which structures within this large surgical removal were responsible for his circumscribed memory impairment; that is, which structures and connections within the human temporal lobe have dedicated memory functions. These matters became understood gradually during the 1980s following the successful development of an animal model of human amnesia in the nonhuman primate.[3] The important structures proved to be the hippocampus and the adjacent entorhinal, perirhinal, and parahippocampal cortices, which make up much of the parahippocampal gyrus (Figure 1).[4] (Anatomically related structures in the thalamus and hypothalamus in the diencephalic midline, an area not part of H.M.'s lesion, are also important for memory, but these will not be discussed.) Damage limited to the hippocampus itself causes moderately severe memory impairment, but the impairment is greatly exacerbated when the damage extends to and includes the parahippocampal gyrus (as was the case with H.M.).[5] In all cases, the disorder is characterized most prominently by an impaired ability to form new memories (anterograde amnesia), but also by difficulty in accessing some memories acquired before the onset of the impairment (retrograde amnesia). Memories acquired shortly before the occurrence of a brain lesion (such as during the previous year) tend to be more impaired than memories acquired in the distant past. Thus, the structures that compose the medial temporal lobe memory system are essential for the initial formation of enduring long-term memories as well as for their maintenance and retrieval for a time after learning. The fact that very remote memory tends to be preserved after medial temporal lobe damage indicates that these structures are not the ultimate repository of long-term memory.

Once the important structures of the medial temporal lobe were identified, the question naturally arose whether the different structures have specialized roles. An early view held that the hippocampus plays an especially important role in spatial memory.[6] This idea was based on the common finding that rodents with selective

Figure 1
The Medial Temporal Lobe Memory System



Top: Schematic view of the memory system, which is composed of the hippocampus and the perirhinal, entorhinal, and parahippocampal cortices. In addition to the connections shown here, there are also weak projections from the perirhinal and parahippocampal cortices to the CA1-subiculum border. *Bottom*: Ventral view of a human brain (upper left) and a monkey brain (upper right) and a lateral view of a rat brain (lower center). The major cortical components of the medial temporal lobe are highlighted and outlined. The hippocampus is not visible from the surface and, in the human, lies beneath the structures of the medial temporal lobe. Its anterior extent lies below the posterior entorhinal and perirhinal cortices, and the main body of the hippocampus lies beneath the parahippocampal cortex. In the rat, the parahippocampal cortex is termed the postrhinal cortex. Abbreviations: DG, dentate gyrus; ENT, entorhinal cortex; PH, parahippocampal cortex; POR, postrhinal cortex; PR, perirhinal cortex; S, subicular complex. Source: Adapted from Figure 2 in Larry R. Squire and John T. Wixted, "The Cognitive Neuroscience of Memory since H.M.," *Annual Review of Neuroscience* 34 (2011): 259 – 288.

hippocampal lesions are severely impaired on spatial learning tasks, such as learning to navigate a maze. However, subsequent work involving humans and monkeys with selective hippocampal lesions demonstrated pronounced spatial and nonspatial memory impairment. For example, patients with hippocampal lesions were impaired in their ability to recognize words that had appeared on an earlier list – a task with no obvious spatial component.[7] Findings like these suggest that the hippocampus plays a broader role in memory encoding and consolidation (the gradual process by which a temporary, labile memory is transformed into a more stable, long-lasting form).

Another popular idea about specialization of function within the medial temporal lobe was based on a long-standing psychological distinction between familiarity and recollection.[8] Familiarity involves knowing only that an item has been previously encountered (for example, when you recognize a face but cannot recall who the person is), and recollection involves recalling specific details about the prior encounter (such as recalling where and when you met the familiar person). Initially, a number of findings were interpreted to mean that hippocampal lesions selectively impair the recollection process but leave memory based on familiarity intact.[9] In addition, neuroimaging studies were often interpreted to mean that recollection-based decisions generate elevated activity in the hippocampus, whereas familiarity-based decisions generate elevated activity in other medial temporal lobe structures, particularly the perirhinal cortex.[10] However, subsequent studies found that bilateral hippocampal lesions in humans have comparable effects on recollection and familiarity, and neuroimaging studies found that both familiarity-based and recollection-based recognition generate elevated hippocampal activity when both kinds of memory are strong.[11] Thus, the specialization of function within the medial temporal lobe does not seem to be informed by this distinction.

