Consolidating Memories

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Abstract

Our own experiences, as well as the findings of many studies, suggest that emotionally arousing experiences can create lasting memories. This autobiographical article provides a brief summary of the author's research investigating neurobiological systems responsible for the influence of emotional arousal on the consolidation of lasting memories. The research began with the finding that stimulant drugs enhanced memory in rats when administered shortly after training. Those findings suggested the possibility that endogenous systems activated by arousal might influence neural processes underlying memory consolidation. Subsequent findings that adrenal stress hormones activated by learning experiences enhance memory consolidation provided strong evidence supporting this hypothesis. Other findings suggest that the enhancement is induced by stress hormone activation of the amygdala. The findings also suggest that the basolateral amygdala modulates memory consolidation via its projections to brain regions involved in processing different aspects and forms of memory. This emotional-arousal-activated neurobiological system thus seems to play an important adaptive role in insuring that the strength of our memories will reflect their emotional significance.

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INTRODUCTION

The title of this autobiographical article has two quite different meanings. First, in order to discuss my research on memory I had to bring together, or consolidate, the main ideas that influenced the research as well as the central findings acquired over many decades. Second, my research has focused primarily on processes that modulate the consolidation of newly acquired memories.

I have studied memory processes simply because memory is highly interesting and critically important. It is our most important capacity. The function of memory is not, of course, simply to allow us to reflect on the past. Memory enables our past experiences to guide our future behavior. It is essential for our survival. In this article I summarize some of the major hypotheses (and hunches) that guided the research in my laboratory. I also review some of what I think are perhaps the most significant findings from my laboratory and the most appropriate observations and conclusions suggested by the findings. I have reviewed research on memory consolidation more generally and in more detail in a number of previous papers (McGaugh 1966, 1973, 1983, 1989, 2000, 2004; McGaugh & Roozendaal 2008, 2009).

What are the conditions and processes that enable us and the other animals to acquire, maintain, and retrieve long-past as well as recently experienced information that guides our current behavior? In the early 1800s, after many centuries of debate, it was finally accepted that memories are formed and maintained in the brain, even though we may continue to say that something well remembered has been "learned by heart" and that "we hold our memories in our heart." But it is only in the past half century that behavioral and neurobiological investigations of memory have begun to provide some understanding of the brain systems that underlie our ability to learn and remember. Studies of processes underlying memory consolidation have contributed to that understanding (McGaugh & Roozendaal 2008, 2009).

It is clear from our own experiences as well as from the pioneering studies of Ebbinghaus (1885) that memory is strengthened by repetition of experiences. The fact that the effects of experience accumulate in influencing memory would seem to argue that each experience must produce a lasting change in the brain. But we don't appear to remember each of our experiences. Over a century ago, William James noted, "Of some (experiences) no memory survives the instance of their passage. Of others, it is confined to a few moments, hours or days. Others, again, leave vestiges that are indestructible, and by means of which may be recalled as long as life endures. How can we explain these differences?" (James 1890, p. 643). I have investigated the processes underlying the

consolidation of memories in order to gain some understanding of how our brains form enduring memories and, hopefully, provide at least a partial answer to William James's question.

EARLY ACADEMIC INFLUENCES

As an undergraduate at San Jose State University in 1949, I was initially interested in drama and music, areas in which I had been active in high school. However, in my second year, after I took an interesting required course in psychology, I selected psychology as my major area of study. Of the advanced courses, I found the course in theories of learning to be the most interesting. The chapters in the textbook for that course summarized the major theories that were proposed following the publications of Pavlov's studies (1927) of classical conditioning and Thorndike's studies (1898) of instrumental conditioning. Those early studies led to the characterization of learning, by many theorists, as the acquisition of responses that are rewarded or punished. And the term "memory," if used at all (and it was rarely used), simply referred to the altered responses. The "S-R" (stimulus-response) view of learning culminated in the elaborate theory proposed by Clark Hull (1943) that dominated much research on learning for several decades.

The view that all learning consists of responses strengthened by rewarding or punishing consequences, however attractive in suggesting interesting experiments and interpreting some forms of learned behavior, did not seem to me to provide an adequate or accurate account of either how learning occurs or what is learned and remembered. I was much more interested in and impressed by Edward Tolman's (1932) cognitive view that learning consists of acquiring information about "what leads to what" and that although rewards clearly influence performance, they are not essential for learning. His basic findings that (*a*) rats can learn about the pathways in a maze without any reward and demonstrate knowledge (latent learning) of the learning after a reward is introduced (Blodgett 1929, Tolman & Honzik 1930) and (*b*) rats can learn about the places where rewards are found and can demonstrate novel responses, on testing, to find them (Tolman 1949) strongly influenced my subsequent interest in investigating learning and memory. The key message that I took away from the Hull-Tolman controversy is that learning is inferred from behavior, not directly observed. Of course we do learn motor responses, but it is not clear that rewards play a critical role in such learning other than influencing what responses are made and, consequently, learned. Changes in behavior that are the result of learning (i.e., memory) must be distinguished from other conditions used in training that directly influence the behavior. That message has been a major influence in my research investigating the conditions that influence the formation of lasting memories.

Although I also took the required courses in anatomy and physiology and physiological psychology when I was an undergraduate student, I did not at that time anticipate further study of neurobiological processes. However, while working for a year in a psychiatric hospital, on wards with psychotic and prefrontal lobotomy patients, while I was an undergraduate student it did seem clear to me that understanding behavior would require neurobiological inquiry. During my college years, when the United States was engaged in a war with North Korea, I was deferred from the military draft until graduation. In the spring of my senior year, when my deferment was ending, I joined the Air Force. Fortunately, within a few weeks a cease-fire was signed and my position in the Air Force was cancelled. Thus, instead of going to war I went to graduate school.

BERKELEY INFLUENCES

When I arrived at the University of California, Berkeley as a graduate student in 1953 I was given a teaching assistant position and assigned to assist Edward Tolman and David Krech. Working directly for Tolman as a teaching assistant, as well as taking seminars with him, significantly

increased my understanding and appreciation of his views about the cognitive nature of learning. I was also fortunate to have him serve as a member of my PhD thesis committee. The work with Krech resulted in my becoming a research assistant in his research project, in collaboration with Mark Rosenzweig and Edward Bennett, investigating brain changes induced by rearing rats in enriched environments. Their studies were the first to determine that early environmental experiences induce significant alterations in brain chemistry and anatomy (Rosenzweig et al. 1960). Perhaps their most well known finding is that enriched rearing experiences increased cortical thickness. Early environmental enrichment also altered cortical acetylcholinesterase (AchE) (Krech et al. 1960), the enzyme that hydrolyzes acetylcholine, which was at that time considered only a "putative" neurotransmitter—that is, not as yet accepted as a neurotransmitter. For part of my thesis research I attempted to determine whether individual differences in rats' learning correlated with cortical AchE. That research experience triggered my lasting interest in the neurobiology of learning and memory.

