Memory: **Old questions, new perspectives**

Howard Eichenbaum

Studies with targeted mouse mutants are helping to clarify our understanding of cellular mechanisms that underlie memory. Now this approach is also providing tools for resolving controversies about cognitive processes in memory that have perplexed behavioral scientists for many years.

Address: Laboratory of Cognitive Neurobiology, Department of Psychology, Boston University, Boston, Massachusetts 02181, USA.

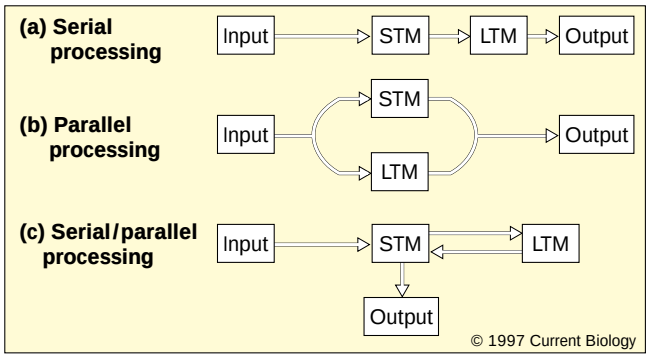
Electronic identifier: 0960-9822-007-R0053

Current Biology 1997, 7:R53–R55

Our understanding of memory has benefited from studies directed at multiple levels: cognitive psychology, neural systems analysis and cellular physiology. As in many areas of research, experiments using these approaches usually offer insights that are meaningful only within the same level of analysis. But memory research is 'hot' these days because recent advances in both systems and cellular neuroscience have offered new perspectives on the cognitive processes that define memory. For example, over the last decade studies at the neural systems level have revealed that many otherwise impenetrable memory phenomena can be unraveled as distinct, and more understandable, operating characteristics of separate neural pathways [1]. Now research on the molecular mechanisms of plasticity, originally aimed at revealing the underlying cellular substrates of memory, is also offering new insights into its psychological phenomena. Two examples of this new direction, one published in last month's *Current Biology* [2] and the other in this issue [3], are the focus of the present commentary.

Among the many conundrums about memory, two fundamental and long-standing questions have never been fully resolved by research at the cognitive level. One of these questions focuses on the transition of memories from short-term to long-term storage. The other concerns how we benefit by practice. A fresh look at both these problems has been provided by the research of Silva and colleagues [2,3], who have exploited advances in molecular genetics by generating targeted mutations in the mouse that disrupt different forms of synaptic plasticity that might underlie memory. Some of the mutations affect short-lived plasticity mechanisms that may mediate briefly held memories, and others selectively disrupt long-term potentiation (LTP), the lasting synaptic enhancement widely believed to reflect a mechanism for storing permanent memories [4]. Silva and colleagues suggest that, by exploring the learning capacities of mice with these different mutations, the tools of molecular genetics can be used to dissociate the cognitive processes that constitute memory.

Figure 1



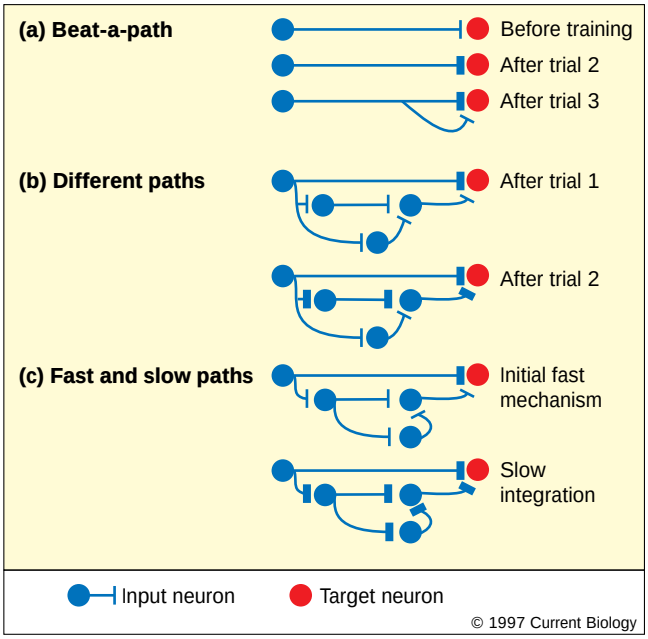
Models of short-term and long-term memory. In model (a), memories are held initially in short-term memory (STM) and may eventually be transferred to a long-term memory (LTM) store. In model (b), inputs are processed independently by brief and long-lasting memory systems. In model (c), short-term (working) memory interacts with a long-term store to hold and retrieve information.

