

Genetics of Childhood Disorders: XLIX. Learning and Memory, Part 2: Multiple Memory Systems

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Memory is a broad topic that has its roots in both biology and psychology. Many of the important questions about memory concern structure, organization, and function and must be addressed at a relatively global, systems level of analysis. Two long-standing and interrelated questions of this kind have been of central interest. The first is whether there is more than one kind of memory. The second concerns what brain structures and pathways are important for memory. Scientific work directed at these questions has introduced the terms *declarative memory* and *nondeclarative memory* to neuroscience and identified a number of parallels between the neural organization of memory in humans and other animals.

The modern era of memory research began in 1957, when the profound effects of bilateral medial temporal lobe resection on memory were described in a patient who became known as H.M. This case became a landmark in the history of memory research for two reasons. First, the medial aspect of the temporal lobe was identified as an important region for memory function as his severe memory impairment could be linked directly to the brain tissue that had been removed. Second, comprehensive testing of this patient indicated that memory impairment could occur on a background of otherwise normal cognitive function. This observation showed that memory is to some extent an isolatable function, largely separable from perception and general intellectual functions.

These discoveries led ultimately to the development of an animal model of amnesia in the monkey and to the identi-

cation of the anatomical structures of what is now known as the medial temporal lobe memory system. The important structures are the hippocampus and the adjacent entorhinal, perirhinal, and parahippocampal cortices. The success of this effort in monkeys led to similar studies in rodents aimed at understanding the contribution of the hippocampus and related structures to memory. At the same time, continuing studies of H.M. and other memory-impaired patients made fundamental discoveries about how memory functions are organized.

A key discovery from the work with patients, monkeys, and rodents was that medial temporal lobe structures are essential for just one kind of memory, which has come to be termed *declarative memory*. Other kinds of memory, collectively termed *nondeclarative memory*, have been linked to other brain systems.

The important insight was that memory is not a single entity but is composed of several separate and parallel systems (Fig. 1). The major distinction is between the capacity for conscious knowledge of facts and events (declarative memory) and other nonconscious (nondeclarative) knowledge systems that support the capacity for skill learning, habit formation, the phenomenon of priming in which an earlier exposure to words or other material facilitates a latter performance, and certain other ways of interacting with the world where memory is experienced through performance rather than recollection.

Declarative memory is dependent on the integrity of the hippocampus and anatomically related structures in the medial temporal lobe and diencephalon. Declarative memory provides

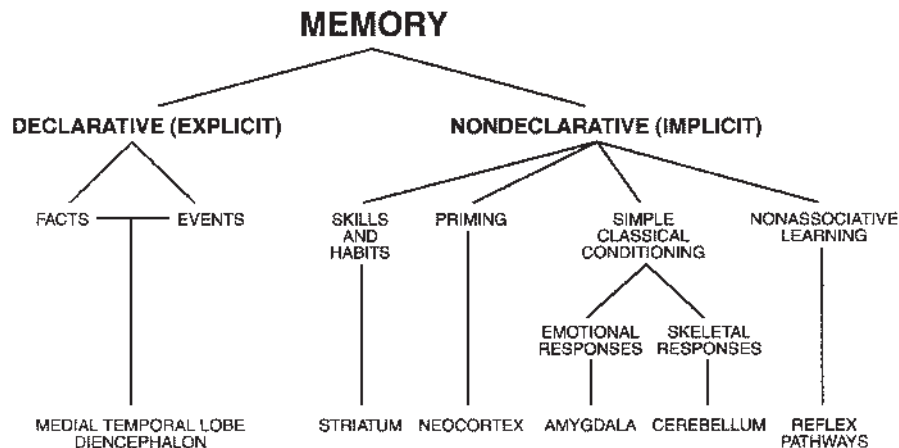


Fig. 1 A taxonomy of long-term memory systems together with specific brain structures especially important for each system.

the ability to associate the various aspects of a context that are present at a particular time and place, thereby creating a memory of an episode. Declarative memory is also well suited for connecting the pieces of information needed to acquire a new fact (e.g., the capitol of North Dakota is Bismarck). It is sometimes pointed out that declarative memory allows one to model the external world, and in that sense it is either true or false.