Although I obtained some supporting evidence (McGaugh 1959), I thought it would be best to investigate the problem by varying the brain processes experimentally rather than simply obtaining correlations between learning and brain processes. In preparing a review for Krech and Rosenzweig's laboratory seminar, my graduate student colleague, Lew Petrinovich, and I found a reference to an early paper by Karl Lashley (1917) reporting that strychnine enhanced rats' maze learning. We also found that strychnine was at that time considered to act as a neural stimulant, at least in part, by inhibiting AchE (Nachmansohn 1938). In a partial replication of his experiment (McGaugh & Petrinovich 1959), we confirmed Lashley's finding that rats given low doses of strychnine each day shortly prior to training in a maze made fewer errors in learning the maze than did control rats. Clearly, strychnine improved the rats' maze performance. But did it do so by enhancing the rats' memory of each day's training experience? As there were many possible ways that the drug might act to improve the maze performance we could not, consequently, conclude that the drug enhanced the maze performance by acting on brain processes underlying learning. That issue guided my subsequent research.

From my undergraduate studies I knew about Müller & Pilzecker's interesting but not well-investigated or appreciated "perseveration-consolidation" hypothesis (1900), which proposed that the neural processes underlying learning become stabilized or consolidated over time after learning. I was also familiar with Hebb's (1949) dual-trace hypothesis that memory is initially based on the reverberation of experience-activated neural circuits and that lasting memory results from synaptic changes induced by the reverberation. And, I had read Duncan's classic paper (Duncan 1949) reporting that electroconvulsive shock (ECS) treatments administered to rats each day immediately after training in a footshock avoidance task impaired their acquisition performance. The findings suggested that the ECS treatments prevented the consolidation of processes underlying memory of each day's training experience.

The hypothesis that lasting memory is formed by processes acting *after* training suggested a way of avoiding at least some of the learning-performance issues that made it difficult to interpret the effects of strychnine on learning. Consequently, my next experiments investigated the effects of strychnine administered to rats each day either immediately after training or after a delay. I was both relieved and delighted to find that immediate—but not delayed—posttraining administration enhanced maze learning. That finding influenced most, if not all, of my subsequent research.

STUDIES OF MEMORY ENHANCEMENT AND IMPAIRMENT

From Berkeley I moved back to San Jose State University, where I established a research laboratory, recruited graduate and undergraduate students to work with me, and continued studies

of drug enhancement of memory consolidation. The initial experiments investigated the effects of strychnine as well as other central nervous system (CNS) stimulants on memory for different kinds of learning tasks. The memory-enhancing effects of strychnine on rats' maze learning were replicated (McGaugh et al. 1962), and comparable memory enhancement was obtained with the GABAergic antagonist picrotoxin, another CNS stimulant (Breen & McGaugh 1961). I also learned from Krech, who had just returned from a trip to Europe, that investigators in a research institute in Rome, Italy, the Istituto Superiore di Sanità, had synthesized several CNS stimulants. I was able to obtain one of the drugs, 1757 I.S. (diazadamantanol), for a study of drug enhancement of latent learning (Westbrook & McGaugh 1964). Following the general procedures of the classic studies of latent learning by Blodgett (1929) and Tolman & Honzik (1930), rats were administered saline or 1757 I.S. after each of five food-rewarded or nonrewarded trials in a maze. The drug was then discontinued, and for both groups all subsequent trials were rewarded. As was expected, the rats that were rewarded and given the drug after each trial made fewer errors than did rewarded saline controls. Additionally, and importantly, on the five nonrewarded trials the performance of the rats given posttraining 1757 I.S. did not differ from that of the controls. As expected, animals in both nonrewarded groups behaved randomly. However, on the subsequent rewarded trials, the performance of both groups given 1757 I.S. after each of the first five trials was comparable and significantly better than that of the two control groups. These findings clearly indicated that the posttraining drug administration enhanced latent learning. Further, the finding that the posttraining drug administration was not rewarding, i.e., did not enhance performance on the nonrewarded trials, clearly indicated that the enhanced maze performance induced by the drug was not due to a rewarding effect of the drug.

Our additional finding (Petrinovich et al. 1965) that posttraining strychnine administration enhanced rats' performance on a delayed alternation task provided further support for this conclusion. Rats were first trained to go to alternate goal boxes of a T-maze, for a food reward, on each successive trial. Then, their memory of the previous response was tested at increasing intervals. The strychnine-treated rats performed significantly better than controls at the longer training-test intervals, indicating that they had enhanced memory of their most recent responses despite the need to demonstrate that by making a response opposite to that made on the previous rewarded trial.

In 1961 I received a postdoctoral fellowship from the US National Academy of Sciences that enabled me to work with Nobel Laureate Daniel Bovet at the Istituto Superiore di Sanità in Rome, where I continued to study the effects of stimulant drugs on learning and memory (Bovet et al. 1966). I subsequently moved to the University of Oregon, where I continued the research program. In 1964 I moved to the newly created University of California, Irvine as the founding chair of the Department of Psychobiology (now renamed Neurobiology and Behavior). At Irvine the research in my new laboratory continued to investigate the effects of CNS stimulants on memory consolidation. The guiding assumption continued to be that understanding the basis of the effects might provide important clues to the neural processes underlying memory consolidation. We investigated the effects of many stimulant drugs, including pentylenetetrazol (Krivanek & McGaugh 1968), amphetamine (Krivanek & McGaugh 1969), and bemegride (Luttges & McGaugh 1971), and found that when administered posttraining, all of the drugs produced dose- and time-dependent effects on memory in rats and mice (McGaugh 1973, McGaugh & Roozendaal 2008). With all of the drugs investigated the greatest enhancement was found with administration immediately after training, and administration an hour or longer after training was ineffective. The findings of the effects of pentylenetetrazol are shown in **Figures 1** and **2**.

