Memory–a Century of Consolidation

Article *in* Science · February 2000

DOI: 10.1126/science.287.5451.248 · Source: PubMed

1 author:

James L Mcgaugh
University of California, Irvine
415 PUBLICATIONS **34,572** CITATIONS

SEE PROFILE

REVIEW: NEUROSCIENCE

Memory—a Century of Consolidation

James L. McGaugh

The memory consolidation hypothesis proposed 100 years ago by Müller and Pilzecker continues to guide memory research. The hypothesis that new memories consolidate slowly over time has stimulated studies revealing the hormonal and neural influences regulating memory consolidation, as well as molecular and cellular mechanisms. This review examines the progress made over the century in understanding the time-dependent processes that create our lasting memories.

A century has passed since Müller and Pilzecker proposed the perseveration-consolidation hypothesis of memory (*1*). In pioneering studies with human subjects, they found that memory of newly learned information was disrupted by the learning of other information shortly after the original learning and suggested that processes underlying new memories initially persist in a fragile state and consolidate over time. At the beginning of this new millennium, the consolidation hypothesis still guides research investigating the time-dependent involvement of neural systems and cellular processes enabling lasting memory (*2–4*).

Retrograde Amnesia and Memory Enhancement

Clinical evidence that cerebral trauma induces loss of recent memory was reported two decades before the publication of Müller and Pilzecker's monograph, and shortly after its publication, it was noted that the consolidation hypothesis provided an explanation for such retrograde amnesia (*5*). Ignored for almost half a century, the consolidation hypothesis was reinvigorated in 1949, when two papers reported that electroconvulsive shock induced retrograde amnesia in rodents (*6, 7*), triggering a burst of studies of experimentally induced retrograde amnesia (*2–4*). That same year, Hebb and Gerard proposed dual-trace theories of memory, suggesting that the stabilization of reverberating neural activity underlying short-term memory produces long-term memory (*7, 8*). The finding that protein synthesis inhibitors did not prevent the learning of tasks but disrupted memory of the training (*9*) supports the view that there are (at least) two stages of memory and indicates that protein synthesis is required only for consolidation of long-term memory. The issue of whether short- and long-term memory (and, perhaps, other memory stages) (Fig. 1) are sequentially linked, as proposed by Hebb and Gerard, or act independently in parallel (*3, 10*) remains central to current inquiry. The discovery that stimulant drugs administered within minutes or hours after training enhance memory consolidation further stimulated studies of memory consolidation (*3, 10, 11*). The use of treatments administered shortly after training to impair or enhance memory provides a highly effective and extensively used method of influencing memory consolidation without affecting either acquisition or memory retrieval (*11*).

Endogenous Modulation of Consolidation

Memory consolidation appears to be a useful function, because evidence of consolidation is found in a wide variety of animal species (*12, 13*). Why do our memories and those of other animals consolidate slowly? The answer might simply be that the molecular and cellular machinery creating memory works slowly. But that answer is clearly wrong, because "short-term" or "working" memories are created almost immediately. All our cognitive and motor skills require quickly accessible new memory. Furthermore, there is no a priori reason to assume that biological mechanisms are not capable of quickly consolidating memory. Considerable evidence suggests that the slow consolidation of memories serves an adaptive function by enabling endogenous processes activated by an experience to modulate memory strength (*14*). Emotionally arousing experiences are generally well remembered (*15*). Adrenal stress hormones, epinephrine and cortisol (corticosterone in the rat), released by emotional arousal appear to play an important role in enabling the significance of an experience to regulate the strength of memory of the experience. Epinephrine (*16*, *17*) and corticosterone (*13, 18, 19*), as well as drugs that activate adrenergic receptors and glucocorticoid (type II) receptors (*13, 18, 19*), enhance memory for many kinds of training experiences.