Short-term and long-term memory: serial or parallel processes?

We have known for many years that memory can be divided into short-term and long-term stages, as shown for example by cases where the capacity for permanent memory is lost as a result of brain damage, while the ability to retain new information briefly is spared [5]. Two different views have guided most thinking about the relationship between short-term and long-term stages of memory storage. By one view, short-term memory is the requisite gateway to permanent storage (Fig. 1a). According to this serial-processing model, sensory events are encoded by perceptual systems and these representations are kept alive by reverberatory circuits — in which activity is continuously generated by one neuron activating another — or rapid 'switches' within synapses that drive nuclear mechanisms for the lasting structural changes underlying permanent memory.

An alternative view is that sensory representations are committed to distinct and parallel subsystems for short-term and long-term memory (Fig. 1b). The short-term subsystem likely involves functions of the prefrontal cortex that support 'working memory', the capacity used, for example, to retain a phone number for several seconds or remember where one put the car in a parking lot that day. According

Figure 2



Network models of associative learning (thin-line 'synapses' are weak; thick-line 'synapses' are strong). In model (a), the synapse mediating a single associative pathway is slowly strengthened and then expanded with repeated trials. In model (b), different paths are each quickly strengthened with a repeated experience. In model (c), a quickly-acquired path initially stores information; afterwards, rehearsal or unconscious re-excitations of this pathway strengthens multiple slowly-acquired pathways allowing integration of new information into a large and diverse network.

to this view, the subsystem for long-term memory involves a separate pathway through the medial temporal region [1]. Support for this parallel systems model comes mainly from the demonstration that specific cortical damage can selectively devastate working memory capacity while sparing the ability to form long-term memories [6].

The recent experiment by Silva *et al.* [2] offers new evidence suggesting short-term memory mechanisms may indeed play a important role in the formation of permanent memories, although not an absolutely required function. The studies focused on different targeted mutations that disrupt two forms of short-lived plasticity. One form, called paired pulse facilitation, involves enhanced synaptic responses on the second of two rapid-fire afferent stimulations. The other, called post-tetanic potentiation, involves several seconds of synaptic enhancement following a burst of input activity. Either or both of these mechanisms could support short-term or working memory. However, neither type of short-lived plasticity is required for LTP, as demonstrated by an intact capacity for LTP in mutant mice lacking short-lived plasticity. The new findings are that mutants defective in either type of short-lived plasticity have severe deficits in both short-term and long-term memory, and the impairment was observed across two different tasks for which performance depends on hippocampal or amygdala function. However, some learning capacity was spared — this was revealed after more intensive training.

This combination of findings suggests, first, that there exist distinct and parallel synaptic mechanisms that could separately support short-term and long-term memory, consistent with the behavioral evidence for independent short-term and long-term memory mechanisms from neuropsychological studies. Second, even though these synaptic mechanisms are independent, they may work cooperatively in the formation of the permanent memory trace. This conclusion favors a combination parallel–serial model, such as the one outlined in Figure 1c, consistent with the view that short-term memory can be fully independent of long-term memory, but that the short-term processing contributes substantially to laying down the permanent memory trace.

Why is spaced training more effective than massed training?

Animals and humans learn fastest when repeated training trials are widely spaced in time. Two divergent views have guided theorizing about this observation [7]. One view is that the molecular machinery that underlies long-term cellular plasticity, probably involving protein synthesis, may achieve maximal production rapidly but requires several minutes or even hours to complete its course (Fig. 2a). Massing training trials closely together may not substantially raise the level of production beyond that initiated by a single trial. By this account, one might view spaced training as the most efficient way to 'beat a path' to a memory.