At Irvine, and previously at San Jose, my students and I also conducted many studies investigating the effects on memory of posttrial administration of ECS as well as direct electrical stimulation

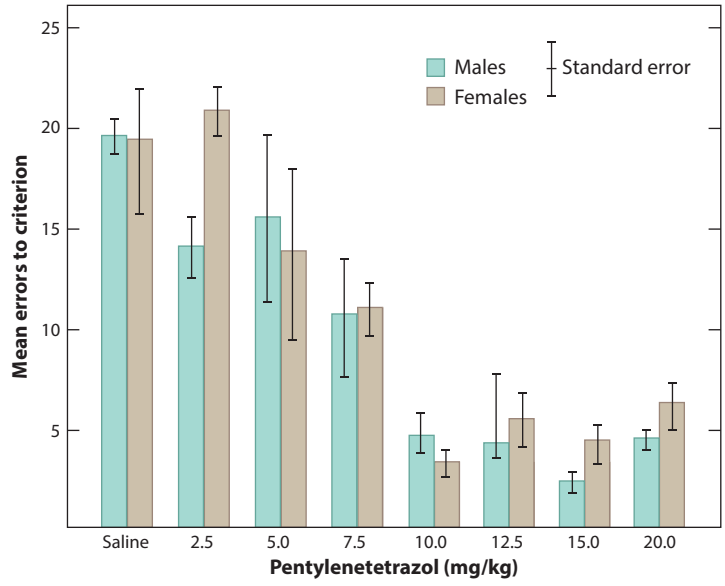

Figure 1

The effect of systemic administration of pentylenetetrazol on visual discrimination in mice. The drug was administered each day immediately after training. The degree of memory enhancement, assessed by the number of errors made in learning the task, varied directly with dose. Adapted with permission from Krivanek & McGaugh (1968).

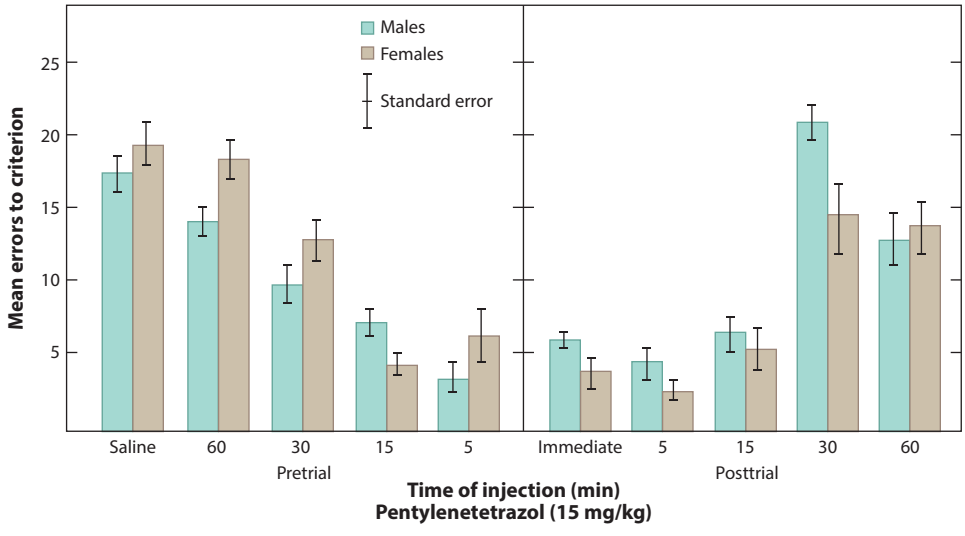

Figure 2

The effect of time of administration of pentylenetetrazol on visual discrimination learning in mice. A dose of 15 mg/kg was administered each day at several intervals of time prior to or after the training. The greatest enhancement of memory was produced by administration within 15 minutes before or after training. Adapted with permission from Krivanek & McGaugh (1968).

of the brain. In those studies we obtained additional evidence that posttraining ECS treatment impaired memory in rats and mice (McGaugh 1966). We found that the tonic convulsions elicited by ECS played no role in inducing retrograde amnesia (McGaugh & Alpern 1966), that the impaired retention was not due to a punishing effect of ECS (Madsen & McGaugh 1961), that the degree of impairment depended on the duration and intensity of the ECS (Alpern & McGaugh 1968), that the amnesia developed during several hours after the ECS treatment (McGaugh & Landfield 1970), and that the memory impairment did not diminish over time (Luttges & McGaugh 1967). These findings together with the findings from many other laboratories provided additional strong support of the perseveration-consolidation hypothesis (McGaugh & Herz 1972).

Additionally, several studies initiated by Paul Gold, who was a postdoctoral fellow in my laboratory, found that, as we found with ECS treatments, direct electrical stimulation of the cortex after training produced retrograde amnesia (Gold et al. 1973, 1974). Additionally, and importantly, the studies found that direct stimulation of the amygdala that did not induce convulsions produced memory impairment with high-intensity stimulation and memory enhancement with low-intensity stimulation (Gold et al. 1975a,b; McGaugh & Gold 1976). As discussed below, these findings, together with findings from other laboratories (Gallagher et al. 1981, Goddard 1964, Kesner & Ellis 1983), provided early suggestions that activity of the amygdala might play a role in memory consolidation (McGaugh et al. 2000).

SIGNIFICANCE AND REMEMBRANCE

These early studies in my laboratories thus provided extensive evidence that many stimulant drugs enhance memory consolidation when administered after training (McGaugh 1968, 1973; McGaugh & Herz 1972; McGaugh & Petrinovich 1965). They also provided strong evidence, consistent with that provided by studies of ECS and other treatments that impair memory when administered posttraining, that memory storage processes are time dependent (Glickman 1961, McGaugh 1966). However, aside from the evidence that all of the drugs used to enhance memory were CNS stimulants, the studies provided no significant evidence or hypotheses concerning possible bases of their effects on memory. They did raise some interesting and important questions, though. Why is it that memories consolidate slowly after experiences? What function does that serve? Are there endogenous processes like those of stimulant drugs that activate or regulate memory consolidation? And if so, are such processes normally activated by learning experiences? These questions guided much subsequent research in my laboratory (McGaugh 1990, 2000; McGaugh et al. 2000).