Critical Involvement of the Amygdala in Memory Consolidation

Epinephrine does not freely pass the blood-brain barrier and appears to modulate memory consolidation by activating β-adrenergic receptors located peripherally on vagal afferents projecting to the nucleus of the solitary tract in the brainstem. Noradrenergic projections from this region influence neuronal activity in other brain regions, including the amygdala (*20*). Glucocorticoids released from the adrenal cortex readily enter the brain and activate intracellular glucocorticoid receptors (Fig. 2). Activation of the amygdala, a brain region important for emotional arousal, is critical for mediating the influences of epinephrine and glucocorticoids, because amygdala lesions block the effects of these modulators on consolidation. Most important, activation of β-adrenergic receptors in the amygdala is essential. Infusions of β-adrenergic receptor antagonists into the amygdala

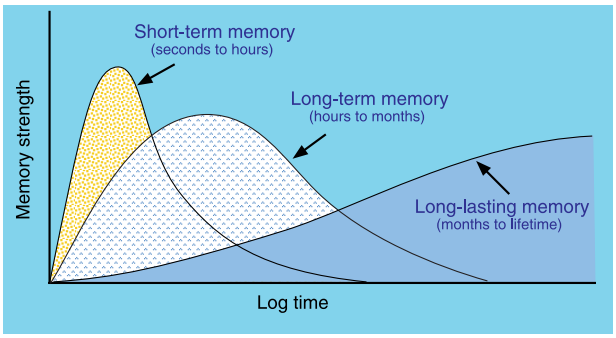

Fig. 1. Memory consolidation phases. Studies of memory and neuroplasticity support Müller and Pilzecker's hypothesis proposing that the consolidation of new memory into long-term memory is time dependent (*1*), but strongly suggest that short-term and different stages of long-term memory are not sequentially linked, as proposed by the dual-trace hypothesis (*9*). Evidence that drugs can selectively block either short-term (seconds to hours) or long-term memory (hours to months) suggests that time-dependent stages of memory are based on independent processes acting in parallel. Later stages of consolidation resulting in memory lasting a lifetime likely involve interaction of brain systems in reorganizing and stabilizing distributed connections.

The author is at the Center for the Neurobiology of Learning and Memory and the Department of Neurobiology and Behavior, University of California Irvine, Irvine, CA 92697, USA. E-mail: jlmcgaug@uci.edu

after training block epinephrine effects, whereas infusions of β-adrenergic receptor agonists enhance memory (*21*). Lesions of the amygdala and infusions of β-adrenergic receptor antagonists into the amygdala also block the memory-modulating effects of drugs affecting systems containing γ-aminobutyric acid (GABA) and opioid peptides (*20*).

The basolateral nucleus of the amygdala (BLA) mediates the influences of drugs and hormones on memory consolidation. β-Adrenergic receptor agonists infused selectively into the BLA after training enhance memory, and lesions of the BLA or infusion of β-adrenergic receptor antagonists into the BLA block the memory-enhancing effects of systemically administered dexamethasone (a synthetic glucocorticoid) (*22, 23*). Modulatory influences on consolidation include release of norepinephrine (NE) within the amygdala. For example, foot-shock stimulation induces NE release in the amygdala; administration of epinephrine or drugs that enhance consolidation (such as GABA and opioid receptor antagonists) increases NE release in the amygdala; and the use of drugs that impair memory (such as GABA and opioid receptor agonists) decreases NE release (*24*).

Locus of Modulation: Brain Systems and Forms of Memory

It is increasingly clear that different brain regions process different forms of memory (*25*). Evidence from rat studies indicates that the hippocampus and striatum process different forms of memory (*26*) and that the amygdala modulates consolidation by regulating processing in these brain regions. Amphetamine infused into the dorsal hippocampus after training selectively enhances memory of the spatial localization of a slightly submerged (and thus not visible to the rat) escape platform in a water-maze, whereas amphetamine infused into the striatum selectively enhances memory of a prominent visual cue located on an escape platform placed in varying locations on different training trials. Most important, amphetamine infused into the amygdala after training enhances memory of both types of training. The amygdala is clearly not the locus of the enhanced memory, because inactivation of the amygdala (with lidocaine infusions) before the retention test does not block expression of the enhanced memory for either type of training (*27*).