Declarative memory is the kind of memory impaired in medial temporal lobe amnesia. While work with amnesic patients has emphasized the notion of conscious recollection, the concept of declarative memory is not defined solely in terms of what amnesic patients can and cannot learn. Other characteristics have been identified that have made it possible to extend the concept to experimental animals. Declarative memory is fast, it is not always reliable (i.e., forgetting and retrieval failure can occur), and it is flexible in the sense that it is accessible to multiple response systems. It is especially suited for one-trial learning and for forming and maintaining an association between two arbitrarily different pieces of material, e.g., as in the case of conventional paired-associate learning in which a person is asked to remember pairs of unrelated words.

A particularly good example of declarative memory involves the capacity to identify a recently encountered item as familiar, a capacity termed *recognition memory*. Recognition memory is impaired in amnesic patients, and it is impaired in monkeys and rats following damage to the hippocampal region. The finding that the hippocampal region is essential for normal recognition memory is consistent with current ideas about the role of the hippocampus in declarative memory and with the view that the hippocampus is essential for acquiring information about relationships or connections between stimuli. The recognition test asks whether an item that had been presented recently now appears familiar. For recognition to be successful, a link must be made at the time of learning between the to-be-remembered stimulus and its context or between the stimulus and an organism's interaction with it. It is this associating and the ability to retain relational information across time that many have supposed is at the heart of declarative memory and in turn is the function of the hippocampal region in both humans and nonhuman animals.

Recently, there has been interest in the possibility that some aspect of memory function might be associated specifically and uniquely with the hippocampus itself and, correspondingly, that some aspect of declarative memory might be independent of the hippocampus (and be supported instead by adjacent medial temporal cortex). These ideas are currently active topics of experimental work.

Whereas declarative memory is a brain-systems construct, tied to the brain structures and connections damaged in amnesia, nondeclarative memory refers to a heterogeneous collection of several kinds of memory that in turn depend on distinct brain systems (Fig. 1). Thus classical conditioning of skeletal

musculature depends on the cerebellum, conditioning of emotional responses depends on the amygdala, and habit learning (win-stay, lose-shift responding) depends on the neostriatum. The amygdala can also modulate the strength of both declarative and nondeclarative forms of memory. Finally, perceptual priming likely depends on changes in early-stage cortical areas involved in processing the stimuli that are primed.

Nondeclarative memory is expressed through performance. Unlike declarative memory, it is neither true nor false. Nondeclarative memory refers to the variety of ways in which experience can lead to altered dispositions, preferences, and judgments without affording any necessary conscious memory content. Performance changes as the result of experience and in this sense deserves the term *memory*, but performance changes without an accompanying sense that memory is being consulted. The organism simply behaves differently than it did previously. In many cases, performance changes slowly, as when one learns gradually about the causal structure of the environment and acquires new procedures for interacting with the world (in the case of conditioning, skill learning, or habit learning). Sometimes performance can change rapidly (in the case of fear conditioning or conditioned taste aversion). In the latter cases, the possibility of rapid change may be built into evolutionarily important systems that are specialized to process or associate particular kinds of information.

Eyeblink classical conditioning has provided a useful paradigm for exploring the distinction between declarative and nondeclarative forms of memory in humans and other animals. In eyeblink classical conditioning, a conditioned stimulus (CS; typically a tone) is presented just prior to an unconditioned stimulus (US; typically a puff of air to the eye). After repeated pairings of the CS and US, subjects begin to blink in response to the CS. The eyeblink response is a learned or conditioned response. The two most commonly studied forms of eyeblink classical conditioning are delay conditioning and trace conditioning. In delay conditioning, the CS is presented and remains on until the US is presented. The two stimuli then overlap and coterminate. In trace conditioning, an empty or "trace" interval separates the CS and the US.

Work with rabbits first demonstrated a clear distinction between delay and trace conditioning. The acquisition and retention of delay conditioning require the cerebellum and associated brainstem structures. No tissue above the level of the midbrain, including the hippocampus, is required. Thus delay conditioning appears to be an example of nondeclarative memory. Trace conditioning is fundamentally different. Like delay conditioning, successful trace conditioning requires the cerebellum but trace conditioning differs from delay conditioning in that it also requires the hippocampus and specific regions of neocortex. Trace conditioning appears to require the hippocampus because declarative knowledge of the CS-US relationship must build up and be maintained across many trials.