Paul Gold and I had extensive discussions about these questions. He subsequently conducted the first study (Gold & van Buskirk 1975) to investigate a possible endogenous modulator of memory consolidation. The training tasks typically used to study learning and memory use emotionally arousing stimulation, such as footshock, which is known to induce the release of the adrenal stress hormones, epinephrine and corticosterone (cortisol in humans). The experiment investigated the effects of the adrenal hormone epinephrine administered either immediately after training on a one-trial inhibitory avoidance task (Jarvik & Kopp 1967) or at several intervals up to two hours after the training. The findings were highly comparable to those we previously obtained with CNS stimulant drugs: Posttraining epinephrine administration produced dose-dependent enhancement of memory. Further, the effects were time dependent. Greatest enhancement was found with epinephrine administration immediately after training, and no enhancement was found with epinephrine administered two hours after training.

Findings of many subsequent studies using a variety of training and testing procedures commonly used in studies of memory in rats and mice including, in addition to inhibitory avoidance,

footshock-motivated active avoidance, discrimination learning, and reversal learning as well as reward-based learning, have provided extensive evidence confirming that posttraining administration of epinephrine enhances memory consolidation (Costa-Miserachs et al. 1994; Introini-Collison & McGaugh 1986, 1987; Izquierdo & Dias 1985; Liang et al. 1985, 1986; Sternberg et al. 1985). Further, the memory-enhancing effects of epinephrine are long lasting. Memory-enhancing effects were obtained when retention was tested at intervals up to one month after training (Introini-Collison & McGaugh 1986). Other investigators subsequently found that epinephrine enhances memory even with training conditions that do not use rewards or punishment. Epinephrine administered systemically to rats immediately after they explored novel objects enhanced subsequent memory of the objects, as assessed by tests administered four days after the exploration (Dornelles et al. 2007).

In an article published more than a decade before we became interested in possible hormonal influences on memory, Ralph Gerard noted, "...as epinephrine is released in vivid emotional experiences, such an adventure should be highly memorable" (Gerard 1961, pp. 29–30). It is perhaps of interest that I knew Gerard, as he was a founding faculty member at UC Irvine. He interviewed me when I was being recruited and was subsequently my colleague. However, I discovered his speculations about the role of epinephrine (as well as the amygdala, as discussed below) only many years later. Considerable evidence now supports Gerard's earlier speculation.

As noted above, emotional arousal also induces the synthesis and release of the stress hormone corticosterone. And, as discussed below, many studies have found that corticosterone, like epinephrine, produces dose- and time-dependent memory enhancement (Cottrell & Nakajima 1977; Okuda et al. 2004; Roozendaal 2000; Roozendaal & McGaugh 1996, 2011; Sandi & Rose 1994; Zorawski & Killcross 2002). Thus, the findings of studies of the effects of stress-activated hormones on memory appear to provide a partial answer to William James's question about why all experiences are not equally well remembered. Another of William James's observations hinted at this possibility when he observed, "An experience may be so exciting emotionally as almost to leave a scar on the cerebral tissues" (James 1890, p. 670). There is, of course, considerable evidence that emotionally arousing experiences tend to be especially well remembered (Brown & Kulik 1977, Christianson 1992, Conway 1995, McGaugh 2003). The findings from my laboratory suggest that the susceptibility of memory consolidation processes to modulating influences shortly after learning, as proposed by Müller & Pilzecker (1900), provides the opportunity for endogenous stress hormones activated by emotionally exciting experiences to influence the strength of subsequent memory of the experiences (McGaugh 1990, 1992, 2000, 2006, 2013; McGaugh & Gold 1989; McGaugh & Roozendaal 2002).

PERIPHERAL PATHWAYS OF MODULATORY INFLUENCES

Stress hormones and other treatments that influence memory consolidation must, of course, act by influencing brain processes. Corticosterone is lipophylic and thus readily enters the brain, when released or administered peripherally, and binds to glucocorticoid and mineralocoid receptors. However, peripheral epinephrine enters the brain poorly, if at all, and thus its effects on memory appear to be initiated by activation of β-adrenergic receptors located in the periphery. In support of this implication we found that sotalol, a β-adrenergic antagonist that does not readily enter the brain, blocked the memory-enhancing effects of epinephrine (Introini-Collison et al. 1992). However, we also found that dipivalyl epinephrine, an adrenergic agonist that readily enters the brain when administered peripherally, had memory-enhancing effects comparable to those of epinephrine and that the memory enhancement was blocked by propranolol, a β-adrenergic antagonist that readily enters the brain. The findings of previous experiments in my laboratory

that epinephrine administration releases norepinephrine (NE) within the brain (Gold & van Buskirk 1978) suggested that both peripheral and central β-adrenergic receptor activation might influence memory consolidation. Other findings suggested that epinephrine effects might be initiated by activation of β-adrenergic receptors on the ascending vagus nerve that projects to brain stem nuclei, including the nucleus of the solitary tract (NTS), that release NE throughout the forebrain (Ricardo & Koh 1978). In support of this possibility we found that inactivation of the NTS with microinfusions of lidocaine impaired memory consolidation and blocked epinephrine effects on memory (McIntyre et al. 2012; Williams & Jensen 1991; Williams & McGaugh 1992, 1993).

In other studies, we found that activation of β-adrenergic receptors is also critical for the memory-modulating effects of drugs affecting GABAergic and opioid peptidergic systems. The adrenergic agonist clenbuterol blocks the memory impairment induced by the opiate receptor agonist β-endorphin and the GABAergic agonist muscimol (Introini-Collison et al. 1994, McGaugh 1989, McGaugh & Cahill 1997). The opiate receptor antagonist naloxone enhances memory, and the enhancement is blocked by propranolol (Gallagher et al. 1981, Introini-Collison et al. 1989). However, the finding that peripherally administered propranolol does not block the memory enhancement induced by the muscarinic cholinergic agonist oxotremorine suggests that cholinergic effects act downstream from adrenergic activation (Power et al. 2003). As discussed below, other findings from my laboratory indicated that adrenergic, GABAergic, opiate, and cholinergic systems also interact within the brain in regulating memory consolidation (McGaugh 2004).

AMYGDALA ACTIVATION AND MEMORY CONSOLIDATION

The findings of many prior studies of the effects of lesions and electrical stimulation of the amygdala on learning suggested the possibility that stimulant drugs and stress hormones might influence memory by activating the amygdala. Lesions of the amygdala impair animals' responsiveness to aversive or rewarding rewards (Blanchard & Blanchard 1972, Weiskrantz 1956), and stimulation of the amygdala evokes emotional responses (Gloor 1992, Halgren 1992). Further, there is now extensive evidence that the amygdala is involved in the acquisition and retention of many tasks that use emotionally arousing aversive stimulation (Davis 1992; Kesner 1982; LeDoux 1995, 2000). And, importantly, as discussed above, we previously found that posttraining electrical stimulation of the amygdala impaired or enhanced memory consolidation, depending on the intensity of the stimulation (Gold et al. 1975a,b; Kesner & Wilburn 1974; McGaugh & Gold 1976).