Because glucocorticoid receptors are densely located in the hippocampus, these receptors are likely involved in mediating glucocorticoid influences on consolidation (*19*). Evidence that infusions of a glucocorticoid agonist into the dorsal hippocampus after training enhance memory supports this view. The BLA is critically involved in enabling this glucocorticoid influence. BLA lesions or infusions of β-adrenergic receptor antagonists into the BLA block the effects of glucocorticoids either administered systemically or infused directly into the dorsal hippocampus (*23, 28*). These findings provide further evidence that modulating influences from the BLA regulate memory consolidation occurring within or mediated by the hippocampus. As discussed below, the molecular and cellular changes mediating the induction of long-term potentiation (LTP) in the hippocampus are widely considered to provide a basis for memory. Thus, it is of considerable interest that lesions of the BLA or infusions of a β-adrenergic receptor antagonist into BLA block the induction of LTP in the dentate gyrus of the hippocampus and that stimulation of the BLA enhances such LTP (*29*).

It is clear from these findings that memory consolidation involves interactions among neural systems, as well as cellular changes within specific systems, and that amygdala is critical for modulating consolidation in other brain regions. Although research has focused primarily on amygdala influences on memory related to the caudate nucleus and hippocampus, the modulation is most certainly not restricted to these brain regions.

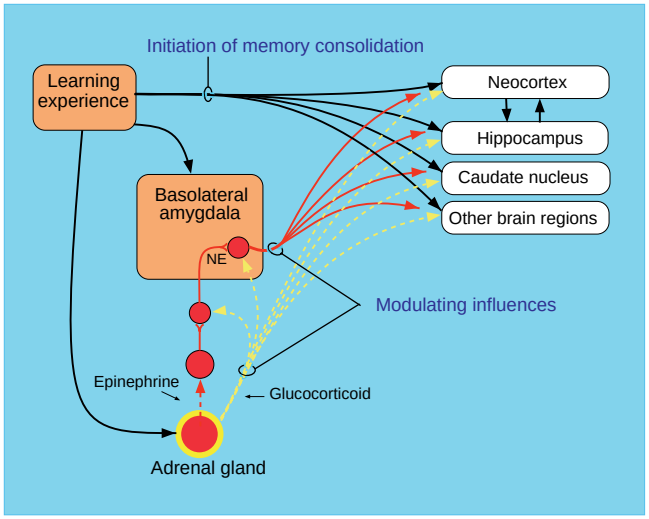

Fig. 2. Neurobiological systems regulating memory consolidation. Experiences activate time-dependent cellular storage processes in various brain regions involved in the forms of memory represented. The experiences also initiate the release of the stress hormones from the adrenal medulla and adrenal cortex and activate the release of norepinephrine in the basolateral amygdala, an effect critical for enabling modulation of consolidation. The amygdala modulates memory consolidation by influencing neuroplasticity in other brain regions.

Emotional Arousal and Memory Consolidation in Humans

Although the consolidation hypothesis was based on human memory results, most research on consolidation has studied memory in animals. The animal memory findings have reactivated interest in human memory consolidation. Amphetamine administered to human subjects either before or after learning of word lists enhances memory of the words (*30*). Results of human studies, like those of animal studies, indicate that adrenergic systems and amygdala activation influence memory consolidation. Recent studies found that β-adrenergic receptor antagonists block the memory-enhancing effects of emotional arousal (*31*). Studies examined the effects of β-adrenergic receptor antagonists or a placebo on the memory of pictures accompanied by an emotionally arousing story. Subjects given a placebo before presentation of the pictures and story remembered best the pictures presented during the most emotional part of the story. In contrast, in subjects given a β-adrenergic receptor antagonist, memory for those pictures was not enhanced. β-Adrenergic receptor antagonists (taken as medication) also blocked arousal-induced enhancement of memory in elderly subjects. Emotional arousal also does not enhance long-term memory of the arousing material in human subjects with selective lesions of the amygdala (*32*). Additionally, studies using PET (positron emission tomography) scans to assess amygdala activity induced by emotionally arousing stimuli (both pleasant and unpleasant) found that long-term memory correlates with the degree of amygdala activation during the original encoding (*33*).