This link between trace conditioning and declarative knowledge was first demonstrated by showing that awareness of the stimulus contingencies is critical for differential trace conditioning. In differential conditioning, the CS+ (e.g., a tone) is followed by the US, and the CS- (e.g., a static noise) is presented alone. Successful differential conditioning occurs when more conditioned responses are elicited by the CS+ than by the CS-. Because there are several relationships among the stimuli about which a participant can become aware, a variety of questions can be asked about the stimulus contingencies, and a participant's answers to these questions can be related to conditioning performance. The finding of interest in the case of trace conditioning was that only individuals who developed awareness of the CS-US relationship conditioned successfully. Individuals who did not develop knowledge of the CS-US relationship did not acquire trace conditioning. Studies of amnesic patients with damage that included the hippocampus have also been informative. Amnesic patients failed to acquire differential trace conditioning and also failed to become aware of the stimulus contingencies. The same patients were subsequently able to acquire differential delay conditioning as readily as intact subjects.

These results indicate that trace conditioning requires an additional level of processing that is not required for delay conditioning. Specifically, trace conditioning (but not delay conditioning) requires the participation of the hippocampus and presumably its interaction with neocortex. Awareness may emerge during trace conditioning because awareness is a typical feature of hippocampus-dependent learning. In this sense, awareness is a reliable indicator of a brain state (a state of interaction between the hippocampus and neocortex) that is essential for forming and storing declarative memory.

Finally, the notion of multiple memory systems provides a way to think about the phenomenon of infantile amnesia (i.e., the relative unavailability of memories for events that occur before the third year of life). There is good evidence that the declarative memory system is functional, to at least some degree, in early life. Accordingly, the absence or slow development of this memory system cannot account for the phenomenon of infantile amnesia.

If declarative memory is available to infants, then what accounts for infantile amnesia? One clue comes from the finding in monkeys that suggests that the capacity for forming and maintaining declarative memories may be limited, not by the maturation of the structures essential for declarative memory but rather by gradual maturation of the neocortical areas that are served by these structures and that are believed to be the repositories of long-term, permanent memory. This perspective is an appealing one because it provides a point of contact between a neurological account of infantile amnesia and accounts grounded in cognitive psychology that emphasize the gradual maturation of cognition, the emergence of skills and strategies

for organizing information into knowledge systems, the development of language, and the growth of individual identity.

The cognitive and neuroanatomical work described here is a first step in analyzing how the brain has organized its memory functions. With respect to declarative memory, neuroscience is approaching a time when it will be possible to study representations directly in neocortex with single-cell recording, to observe directly the development of neural plasticity, and to determine how the medial temporal lobe interacts with neocortex during learning, the consolidation of memories, and their retrieval. With respect to nondeclarative memory, it has been possible to identify particular brain systems that are essential for particular kinds of memory. The next step will be to determine whether these systems are essential for the acquisition, storage, or expression of memory and to identify exactly where the synaptic changes occur that support each kind of memory. Cellular and molecular studies of experimental animals will be particularly useful in this work; some of the work in this area will be examined over the next several months in this column.

WEB SITES OF INTEREST

<http://www.brembs.net/learning/>
<http://www.cns.nyu.edu/home/ledoux/html>

ADDITIONAL READINGS

- Baddeley AD, Wilson BA, Kopelman M (2002), *Handbook of Memory Disorders*, 2nd ed. New York: Wiley
- Clark RE, Manns JR, Squire LR (2002), Classical conditioning, awareness and brain systems. *Trends Cogn Sci* 6:524-531
- Eichenbaum H, Cohen NJ (2000), *From Conditioning to Conscious Recollection: Memory Systems of the Brain*. New York: Oxford University Press
- Schacter D (1996), *Searching for Memory*. New York: Basic Books
- Schacter D, Buckner RL (1998), Priming and the brain. *Neuron* 20:185-195
- Squire LR, Kandel ER (1999), *Memory: From Mind to Molecules*. New York: WH Freeman
- Squire LR, Schacter DL (2002), *The Neuropsychology of Memory*, 3rd ed. New York: Guilford
- Squire LR, Zola-Morgan S (1991), The medial temporal lobe memory system. *Science* 253:1380-1386
- Tulving E, Craik FIM (2000), *The Oxford Handbook of Memory*. New York: Oxford University Press

Accepted November 22, 2002.

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0890-8567/03/4204-0504©2003 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.CHI.0000046815.95464.34