We also found that posttrial electrical stimulation of the amygdala impaired memory in normal rats and enhanced retention in rats whose adrenals were surgically removed (Bennett et al. 1985, Liang et al. 1985). These findings were the first to suggest the possibility that the amygdala might be involved in modulating memory consolidation. If the stimulation produced only memory impairment, it might be that the impairment was simply due to elicitation of abnormal activity in the amygdala. The finding of memory enhancement suggested the possibility that variations in amygdala activity might regulate processes underlying memory consolidation (McGaugh 1989, 1990). These findings were also our first to suggest an influence of adrenal activity on amygdala functioning in memory consolidation. Subsequently experiments in my laboratory found that propranolol infused into the amygdala blocked the memory enhancement induced by posttraining administration of epinephrine. Additionally, and importantly, NE infused into the amygdala after training enhanced memory (Liang et al. 1985).

These findings suggested the possibility that the effects of other drugs on memory consolidation when administered peripherally, including cholinergic, GABAergic, and opioid agonists and antagonists (Breen & McGaugh 1961; Brioni & McGaugh 1988; Castellano & McGaugh 1991;

Table 1 Treatment effects on memory and amygdala norepinephrine levels

Treatment	Effect on memory	Effect on amygdala norepinephrine levels	Reference
Footshock	Varies directly with footshock intensity	Varies with footshock intensity	Quirarte et al. (1998)
Epinephrine	Enhances	Increases	Williams et al. (1998)
Corticosterone	Enhances	Increases	McReynolds et al. (2010)
Muscimol	Impairs	Decreases	Hatfield et al. (1999)
Picrotoxin	Enhances	Increases	Hatfield et al. (1999)
β-endorphin	Impairs	Decreases	Quirarte et al. (1998)
Naloxone	Enhances	Increases	Quirarte et al. (1998)

Introini-Collison & McGaugh 1987, 1988), might involve the amygdala. Subsequent findings provided clear support for this possibility (McGaugh et al. 1996, 2000; Salinas & McGaugh 1996). When administered into the amygdala after training, propranolol blocked the memory-enhancing and memory-impairing effects of GABAergic as well as opioid peptidergic drugs (Brioni et al. 1989; Introini-Collison et al. 1989, 1995). Thus, the findings suggest that GABAergic and opioid peptidergic influences in the amygdala modulate the release of NE. However, muscarinic cholinergic influences act downstream from NE activation in the amygdala (Dalmaz et al. 1993, Introini-Collison et al. 1996, Power et al. 2003). Noradrenergic activation of the amygdala is also critical in enabling the memory-enhancing effects of other treatments, including cannabinoid receptor agonists (Campolongo et al. 2009a,b).

All of these findings clearly suggested that NE must be released within the amygdala by training as well as by the drugs that influence memory consolidation. To investigate this implication we assessed NE release by implanting microdialysis probes into the amygdala and assessing changes in NE with in vivo microdialysis and high-performance liquid chromatography. The findings strongly supported the implication. Footshock releases NE and epinephrine, and drugs that enhance memory consolidation (e.g., picrotoxin and naloxone) potentiate NE release. Drugs that impair memory (e.g., muscimol and β-endorphin) decrease NE release (Galvez et al. 1996, Hatfield et al. 1999, Quirarte et al. 1998, Williams et al. 1998) (see **Table 1**). Moreover, and importantly, inhibitory avoidance training produced greater increases than those produced by footshock alone. Further, the increases in NE released in the amygdala correlated highly with retention performance tested the following day (McIntyre et al. 2002).

GLUCOCORTICOID INFLUENCES ON MEMORY CONSOLIDATION

The adrenal stress hormone corticosterone (cortisol in humans) is also activated (i.e., synthesis is initiated) by emotional arousal, but unlike epinephrine it readily enters the brain, where it activates glucocorticoid receptors. The effects of glucocorticoids on memory are highly comparable to those of epinephrine. As noted above, many laboratories have reported that corticosterone and drugs that activate glucocorticoid receptors enhance memory consolidation (Cottrell & Nakajima 1977, Micheau et al. 1981, Roozendaal 2000, Sandi & Rose 1994, Zorawski & Killcross 2002). Findings of many studies in my laboratory indicate that glucocorticoid effects on memory consolidation involve the basolateral amygdala (BLA). Lesions of the BLA or infusions of muscarinic receptor antagonists into the BLA block the memory-enhancing effects of corticosterone and glucocorticoid agonists administered systemically posttraining (Power et al. 2000, Roozendaal et al. 1996, Roozendaal & McGaugh 1996). Further, noradrenergic activation is critical: β-adrenoceptor antagonists infused

into the BLA block the memory-enhancing effects of systemically administered glucocorticoid agonists (Quirarte et al. 1997). And, like the effects of NE, glucocorticoid agonists enhance memory when infused selectively into the BLA after training (Roozendaal & McGaugh 1997).

As found with epinephrine and NE, the memory-enhancing effects of glucocorticoids are not restricted to studies using aversive training experiences. Corticosterone administered systemically after training enhances novel object recognition memory (Roozendaal et al. 2006). However, and importantly, we also found in that study that corticosterone enhancement of memory consolidation requires concurrent adrenergic activation. When the rats were allowed to explore objects without prior habituation to the training context, and were thus emotionally aroused during training, post-training corticosterone enhanced memory of the objects. However, when rats were extensively habituated to the training apparatus prior to training and, thus, were not aroused when trained, posttraining systemic administration of corticosterone failed to enhance memory of objects explored in the apparatus. These findings suggested concurrent adrenergic activation is essential in enabling corticosterone enhancement of memory. In support of this implication, we found that corticosterone administered together with a low dose of the adrenergic stimulant yohimbine enhanced consolidation. Importantly, the dose of yohimbine was ineffective when administered alone (Roozendaal et al. 2006). We also found that corticosterone influences on consolidation of objection recognition memory require noradrenergic activation of the BLA. Propranolol infused into the BLA blocked the memory-enhancing effects of peripherally administered corticosterone (Roozendaal et al. 2006).