Because the functions of the different medial temporal lobe structures do not apparently divide up along the lines of spatial versus nonspatial memory or recollection versus familiarity, we must look elsewhere to identify functional differences between the structures. An important consideration is the fact that the inputs to each structure are quite different.[12] For example, the perirhinal cortex receives the majority of its cortical input from areas supporting visual object perception. Thus, the perirhinal cortex may be particularly important for forming memories of visual objects. Similarly, the parahippocampal cortex receives significant input from areas supporting spatial processing (for example, the ability to perceive that objects A and B are closer together than objects C and D). This area may therefore be particularly important for forming memories about the spatial locations of objects. A growing body of evidence is consistent with these ideas.[13] That is, the functional specialization of different medial temporal lobe structures is sensibly related to the domain of information they process – information that is carried to these structures from upstream regions supporting different kinds of perceptual processing.[14]

Within the medial temporal lobe, the hippocampus is the ultimate recipient of convergent projections from the entorhinal, perirhinal, and parahippocampal cortices. Thus, the hippocampus itself is in a position to play a role in the encoding and consolidation of all aspects of an experience (its visual, spatial, auditory, and olfactory qualities, as well as other contextual information). These anatomical facts can therefore explain why damage to the hippocampus results in broad memory impairment that covers all modalities and ex-

tends across multiple domains. Current studies are using new genetic methods in mice and other techniques to analyze the separate contributions of specific connections and cell types within the hippocampus.[15]

The memory impairment associated with medial temporal lobe lesions is narrower than once thought, because not all forms of learning and memory are affected. The first clue came in 1962 when H.M. was found capable of acquiring a motor skill (mirror drawing) over a period of three days, though he could not recall these periods of practice. While this finding showed that memory is not unitary, discussions at the time tended to set aside motor skills as a special case representing a less cognitive form of memory. The suggestion was that the rest of memory is of one piece and is dependent on medial temporal lobe structures.

Yet during the subsequent years, it was discovered that motor-skill learning is but one example of a large domain of abilities that are independent of the medial temporal lobe. An early discovery was that perceptual and cognitive skills – not just motor skills – are intact in patients like H.M. Thus, memory-impaired patients acquired at a normal rate the skill of reading mirror-reversed words, despite poor memory for the words themselves.[16] This finding led to the proposal of a brain-based distinction between declarative and procedural knowledge. Declarative knowledge referred to knowledge available as conscious recollections about facts and events. Procedural knowledge referred to skill-based information: knowledge expressed through performance rather than recollection.

Soon after this discovery was made, the phenomenon of priming was also found to be spared in amnesia.[17] Priming refers to an improved ability to detect or identify stimuli based on a recent encounter with the same or related stimuli. For example, memory-impaired patients could (like healthy volunteers) name recently presented object drawings one hundred milliseconds faster than new drawings, despite having poor memory for the drawings themselves.[18] Perhaps the most compelling evidence for the independence of priming and ordinary memory ability was that severely amnesic patients can exhibit fully intact priming for words while performing only at chance levels on conventional recognition memory tests for the same words.[19]

Another important insight was the idea that the neostriatum (a subcortical region of the brain that includes the caudate nucleus and putamen), and not the medial temporal lobe, is important for the sort of gradual, feedback-guided learning that results in habit memory.[20] For example, memory-impaired patients learned tasks at a normal rate when the outcome of each learning trial was determined probabilistically, and performance therefore needed to be based on a gut feeling rather than on conscious memory of past events.[21] Work with experimental animals was also the source of new insights, including the discovery in the early 1980s that the cerebellum is essential for delay eyeblink conditioning,[22] a kind of learning entirely preserved after hippocampal lesions.[23] Still other types of learning, which involve attaching a positive or negative valence to a stimulus (as in fear conditioning), depend on the amygdala.[24]