As Time Goes By: The Orchestration of Consolidation

Changes in brain activity after learning provide additional insights into the time course of consolidation processes. A study of functional brain activity in human subjects (with PET) revealed shifts in activity among different brain regions occurring over a period of several hours after the learning of a motor skill, suggesting that consolidation involves time-dependent reorganization of the brain representation underlying the motor skill (*34*). Studies of learning-induced changes in receptive fields in the auditory cortex provide additional evidence that neural processes activated by training continue to change for several days, after completion of training (*35*). Neurons in the auditory cortex of ani-

mals given a brief training session in which a specific tone was paired with foot shock subsequently responded more to that tone and less to other tones. Furthermore, the degree of selectivity in the "frequency tuning" continued to increase for several days, suggesting continuing consolidation of the memory of the tone's increased significance. It would be of considerable interest to know whether inactivation of the BLA blocks such consolidation.

Most research on memory consolidation examined the effects of treatments administered within several hours after training. It cannot be concluded from such research that consolidation is completed within hours, because the effectiveness of a treatment in modulating consolidation depends on the locus and mechanism(s) of action of the treatment, as well as the state of consolidation when the treatment is administered (*14*). Lesions of the hippocampus (or adjacent cortical areas) and sustained drug infusions into the hippocampus impair memory for training given days, or even weeks, earlier (*36*). Thus, although the hippocampus and anatomically related structures are no doubt involved in consolidation, and may well be a locus of temporary neural changes that influence the establishment of long-term memory, those brain regions are clearly not unique loci of long-term memory. This conclusion was first drawn from studies of the patient H.M. after bilateral surgical excision of his medial temporal lobes (*37*) The hippocampus may have a long-term or perhaps even a sustained role in consolidating memory (*36*, *38*). Such consolidation may involve extensive interaction of the hippocampus and related cortex with the neocortex as well as other brain regions, serving to link the sites and enable regions to strengthen or reorganize connections with the others, as well as to organize and reorganize the information being consolidated (*38, 39*).

Cellular Machinery of Consolidation

Because of evidence suggesting that the hippocampus is active in memory consolidation (for some forms or aspects of memory), as well as the hypothesis that cellular and molecular mechanisms underlying LTP may enable memory consolidation, the relation between hippocampal LTP and memory is the focus of intense investigation (*40*, *41*). It is important to note that because the cellular and molecular changes occur mostly within hours after LTP induction or training, they are reasonable candidates for consolidation mechanisms occurring within that time frame. Different processes occurring in other brain regions are likely involved in memory consolidation occurring over days, months, or years (*36*).

As discussed above, extensive evidence indicates that the BLA influences memory processes and LTP in other brain regions. Treatments known to affect memory consolidation also modulate the maintenance of hippocampal LTP in freely moving rats (*42*). Water given to thirsty rats within 30 min after induction of LTP enhanced the maintenance of LTP. Foot shock administered after LTP induction also enhanced LTP. A β-adrenergic receptor antagonist blocked the enhancing effects of both the water reward and foot shock on LTP. As with learning in intact animals, inhibition of protein synthesis after the induction of LTP in a hippocampal slice blocks the maintenance (that is, late phase) of LTP but does not block the induction (that is, early phase) of LTP (*43*).

Many recent experiments examined the effects, on memory consolidation, of drugs regulating specific molecular stages in the development and maintenance of LTP. Extensive evidence indicates the involvement of CaMKII (calcium-calmodulin–dependent protein kinase II) in both consolidation and LTP. CaMKII is known to phosphorylate the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluR1. Inhibitors of CaMKII block the induction of LTP and impair consolidation when infused into the amygdala or CA1 region of the hippocampus immediately after training (*41*, *44*). However, CaMKII appears to have different roles in consolidation in these two brain regions (*44*). Infusions of any of several drugs, including 8-bromo cyclic adenosine monophosphate (8-Br-cAMP), a dopamine D1 receptor agonist, or NE into the hippocampus (CA1 region) 3 hours after training attenuate the amnesic effect of a CaMKII inhibitor infused into the amygdala immediately after training. In contrast, such treatments administered 3 hours after training do not block the amnesia induced by a CaMKII inhibitor infused into the hippocampus immediately after training. These findings provide additional evidence that the amygdala plays a modulatory role in consolidation, whereas the hippocampus is more likely a locus of memory processing or consolidation.