THE MEMORY-PROMISCUOUS BASOLATERAL AMYGDALA

Four decades after obtaining the initial findings suggesting that stimulant drugs can enhance memory consolidation, subsequent experiments in my laboratory had determined that (*a*) the drug effects were due to influences on memory and not to other effects on retention performance, (*b*) adrenal hormones produced comparable effects, and (*c*) the drug and hormone effects on memory consolidation involve converging noradrenergic influences within the amygdala. But, of course, many questions remained to be investigated. Does the memory modulation involve specific subregions of the amygdala? Is the amygdala the locus of the processes underlying consolidated memories, or does activation of the memory influence memory processing elsewhere in the brain? Does learning activate the release of NE within the amygdala, and do the memory-modulating drugs and hormones influence the release? Are the effects of cortisol like those of epinephrine and NE? And are the findings obtained in animal studies also obtained in human studies? Subsequent research in my laboratory investigated these questions.

In many studies we found that the BLA is the critical region of the amygdala involved in influencing memory consolidation. Our findings also suggested, however, that the BLA is not likely to be a locus of neural changes underlying stress-influenced memory. Experiments addressing this issue have typically used footshock-based fear-conditioning tasks, including inhibitory avoidance and contextual fear conditioning, and have used freezing behavior to infer memory impairment produced by lesions of the BLA (Maren 2003, Maren & Fanselow 1997, Ponnusamy et al. 2007). It is important to note that unlearned freezing behavior is also disrupted by treatments that impair BLA functioning (Cahill et al. 1999, Vazdarjanova et al. 2001). Of course, freezing is but one of many responses that might be used to assess memory. As Tolman had taught us many years earlier, learning and memory are inferred, not observed. When we used avoidance of or escape from a place where footshock had previously been delivered to assess memory, rats with lesions of the BLA induced prior to training showed significant evidence that they remembered where they had received footshock without freezing (Berlau & McGaugh 2003, Cahill et al. 1999, Parent

et al. 1995, Roozendaal & McGaugh 1996, Vazdarjanova & McGaugh 1998). Thus, our findings suggest that the BLA is not a critical lasting locus of systems underlying the memory of aversive training experiences. However, our finding that selective inactivation of the BLA immediately after such training impairs memory clearly indicates that the BLA is involved in modulating memory consolidation (Vazdarjanova & McGaugh 1999).

In other experiments we found that NE or noradrenergic agonists infused selectively into the BLA immediately after inhibitory avoidance training or contextual fear conditioning enhanced rats' memory as assessed by their latency to enter the place where they had received footshock after either entering the shock area (inhibitory avoidance) or after being placed in it (contextual fear conditioning) (Ferry & McGaugh 1999, Ferry et al. 1999, LaLumiere et al. 2003). Additionally, and importantly, we also found that NE or the muscarinic cholinergic agonist oxotremorine infused into the BLA after extinction training enhanced extinction of contextual fear conditioning (Berlau & McGaugh 2006, Boccia et al. 2009). Thus, the BLA is indifferent to whether the critical information acquired is that footshock is received in a specific context or that footshock is no longer received there.

Lessons learned from Tolman also influenced our study of other brain systems, including the hippocampus and caudate nucleus, that are influenced by amygdala activation. These brain regions are clearly less indifferent than the BLA to the kinds of information acquired. There is extensive evidence that the hippocampus is selectively engaged in learning about contexts, whereas the caudate nucleus is engaged by response learning (Hirsh 1974, Matus-Amat et al. 2004, Packard & McGaugh 1996, Rudy & Sutherland 1989). In an experiment using the "place versus response" T-maze task to determine whether rats learn the place where food is found or a specific turning response (Ritchie et al. 1950), we found that they learned both the place and the response. However, the learning of the two tasks involved different brain systems, and place is learned more quickly. Selective inactivation of the hippocampus by infusing lidocaine before testing disrupted place memory, and selective inactivation of the caudate nucleus disrupted response memory (Packard & McGaugh 1996). To assess amygdala influences on place and response learning (Packard et al. 1994), rats were trained in a water maze (Morris 1984) to swim either to a platform in a constant location and slightly below the surface of the water or to a visible platform that was in a different place on each day of training. Amphetamine (an adrenergic and dopaminergic agonist) infused into the hippocampus each day after training selectively enhanced memory of the place where the platform was located, and amphetamine infused into the caudate nucleus selectively enhanced memory assessed by swimming to the visible platform. In contrast, amphetamine infused into the amygdala after training enhanced both place and response learning. Additionally, and importantly, on subsequent tests lidocaine infused into the hippocampus prior to testing selectively impaired performance of the spatial task, and lidocaine infused into the caudate selectively impaired performance of the response task. Thus, these two brain regions were involved in the maintenance of the memory possibly as a locus of consolidated memory. In contrast, infusions of lidocaine into the amygdala prior to testing did not impair memory of either task. Clearly, the amygdala was effective in modulating two different forms or types of memory and was not a locus involved in the maintenance of the modulated memory (Packard et al. 1994). Although the amphetamine was infused into the entire amygdala in this experiment, it is likely that the BLA was selectively responsible for the modulating influence. We subsequently found that NE infused selectively into the BLA posttraining enhanced rats' memory of water-maze spatial training (Hatfield & McGaugh 1999).

In another study, we examined the influence of the BLA on consolidation of memory for different kinds of information acquired in contextual fear conditioning. Context learning can be produced by placing rats in a specific context on one day and giving them a brief footshock in that

context on the following day. Although the brief footshock alone, that is, without prior context exposure, does not produce contextual fear conditioning, rats can associate the brief footshock with the previously experienced context, as indicated by subsequent freezing in the context (Fanselow 1990, Pugh et al. 1997). We used these procedures to investigate the effects of oxotremorine infused into the BLA, hippocampus, or rostral anterior cingulate cortex, a brain region activated by noxious stimulation, after either context exposure on the first day of training or brief footshock on the second day. Hippocampal infusions were effective in enhancing memory only when administered after context exposure, whereas cingulate cortex infusions were effective only when administered after footshock training. In contrast, BLA infusions of oxotremorine enhanced memory when administered after either context or footshock training. Thus, the hippocampus and rostral anterior cingulate cortex were selectively involved in influencing memory of different kinds of experiences—context or footshock. In contrast, and consistent with findings discussed above, the BLA influenced both context and footshock memory (Malin & McGaugh 2006).