Given the variety of tasks explored in these studies and the number of brain structures implicated, an account of memory based on a two-part dichotomy (declarative versus procedural) began to seem too simplistic. Accordingly, the perspective eventually shifted to a framework that accommodated more than two memory systems. At that time, the umbrella term "nondeclarative memory" was introduced with the intention of distinguishing between

declarative memory (which refers to one memory system) and other types of memory (in which several additional systems are involved).[25] Figure 2 illustrates this idea.[26]

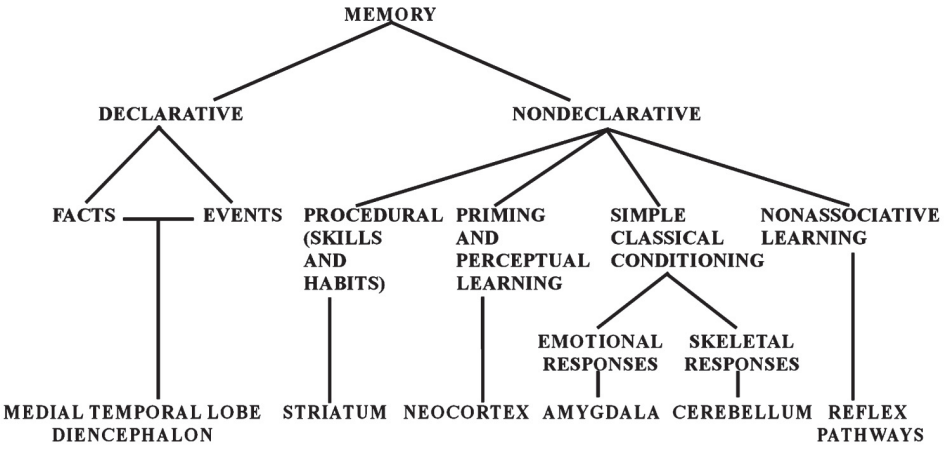
Declarative memory is what the term *memory* signifies when we use it in everyday language. The stored representations are flexible and thought to be accessible to conscious awareness. Declarative memory is representational; it provides a way to model the external world and is either true or false. In contrast, nondeclarative memory is neither true nor false: it is dispositional and occurs as modifications within specialized performance systems. Thus, the various memory systems can be distinguished in terms of the different kinds of information they process and the principles by which they operate. These systems work in parallel to support behavior. For example, an aversive event in childhood (such as being knocked down by a large dog) can lead to an enduring declarative memory of the event itself (dependent on the hippocampus and related structures) as well as a long-lasting, nondeclarative fear of dogs (a phobia, dependent on the amygdala) that is experienced as part of the personality rather than as a memory.

The hippocampus and related structures in the medial temporal lobe have a time-limited role in the formation and storage of memory. Two lines of work underlie this idea. First, damage to these structures typically spares remote memory and impairs more recent memory in a temporally graded fashion. In humans, hippocampal lesions affect memory for up to a few years after learning. In experimental animals (usually rats or mice), similar damage impairs memory for up to thirty days after learning.[27] Thus, long-term, stable memory develops more slowly in humans than in experimental animals. Discussion in the field continues about the possible special status of spatial memory and autobiographical memory in humans and the idea that these forms of memory might depend on medial temporal lobe structures as long as memory persists.[28] Yet there are reports of patients with medial temporal lobe lesions in whom remote spatial and autobiographical memory has been spared.[29]

The second line of work involves studies of experimental animals that track neural activity or structural changes in the hippocampus and neocortex after learning. For example, expression patterns of activity-related genes like c-Fos describe gradually decreasing activity in the hippocampus after learning and parallel increases in activity in a number of cortical regions.[30] These findings and others describe the increasing importance of distributed cortical regions for the representation of memory as time passes after learning.[31] Similar findings have been obtained in neuroimaging studies; for example, when volunteers attempt to recall news events that occurred anywhere from one to thirty years earlier.[32] The idea is not that memory is literally transferred from the hippocampus to the neocortex. Memory is always in the neocortex, but gradual changes occur to increase the complexity, distribution, and connectivity of memory representations among multiple cortical regions. At the same time the role of the hippocampus gradually diminishes (Figure 3).