Inhibitors of the signal-transducing enzyme protein kinase C (PKC) are also known to block the maintenance of hippocampal LTP and to induce retrograde amnesia when infused into the hippocampus of rats after training. Similarly, inhibitors of protein kinase A (PKA) disrupt the late, protein synthesis–dependent phase of LTP and impair memory when infused into the hippocampus several hours after training (*45*). Additionally, PKA activity and CREB (cAMP response element–binding protein) immunoreactivity increase in the hippocampus after training. Such findings suggest that late-phase LTP and memory consolidation involve cAMP-mediated activation, by PKA phosphorylation, of the CREB transcription factor (*46*). Evidence that infusions of CREB antisense oligonucleotides into the hippocampus block the consolidation of water-maze learning without affecting acquisition also supports this hypothesis (*47*). Discovering which of the myriad of CREB-regulated genes is (or are) selectively involved in memory consolidation will be an interesting quest. Selective gene activation or inactivation after learning may regulate consolidation by modulating the stabilization of synaptic changes required for long-term memory (*4, 48*). Neural cell adhesion molecules also appear to play a role in memory consolidation by regulating time-dependent processes underlying synaptic stabilization (*49*).

Memory: The Short and the Long of It

Many treatments affect late LTP and memory consolidation without affecting early LTP or short-term or working memory. Although such findings are consistent with the hypothesis that early and later stages of memory are serially linked (*9*), they do not exclude the possibility that different stages of memory are based on parallel, independent processes (*3, 10*). Moreover, studies of memory in many species strongly support this latter view (*12, 13*), and studies of synaptic facilitation in *Aplysia* clearly indicate that short-term facilitation (STF) and long-term facilitation (LTF) are not serially linked (*50*). Drugs and other conditions that block STF do not block the expression of LTF and, as with other forms of plasticity and memory, only LTF requires protein synthesis. Additionally, evidence that some drugs infused into the hippocampus and entorhinal cortex after training block short-term memory without affecting long-term memory provides critical evidence that short- and long-term memory processes are independent (*51*).

Evaluation of this evidence requires several caveats. First, it remains a hypothesis that the synaptic mechanisms of LTP and LTF underlie memory, whether fleeting or lasting (or long-lasting). Second, although studies of the mechanisms of LTP and memory have focused on the involvement of the hippocampus, much evidence indicates that the hippocampus has a time-limited role in the consolidation or stabilization of lasting memory, or both. Third, there are forms of memory that do not involve the hippocampus and may not use any known mechanisms of synaptic plasticity. Third, despite theoretical conjectures, little is as yet known about system and cellular processes mediating consolidation that continues for several hours or longer after learning to create our lifelong memories. These issues remain to be addressed in this new century of research on memory consolidation.

References and Notes

1. G. E. Müller and A. Pilzecker, *Z. Psychol.* **1**, 1 (1900).
2. S. E. Glickman, *Psychol. Bull.* **58**, 218 (1961); J. L. McGaugh and M. J. Herz, *Memory Consolidation*