Thus, the BLA is promiscuous with respect to modulation of what is learned and remembered. It appears not to be devoted to selective learning and remembering of any specific kinds of information. The promiscuity appears to result from BLA projections to brain systems engaged in memory of different kinds of experiences (McGaugh 2004). This is perhaps not surprising because the BLA projects widely to many brain regions (Young 1993), and some of these target regions are critically engaged in processing lasting memories of different kinds of information. The hippocampus is clearly a target for tasks that require learning about places or contexts, and other brain regions are targets for learning of different kinds of information. Inhibitory avoidance performance involves memory of the place where footshock was received. Thus, it would be expected that the training should involve the hippocampus. In support of this, we (McIntyre et al. 2005) found that posttraining noradrenergic stimulation of the BLA after training that enhanced memory also increased hippocampal levels of Arc (activity-regulated cytoskeletal-associated protein), an early immediate gene implicated in synaptic plasticity and memory (Guzowski et al. 2000). Additionally, aversive training activates several transcriptionally regulated genes implicated in synaptic plasticity in many areas, including the cortex, and striatum as well as the hippocampus (Ressler et al. 2002). These findings were not simply the result of nonspecific effects of stress, as they were obtained only when the aversive training induced learning.

However, aversive training is not essential for BLA enhancement of memory. Noradrenergic activation of the BLA or electrical stimulation of the BLA after training also enhances rats' memory of where they have been and what they have seen based on their exploration of objects and contexts without any aversive consequences (Barsegyan et al. 2014, Bass et al. 2014, Roozendaal et al. 2008). But, importantly, the two tasks, object recognition and object in context recognition, engage different brain systems downstream from the BLA (Bussey et al. 1999, Ennaceur et al. 1996). Memory of objects explored selectively involves the perirhinal and insular regions of the cortex, whereas, consistent with the findings discussed above, memory of contexts in which objects are explored involves the hippocampus (Balderas et al. 2008). Importantly, evidence also suggests that training-induced firing of cells in the BLA modulates memory processing in the entorhinal cortex and hippocampus (Paré 2003, Paré et al. 2002).

Thus, the findings of many studies indicate that the BLA activates cortical regions (Dringenberg & Vanderwolf 1996) as well as other brain regions and that the activation influences memory consolidation. The insular cortex is involved in memory for taste as well as footshock. Oxotremorine administered into the insular cortex after training enhanced memory for both kinds of training, and propranolol administered into the BLA blocked memory of both kinds of training (Miranda & McGaugh 2004). Lesions of the BLA also block the memory enhancement induced by posttraining infusions of drugs into the entorhinal cortex (Roesler et al. 2002).

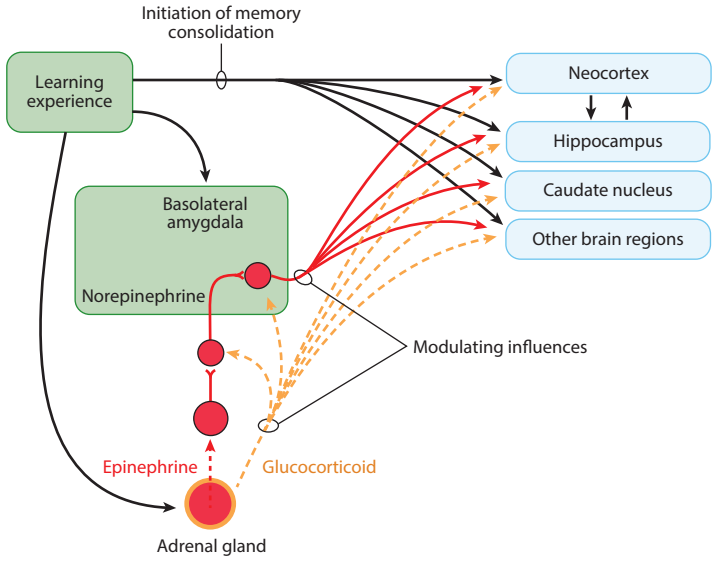

Figure 3

Schematic summary of arousal-activated stress hormones and basolateral amygdala interactions with other brain systems in modulating memory consolidation. Emotional arousal activates adrenal epinephrine and corticosterone (cortisol in humans). The stress hormones influence the release of norepinephrine in the basolateral amygdala. The basolateral amygdala modulates memory consolidation through its projections to brain systems involved in the forms and aspects of memory. Adapted with permission from McGaugh (2000).

Stimulation of the BLA also modulates the consolidation of plasticity in the auditory cortex. It is well established that pairing a specific tone with a footshock changes the representation of the tone in the auditory cortex, resulting in an increase in the cortical representation of significant sounds (Weinberger 2007). BLA stimulation paired with tones enhances the shift of the tuning responsiveness to the frequency of that tone. Additionally, the tuning curve shift continues to develop after training is discontinued and is maintained for several weeks (Chavez et al. 2012, 2013). Cholinergic projections from the nucleus basalis to the cortex appear to be essential for such learning-induced cortical plasticity (Weinberger 2003). The finding that lesions of the nucleus basalis block the memory-enhancing effects of noradrenergic activation of the BLA suggests that BLA modulation of cortical plasticity very likely involves activation of the nucleus basalis (Power et al. 2002). That implication is consistent with our findings suggesting that cholinergic effects act downstream from adrenergic activation.

Thus, the findings of many studies in my laboratory provide extensive evidence indicating that (*a*) noradrenergic and glucocorticoid activation of the BLA modulates the consolidation of many forms of learning and that (*b*) the modulation involves interactions of the BLA with many other brain regions that are more selectively involved in processing different forms of memory. The involvement of the BLA in promiscuously modulating memory consolidation, as indicated by the findings briefly reviewed above, is summarized in **Figure 3**.

MODULATION OF HUMAN MEMORY CONSOLIDATION

The findings and conclusions discussed above are all based on experiments investigating learning and memory in mice and rats. However, human studies have also provided confirming evidence. Studies from other laboratories investigating memory in human subjects reported that memory

is enhanced by posttraining administration of stimulant drugs, including amphetamine (Soetens et al. 1993, 1995) and caffeine (Borota et al. 2014). There is also extensive evidence that human memory is influenced by emotional arousal. As noted by Francis Bacon in 1620, "memory is assisted by anything that makes an impression on a powerful passion, inspiring fear, for example or wonder, shame or joy" (Bacon 1620, 2000). In support of Bacon's observation, many studies have reported that highly emotionally arousing experiences such as earthquakes (Neisser et al. 1996) and terrorist attacks (Sharot et al. 2007) are well remembered. But even mild arousal enhances subsequent memory. Many studies have reported that pictures or words that are only mildly arousing tend to be well remembered (e.g., Anderson et al. 2006).