The other view is that widely spaced repetitions of information are likely to occur in different informational contexts, that is among different preceding and following events, thus creating or extending a large network of convergent associations (Fig. 2b). By contrast, closely spaced repetitions are likely to occur within the same context, and correspondingly activate the identical association pathway during repetitions. Because the likelihood of retrieval is improved by increasing the number of access routes to a memory, it may be more effective to have more associations than a stronger single association. By this account, one might view spaced training as more effective because it generates 'different paths' to the representation.

In this issue of *Current Biology*, Kogan *et al.* [3] confirm earlier findings that mice lacking cAMP response-element-binding protein (CREB), and consequently deficient in LTP, show severe memory impairments in single trial or massed trial learning [8]. They go on to show, however, that spaced training can overcome memory

deficits across several different types of learning. These and other results suggest the existence of multiple forms of cellular plasticity supporting permanent memory. One form, mediated by CREB activation, may have a brief time course, or may not reach saturation with single trial experiences, and so would be expected to benefit from repetition even when trials are closely spaced. This mechanism might work best where different paths are activated across trials. There may be another form of long-term plasticity, not dependent on CREB, that normally requires repeated experiences and has a longer time course, so that there is a greater benefit of spaced over massed trials. This mechanism can be viewed as most consistent with the beat-a-path model.

The observations of Kogan *et al.* [3] also reveal a surprising universality of CREB involvement in laying down the path for such diverse situations as fear conditioning, maze memory and social learning. Furthermore, the existence of the two kinds of long-term plasticity — one rapid and CREB-dependent, the other slow and CREB-independent — generates interesting possibilities for the organization of memory across trials and potentially across different types of learning experience. Perhaps the modulation of rapid and slow processes allows the interleaving of divergent associations, by having rapidly formed memories guide a slower reorganization of a large network into which new memories must fit. Such an interplay of fast and slow processing (Fig. 2c) has been suggested in recent theorizing about memory consolidation mediated by the hippocampus and cortex [9,10].

These new findings on cellular plasticity and memory performance do not fully resolve the long-standing controversies about short-term and long-term memory or massed and spaced training. But they add new and sophisticated perspectives to these problems, and suggest that exploiting the tools of molecular biology can provide us with new ways to dissect, and ultimately to understand, some very complicated aspects of cognition.

References

1. Schacter DL, Tulving E (eds): *Memory Systems*. Cambridge: MIT Press;1994.
2. Silva AJ, Rosahl TW, Chapman PF, Marowitz Z, Friedman E, Frankland PW, Cestari V, Cioffi D, Sudhof TC, Bourtchuladze R: Impaired learning in mice with abnormal short-lived plasticity. *Curr Biol* 1996, 6:1509–1518.
3. Kogan JH, Frankland PW, Blendy JA, Coblentz J, Marowitz Z, Schultz G, Silva AJ: Spaced training rescues the memory deficits of CREB mutant mice. *Curr Biol* 1997, 1:1–11.
4. Goda Y, Stevens CF: Synaptic plasticity: the basis of particular types of learning. *Curr Biol* 1996, 6:375–378.
5. Squire, LR: *Memory and Brain*. New York: Oxford Univ Press; 1987.
6. Warrington EK, Shallice T: The selective impairment of auditory verbal short term memory. *Brain* 1969, 92:885–896.
7. Greene RL: Spacing effects in memory: evidence for a two-process account. *J Exp Psychol: Learn Mem Cog* 1989, 15:371–377.
8. Frank DA, Greenberg ME: CREB: a mediator of long-term memory from mollusks to mammals. *Cell* 1994, 79:5–8.
9. Alvarez P, Squire L: Memory consolidation and the medial temporal lobe: a simple network model. *Proc Nat Acad Sci USA* 1994, 91:7041–7045.
10. McClelland JL, McNaughton BL, O'Reilly RC: Why there are complementary learning systems in the hippocampus and neocortex: insights from successes and failures of connectionist models of learning and memory. *Psychol Rev* 1995, 102:419.