(Albion, San Francisco, 1972); H. Weingartner and E. S. Parker, Eds., *Memory Consolidation* (Erlbaum, Hillsdale, NJ, 1984); H. A. Lechner, L. R. Squire, J. H. Byrne, *Learn. Mem.* **6**, 77 (1999); M. R. Polster, L. Nadel, D. L. Schacter, *J. Cogn. Neurosci.* **3**, 95 (1991).
3. J. L. McGaugh, *Science* **153**, 1351 (1966).
4. Y. Dudai, *Neuron* **17**, 367 (1996).
5. T. Ribot, *Diseases of Memory* (Appleton, New York, 1882); W. McDougall, *Mind* **10**, 388 (1901); W. H. Burnham, *Am. J. Psychol.* **14**, 382 (1903).
6. C. P. Duncan, *J. Comp. Physiol. Psychol.* **42**, 32 (1949).
7. R. W. Gerard, *Am. J. Psychiatry* **106**, 161 (1949).
8. D. O. Hebb, *The Organization of Behavior* (Wiley, New York, 1949) and (7). It is of interest that Hebb did not refer to the perseveration-consolidation hypothesis in his seminal 1949 book.
9. B. W. Agranoff, R. E. Davis, J. J. Brink, *Brain Res.* **1**, 303 (1965).
10. J. L. McGaugh, in *Recent Advances in Learning and Retention*, D. Bovet, F. Bovet-Nitti, A. Oliverio, Eds. (Accademia Nazionale dei Lincei, Rome, 1968), pp. 13–24.
11. J. L. McGaugh, *Annu. Rev. Pharmacol.* **13**, 229 (1973); *Brain Res. Bull.* **23**, 339 (1989).
12. T. M. Alloway and A. Routtenberg, *Science* **158**, 1066 (1967); T. Tully, T. Preat, S. C. Boynton, M. Del Vecchio, *Cell* **79**, 35 (1994); R. Menzel and U. Müller, *Annu. Rev. Neurosci.* **19**, 379 (1966); U. Müller, *Neuron* **16**, 1249 (1996).
13. C. Sandi and S. P. R. Rose, *Brain Res.* **647,** 106 (1994).
14. P. E. Gold and J. L. McGaugh, in *Short-Term Memory*, D. Deutsch and J. A. Deutsch, Eds. (Academic Press, New York, 1975), pp. 355–378.
15. S.-A. Christianson, Ed., *Handbook of Emotion and Memory*: *Current Research and Theory* (Erlbaum, Hillsdale, NJ, 1992).
16. P. E. Gold and R. van Buskirk, *Behav. Biol.* **13**, 145 (1975).
17. J. L. McGaugh and P. E. Gold, in *Psychoendocrinology*, R. B. Brush and S. Levine, Eds. (Academic Press, New York, 1989), pp. 305–339.
18. E. R. de Kloet, *Front. Neuroendocrinol.* **12**, 95 (1991); _____, S. Kock, V. Schild, H. D. Veldhuis, *Neuroendocrinology* **47**, 109 (1988); B. Roozendaal, L. Cahill, J. L. McGaugh in *Brain Processes and Memory*, K. Ishikawa, J. L. McGaugh, H. Sakata, Eds. (Elsevier, Amsterdam, 1996), pp. 39–54.
19. S. J. Lupien and B. S. McEwen, *Brain Res. Rev.* **24**, 1 (1997).
20. M. G. Packard, C. L. Williams, L. Cahill, J. L. McGaugh, in *Neurobehavioral Plasticity*: *Learning*, *Development and Response to Brain Insults*, N. E. Spear, L. Spear, M. Woodruff, Eds. (Erlbaum, Hillsdale, NJ, 1995), pp. 149–184; J. L. McGaugh, L. Cahill, B. Roozendaal, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 13508 (1996). There is also evidence that epinephrine influences memory through the release of glucose, which then enters the brain; however, the effects of glucose on memory differ from those mediated by the activation of vagal afferents. P. E. Gold, in *Cellular Mechanisms of Conditioning and Behavioral Plasticity*, C. D. Woody, D. L. Alkon, J. L. McGaugh, Eds. (Plenum, New York, 1988), pp. 329–341.