There is also extensive evidence that the arousal influences on memory assessed in human subjects involve adrenergic/noradrenergic and cortisol activation. Experiments in my laboratory found that propranolol administered to subjects before they viewed emotionally arousing photos accompanied by an emotional story blocked the influence of emotional arousal on subsequent memory (Cahill et al. 1994). In another study, Cahill & Alkire (2003) found that epinephrine enhanced memory when administered immediately after subjects viewed emotionally arousing photos or words. Comparable enhancement was produced by cold pressor stress induced by having subjects hold an arm in ice water after viewing a series of photos (Cahill et al. 2003). Further, levels of cortisol and alpha amylase—a biomarker for adrenergic activity—assessed after subjects viewed pictures, films, or textual material correlate significantly with subsequent memory (Beckner et al. 2006, Hupbach & Fieman 2012, Segal & Cahill 2009, Segal et al. 2012).

We also found that the influences of emotional arousal on memory involve activation of the amygdala. In an initial study using positron emission tomography (PET) imaging, we found that amygdala activity assessed after subjects watched emotionally arousing films correlated highly with the subjects' memory of the films when they were tested several weeks later (Cahill et al. 1996). Subsequent studies using PET as well as functional magnetic resonance imaging confirmed this finding and found that the correlation between amygdala activity and subsequent memory varied directly with the degree of emotional arousal induced during learning (Canli et al. 2000, Hamann et al. 1999). Importantly, other studies reported that emotionally arousing learning experiences induce interactions of the amygdala with other brain regions, including the hippocampus (Dolcos et al. 2004, Kilpatrick & Cahill 2003). Further, consistent with the findings of animal studies, glucocorticoid and adrenergic drugs administered before viewing emotionally arousing stimuli increased amygdala activation and enhanced subsequent memory (Van Stegeren et al. 2007). In contrast, and consistent with findings of animal studies, propranolol administered to subjects before learning blocked amygdala activation and impaired memory of the stimuli (Van Stegeren et al. 2005, 2006). In recent investigations we have also studied individuals who have highly superior autobiographical memory. These individuals maintain accurate memories of many details of their personal experiences and can readily indicate the date and day of the week on which the experiences occurred (LePort et al. 2012, Parker et al. 2006). However, the research has not as yet determined whether this ability involves the amygdala memory modulatory system.

CONSOLIDATING COMMENTS

The findings of six decades of research in my laboratory reviewed in this autobiographical article provide extensive evidence that stress hormones activated by emotionally significant experiences modulate the consolidation of recently acquired memories. Further, the findings indicate that the modulation involves activation of the BLA, which in turn influences the processing of different aspects of memory in efferent brain systems. Thus, the findings provide strong support for Müller & Pilzecker's (1900) memory consolidation hypothesis. They also appear to provide a partial answer

to William James's (1890) question about why it is that some experiences are well remembered whereas many, perhaps most, are not. Finally, the findings offer at least a partial explanation of why it is, as Bacon asserted in 1620, that memory is assisted by ". . .anything that makes an impression on a powerful passion" (Bacon 1620, 2000).

However, we also found that systems activated by emotional arousal do not always assist memory. In both rats and human subjects, administration or activation of glucocorticoids prior to testing of previously acquired information impairs memory retrieval and working memory (de Quervain et al. 1998; Roozendaal et al. 2004a,b). Additionally, a glucocorticoid agonist administered into the prefrontal cortex impairs working memory and enhances memory consolidation (Barsegyan et al. 2010). The enhancement is blocked by lesions of the BLA (Roozendaal et al. 2009). Interestingly, as found with memory consolidation, glucocorticoid-induced impairment of memory retrieval requires concurrent adrenergic activation. Administration of propranolol blocks the retrieval impairment induced by corticosterone (Roozendaal et al. 2004a). Also, as was found with memory consolidation, the BLA plays a critical role: Inactivation of the BLA blocks glucocorticoid-induced impairment of memory retrieval (Roozendaal et al. 2003). Understanding why the neuromodulatory conditions that enhance memory consolidation also impair memory retrieval and working memory is clearly an important problem for future research.

Although I have mostly discussed findings from my laboratory in this article, the findings of many other laboratories, as discussed in more comprehensive reviews of memory consolidation research, have contributed very significantly to the conclusions I have offered (McGaugh 2004, McGaugh & Roozendaal 2008). Also, of course, the research hunches, hypotheses, and findings were highly influenced by the ideas and efforts of the many talented postdoctoral fellows, graduate students, undergraduate students, and visiting scientists who worked with me over the past many decades.

SUMMARY POINTS

1. Stimulant drugs enhance memory in rats and mice when administered shortly after training. Such findings suggest that the drugs act by enhancing the consolidation of newly acquired memories.
2. The stress hormones corticosterone (cortisol in humans) and epinephrine administered after training produce similar results. Such findings suggest that stress hormones normally released by arousing experiences regulate the consolidation of memories of the experiences.
3. Stress hormone enhancement of memory consolidation involves noradrenergic activation of the basolateral amygdala.
4. Noradrenergic activation of the basolateral amygdala, as assessed by measurement of norepinephrine, results in enhanced memory.
5. Amygdala regulation of memory is not restricted to fear memory. Amygdala activation modulates memory of a wide variety of training experiences.
6. Stress and amygdala activation effects on memory are not restricted to studies with rats and mice. Comparable effects are obtained in human studies.
7. Overall, the findings provide an understanding of why the strength of our memories depends on their emotional significance.

FUTURE ISSUES

1. What are the specific amygdala efferent pathways and neural targets that modulate different forms of memory?
2. What neural pathways and processes are involved in amygdala modulation of extinction? Are they the same as or different from those involved in original learning?
3. What are the critical molecular processes activated in amygdala-modulated brain systems?
4. How do other neurotransmitter systems interact with noradrenergic and glucocorticoid neuromodulatory systems in influencing memory?
5. What is the basis (or bases) of the inverted-U dose response effect of stress hormones on memory consolidation? That is, why does greater activation result in poorer memory?
6. Is the enhanced memory induced by stress hormone–induced amygdala activation due to enhanced storage of experiences or to alteration of retrieval of stored information?

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