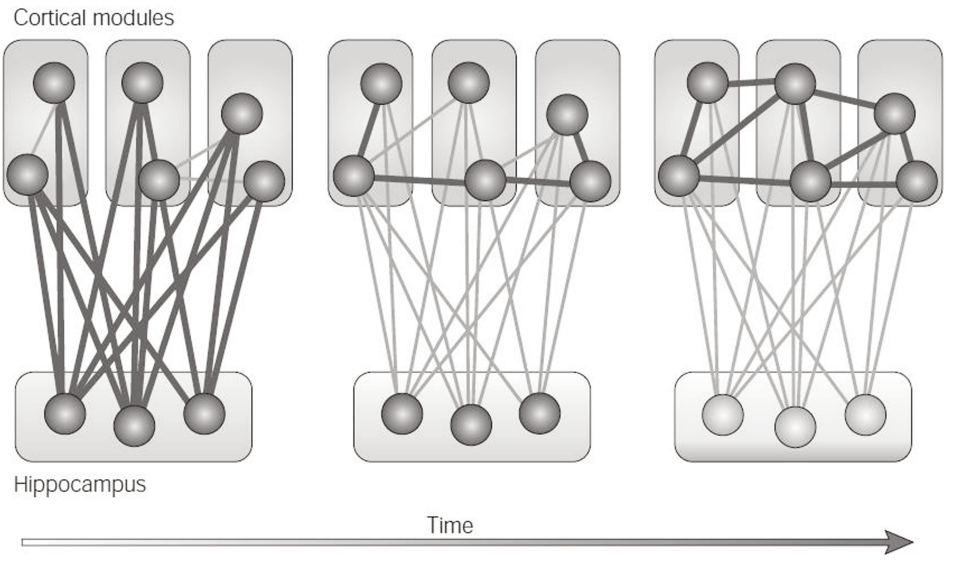
One way to view this process is to suppose that a time-and-place-specific new memory (a so-called episodic memory) is represented initially by an ensemble of distributed changes in the neocortex and by changes in the hippocampus (and anatomically related structures) as well. The neocortical ensemble is viable so long as the episode is maintained within active memory. However, when one's attention is directed elsewhere, a problem arises. How can the unique distribution of sites that represent this new memory be revivified by

Figure 2
Organization of Mammalian Long-Term Memory Systems



The figure lists the brain structures thought to be especially important for each form of declarative and nondeclarative memory. In addition to its central role in emotional learning, the amygdala is able to modulate the strength of both declarative and nondeclarative memory. Source: Figure prepared by Larry R. Squire.

Figure 3
Consolidation of Memory in the Neocortex



Encoding of new information initially engages the hippocampus and a distributed set of specialized cortical areas (left panel). Subsequent reactivation of this hippocampal-cortical network progressively strengthens cortico-cortical connections or establishes new ones (middle panel). Eventually the cortico-cortical connections are sufficiently strong and stable for memory to be maintained and retrieved independently of the hippocampus (right panel). Source: Paul W. Frankland and Bruno Bontempi, "The Organization of Recent and Remote Memories," *Nature Reviews Neuroscience* 6 (2005): 119 – 130.

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unaided recall or after the presentation of a partial reminder? The notion is that remembering becomes possible because medial temporal lobe structures, by way of their widespread, divergent connections to the neocortex, effectively bind together the distributed neocortical sites that together constitute the new memory. This connectivity supports the capacity for remembering during the consolidation process until the connectivity among the relevant cortical sites becomes strong enough to represent a stable memory without the support of the medial temporal lobe.