21. K. C. Liang, R. G. Juler, J. L. McGaugh, *Brain Res.* **368**, 125 (1986).
22. B. Roozendaal and J. L. McGaugh, *Neurobiol. Learn. Mem.* **65**, 1 (1996); T. Hatfield and J. L. McGaugh, *Neurobiol. Learn. Mem.* **71**, 232 (1999); B. Ferry and J. L. McGaugh, *Neurobiol. Learn. Mem.* **72**, 8 (1999).
23. G. L. Quirarte, B. Roozendaal, J. L. McGaugh, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 14048 (1997).
24. R. Galvez, M. Mesches, J. L. McGaugh, *Neurobiol. Learn. Mem.* **66**, 253 (1996); G. L. Quirarte, R. Galvez, B. Roozendaal, J. L. McGaugh, *Brain Res.* **808**, 134 (1998); C. L. Williams, D. Men, E. C. Clayton and P. E. Gold, *Behav. Neurosci.* **112**, 1414 (1998); T. Hatfield, C. Spanis, J. L. McGaugh, *Brain Res.* **835**, 340 (1999).
25. L. R. Squire and E. R. Kandel, *Memory from Mind to Molecules* (Scientific American Library, New York, 1999).
26. For example, M. G. Packard and N. M. White, *Behav. Neurosci.* **105**, 295 (1991); M. G. Packard, R. Hirsh, N. M. White, *J. Neurosci.* **9**, 1465 (1989).
27. M. G. Packard, L. Cahill, J. L. McGaugh, *Proc. Natl. Acad. Sci. U.S.A.* **91**, 8477 (1994); M. G. Packard and L. Teather, *Neurobiol. Learn. Mem.* **69**, 163 (1998).
28. B. Roozendaal and J. L. McGaugh, *Euro. J. Neurosci.* **9**, 76 (1997); B. Roozendaal, B.T. Nguyen, A. Power, J. L. McGaugh, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 11642 (1999).
29. Y. Ikegaya, H. Saito, K. Abe, *Brain Res.* **671**, 351 (1995); *Neurosci. Res.* **22**, 203 (1995); _____, K. Nakanishi, *NeuroReport* **8**, 3143 (1997). BLA stimulation also induces NMDA-dependent LTP in the insular cortex, a brain region known to be important for several forms of learning [F. Bermudez-Rattoni, I. B. Introini-Collison, J. L. McGaugh, *Proc. Natl. Acad. Sci. U.S.A.* **88**, 5379 (1991); M. L. Escobar, V. Chao, F. Bermudez-Rattoni, *Brain Res.* **779**, 314 (1998); M. W. Jones, P. J. French, T. V. P. Bliss, K. Rosenblum, *J. Neurosci* **19**, RC36 (1999)].
30. E. Soetens, S. Casaer, R. D'Hooge, J. E. Hueting, *Psychopharmacology* **119**, 155 (1995).
31. L. Cahill, B. Prins, M. Weber, J. L. McGaugh, *Nature* **371**, 702 (1994); A. H. van Stegeren, W. Everaerd, L. Cahill, J. L. McGaugh, L. J. G. Gooren, *Psychopharmacology* **138**, 305 (1998); K. Nielson and R. Jensen, *Behav. Neural Biol.* **62**, 190 (1994).
32. L. Cahill, R. Babinsky, H. J. Markowitsch, J. L. McGaugh, *Nature* **377**, 295 (1995); R. Adolphs, L. Cahill, R. Schul, R. Babinsky, *Learn. Mem.* **4**, 291 (1997).
33. L. Cahill et al., *Proc. Natl. Acad. Sci. U.S.A.* **93**, 8016 (1996); S. Hamann, T. Ely, S. Grafton, C. Kilts, *Nature Neurosci.* **2**, 289 (1999).
34. R. Shadmehr and H. H. Holcomb, *Science* **277**, 821 (1997).
35. N. M. Weinberger, in *The Cognitive Neurosciences*, M. S. Gazzaniga, Ed. (MIT Press, Cambridge, MA, 1995), pp. 1071–1089; N. M. Weinberger, *Trends Cogn. Sci.* **2**, 271 (1998); T. S. Bjordahl, M. A. Dimyan, N. M. Weinberger, *Behav. Neurosci.* **112**, 467 (1998); V. V. Galvan, J. Chen, N. M. Weinberger, *Soc. Neurosci. Abstr.* **24**, 1422 (1998).
36. G. Winocur, *Behav. Brain Res.* **38**, 145 (1990); S. Zola-Morgan and L. R. Squire, *Science* **250,** 288 (1990); J. J. Kim and M. S. Fanselow, *Science* **256**, 675 (1992); Y. H. Cho, D. Beracochea, R. Jaffard, *J. Neurosci.* **13**, 1759 (1993); J. J. Kim, R. E. Clark, R. F. Thompson, *Behav Neurosci.* **109**, 195 (1995); G. Reidel *et al*., *Nature Neurosci.* **3**, 898 (1999).
37. W. B. Scoville and B. Milner, *J. Neurol. Neurosurg. Psychiatry* **20**, 11 (1957); B. Milner, in *Amnesia*, C. W. M. Whitty and O. L. Zangwill, Eds. (Butterworths, London, 1966), pp. 109–133.
38. L. R. Squire and P. Alvarez, *Curr. Opin. Neurobiol.* **5**, 169 (1995).
39. T. J. Tyler and P. DiScenna, *Behav. Neurosci.* **100**, 147 (1986); J. L. McClelland, B. L. McNaughton, R. C. O'Reilly, *Psychol. Rev.* **102**, 419 (1995).
40. T. J. Shors and L. D. Matzel, *Behav. Brain Sci.* **20**, 597 (1997).
41. R. C. Malenka and R. A. Nicoll, *Science* **285**, 1870 (1999).
42. T. Seidenbacher, K. G. Reymann, D. Balschun, *Proc. Natl. Acad. Sci U.S.A.* **94**, 1494 (1997)
43. U. Frey, M. Krug, K. G. Reymann, H. Matthies, *Brain Res.* **452**, 57 (1988).
44. D. M. Barros *et al*., *Neurobiol. Learn. Mem.* **71**, 94 (1999).
45. P. A. Colley, F. -S. Sheu, A. Routtenberg, *J. Neurosci.* **10**, 3353 (1990); Y.-Y. Huang, P. A. Colley, A. Routtenberg, *Neuroscience* **49**, 819 (1992); D. Jerusalinsky *et al*., *Behav. Neural Biol.* **61**, 107 (1994).
46. Y.-Y. Huang and E. R. Kandel, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 2446 (1995); R. Bernabeu et al., *Proc. Natl. Acad. Sci. U.S.A.* **94**, 7041 (1997); G. E. Schafe, N. V. Nadel, G. M. Sullivan, A. Harris, J. E. LeDoux, *Learn. Mem.* **6**, 97 (1999).
47. J. F. Guzowski and J. L. McGaugh, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 2693 (1997); T. Tully, *Proc. Natl. Acad. Sci. U.S.A.* **94**, 4239 (1997).
48. A. Routtenberg, in *Four Decades of Memory*, P. E. Gold. and W. T. Greenough, Eds. (American Psychological Association, Washington, DC, in press); T. Abel, K. C. Martin, D. Bartsch, E. R. Kandel, *Science* **279**, 338 (1998).
49. K. J. Murphy and C. .M. Regan, *Neurobiol. Learn. Mem.* **70**, 73 (1998); P. Roullet, R. Mileusnic, S. P. R. Rose, S. J. Sara, *NeuroReport* **8**,1907 (1997).
50. N. J. Emptage and T. J. Carew, *Science* **262**, 253 (1993); J. Mauelshagen, G. R. Parker, T. J. Carew, *J. Neurosci.* **15**, 7099 (1996); U. Müller and T. J. Carew, *Neuron* **21**, 1423 (1996).
51. I. Izquierdo, D. M. Barros, T. Mello e Souza, M. M. de Souza, L. A. Izquierdo, *Nature* **393**, 635 (1998).
52. I thank L. Cahill, I. Izquierdo, A. Routtenberg, G. Streidter, and N. M. Weinberger for their helpful comments and N. Collett for assistance in preparation of the manuscript. Supported by National Institute of Mental Health grant MH12526.