A long-standing idea, which has received renewed attention in recent years, is that retrieval of memory provides an opportunity for updating or modulating what was originally learned and even the possibility of severely disrupting it.[33] The process by which a long-term memory transiently returns to a labile state (and then re-stabilizes) has been termed reconsolidation. Although it is clear that memory can be modified or distorted by memory retrieval, questions remain about the conditions under which memory can actually be abolished. Some studies in experimental animals report that a reactivated memory can be impaired but that the disruption is transient.[34] Other studies in animals report that only recent memories (ones that are one or seven days old, but not fourteen or twenty-eight days old) can be impaired after reactivation.[35]

Consolidation presumably requires some relatively long-lasting form of communication between the medial temporal lobe and the neocortex. One proposal for how this could be accomplished is through the phenomenon of neural replay. Recordings of neural activity in rodents showed that firing sequences of hippocampal neurons during waking behavior are then spontaneously replayed during subsequent slow-wave sleep.[36] Later it was found that hippocampal replay was coordinated with firing patterns in the visual cortex, which is consistent with the idea that a dialogue occurs between hippocampus and neocortex.[37] This coordination could be part of the process by which recent memories eventually become consolidated remote memories. Interestingly, disrupting replay activity in rodents during a rest period (filled by quiet wakefulness and slow-wave sleep) following spatial learning impairs later memory for the task.[38]

These studies with rodents led to conceptually similar studies with humans. For example, volunteers memorized the locations of card pairs on a computer screen while being exposed to a particular odor (the smell of a rose). Later, odor reexposure, specifically during slow-wave sleep, increased hippocampal activity (measured by neuroimaging) and lessened forgetting of the card pair locations following sleep.[39] In another study, the hippocampus and parahippocampal gyrus were active while participants learned routes in a virtual reality environment and were active again during subsequent slow-wave sleep.[40] The degree of activation during slow-wave sleep correlated with memory performance the next day. Studies like these have been interpreted to mean that consolidation results from the reactivation of newly encoded hippocampal representations, specifically during slow-wave sleep.[41]

An important question is whether neural replay and the consolidation process are specific to slow-wave sleep or whether these events might occur whenever the brain is not actively encoding new memories, such as during quiet wakefulness.[42] In rodents, neural replay can occur during wakefulness.[43] Moreover, in a neuroimaging study with humans, coordinated hippocampal-cortical activity occurred during a rest period that followed learning, and this activity predicted later memory performance.[44] Accordingly, an intriguing pos-

sibility is that the neural replay activity proposed to underlie memory consolidation may occur whenever the brain is in a quiet state (not just during slow-wave sleep).

Where are memories ultimately stored in the brain? A variety of evidence has converged on the view that the different aspects of remembered information are stored in the same regions of the brain that initially perform the processing and analysis of that information. According to this view, remembering a previous experience consists of the coordinated reactivation of the distributed neocortical regions that were activated during initial perceptual processing.[45] While the memory is still new, this reactivation of distributed cortical activity depends on the hippocampus and other medial temporal lobe structures, but once memory is fully consolidated, reactivation can occur within the neocortex itself. Each neocortical region operates within a specific domain and stores only the features of an experience – such as visual, auditory, or spatial information – that belong to that domain. Thus, as proposed by psychologist Karl Lashley long ago, memories are distributed throughout the neocortex.[46] However, contrary to his view, memory is not uniformly distributed. Some areas are more important for storing the visual aspects of an experience, and other areas are more important for storing other aspects.

An implication of this view is that neocortical lesions that selectively impair perceptual processing in a particular domain (such as the perceptual processing of color) should also cause correspondingly specific anterograde and retrograde memory impairment within the same domain. This circumstance is illustrated by "The Case of the Colorblind Painter," a case described by the neurologist Oliver Sacks.[47] An accomplished painter was involved in an automobile accident at the age of sixty-five, which rendered him color-blind. The disability was striking: he could discriminate between wavelengths of light, even though the different wavelengths gave rise to the perception of various shades of gray rather than the perception of different colors. Because his condition was acquired (it was not congenital), it was possible to interrogate not only his ability to form new color memories, but also the status of previously established memories that had once included the subjective experience of color. The case description leaves little doubt that the patient's experience – both going forward and looking back – was now completely (and selectively) devoid of color. Although he retained abstract semantic knowledge of color, he could neither perceive nor later remember the color of objects presented to him (anterograde impairment). In addition, he could not subjectively experience color in his earlier (and once chromatic) memories. For example, he knew that his lawn was green, but he reported that he could no longer visualize it in green when he tried to remember what it once looked like.

Note the difference between the effect of this cortical lesion on memory and the effect of bilateral medial temporal lobe lesions. With respect to remote memories that have already been fully consolidated, medial temporal lobe lesions have little effect. In contrast, focal cortical lesions can selectively abolish one feature (like color) of a long-consolidated memory. With respect to new experiences, bilateral medial temporal lesions lead to severe anterograde amnesia (no subsequent memory for a recent experience). In contrast, focal cortical lesions of the kind suffered by the painter prevent the encoding and retrieval of only one aspect of the experience (color in his case). Because the processing of color in the painter's neocortex was impaired, his experience of color was eliminated in both perception and memory.

Selective deficits in long-term knowledge of the kind suffered by the painter are not limited to perceptual experience. Semantic knowledge (knowledge about objects, facts, and word meanings) is also stored in neocortical regions that can be selectively damaged.[48] Thus, damage limited to lateral regions of patients' temporal lobe (close to, but not including, medial temporal lobe structures) can disrupt previously stored information – such as what an animal looks or sounds like. Such patients have difficulty naming pictures of animals and providing information about them. Other patients with damage to the parietal cortex can have difficulty identifying small manipulable objects (like spoons and brushes) and knowing how to use them. Neuroimaging studies support the findings from lesion studies and show that the properties of objects, together with how they are perceived and used, influence which brain areas store long-term knowledge about their identity.[49]

The information in the preceding sections helps illuminate some of the memory deficits associated with normal aging and dementia. One of the most common experiences associated with normal aging is the decline in memory function. Oftentimes, the memory difficulty is characterized as poor "short-term" memory. In its common usage, a short-term memory problem means having trouble remembering recent experiences (such as when someone tells a story for the second time without remembering having told it before) while at the same time having no trouble remembering events from decades ago. Older adults who exhibit these symptoms are having difficulty encoding and consolidating new memories, while memories that were acquired and consolidated long ago are easy to retrieve. These changes in memory ability are related to changes within medial temporal lobe structures. In experimental animals, the dentate gyrus within the hippocampus is most sensitive to the effects of aging.[50] Studies in humans have reported between 1 and 2 percent annual hippocampal atrophy in non-demented adults older than fifty-five years.[51] Aerobic exercise can reverse age-related volume loss by one to two years.[52]

Alzheimer's disease, the most common form of dementia, is a progressive neurodegenerative condition. It is a distinct condition, not an acceleration of the normal aging process. The first targets of the disease are the entorhinal cortex and the CA1 field of the hippocampus, which explains why memory is especially affected in its early stages.[53] The rate of hippocampal volume loss is at least 2.5 times greater in Alzheimer's disease than in normal aging.[54] The disease progresses to involve intellectual functions quite broadly. The neocortex becomes involved (though sensory and motor areas are relatively spared) and patients develop difficulty with language, problem solving, calculation, and judgment.

Semantic dementia, another progressive disorder, begins elsewhere in the brain and is associated with a different pattern of symptoms.[55] This condition prominently involves atrophy of the anterior and lateral temporal lobes.[56] Unlike patients with Alzheimer's disease, these patients have severe loss of previously stored and long-consolidated semantic knowledge (that is, loss of conceptual knowledge about objects, facts, and word meanings). Yet their ability to form new memories can be relatively spared. Thus, patients could recognize which drawings of animals they had seen recently but failed at tests of conceptual knowledge about the same items.[57] Not just the name of the item is lost – the concept itself is degraded.

The understanding of memory has changed in ways that might have seemed

revolutionary to Karl Lashley when he searched for sites of memory storage in the brains of rats.[58] All that has been learned about the structure and organization of memory and about brain systems is the result of basic, fundamental research, mostly in rodents, monkeys, and humans. Although we did not review it here, much has also been learned from studies of the cellular and molecular basis of memory, an enterprise that has depended heavily on mice as well as invertebrate animals like *Aplysia* and *Drosophila*. As this work continues, one can expect not only new insights into how memory operates but also improved understanding of human health and disease, including improved ways to diagnose, treat, and prevent the diseases that affect memory.

ENDNOTES

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