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Mechanisms of emotional arousal and lasting declarative memory

Larry Cahill and James L. McGaugh

Neuroscience is witnessing growing interest in understanding brain mechanisms of memory formation for emotionally arousing events, a development closely related to renewed interest in the concept of memory consolidation. Extensive research in animals implicates stress hormones and the amygdaloid complex as key, interacting modulators of memory consolidation for emotional events. Considerable evidence suggests that the amygdala is not a site of long-term explicit or declarative memory storage, but serves to influence memory-storage processes in other brain regions, such as the hippocampus, striatum and neocortex. Human-subject studies confirm the prediction of animal work that the amygdala is involved with the formation of enhanced declarative memory for emotionally arousing events.

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> 'Selection is the very keel on which our mental ship is built. And in the case of memory its utility is obvious. If we remembered everything, we should on most occasions be as ill off as if we remembered nothing.'
>
> (William James, 1890)[1].

A MAN WE MET RECENTLY was only a few blocks from Oklahoma City's Alfred R. Murrah building when the deadly bomb exploded on 19 April, 1995. He described that experience as 'engraved' in his brain, saying, 'I'll have that memory forever'. Although most of us have not had a comparable experience, we all have conscious memories of emotionally arousing experiences, long-lasting memories that are striking in their vividness, duration and detail. Experimental studies amply demonstrate that emotionally arousing experiences tend to be well-remembered[2].

Why do explicit (or 'declarative') memories of emotional experiences endure? Some psychological accounts suggest that emotional events are better remembered because they are novel, focus attention, or are often rehearsed. Such hypotheses have failed fully to account for the experimental findings[2]. Other accounts focus on emotional responses learned through Pavlovian conditioning, and much is known about brain processes mediating the expression of fear[3,4]. However, explanations based solely on Pavlovian conditioning of emotional responses are likely to be insufficient because emotionally influenced memories generally involve declarative knowledge and are not restricted to evocation of learned emotional responses. Furthermore, Pavlovian conditioning can be dissociated from declarative-memory formation[5,6].

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The evidence summarized here supports the view that specific hormonal and brain systems activated by emotional arousal regulate long-term memory storage[7–9]. Much evidence for this view comes from animal studies using memory tasks that are rapidly acquired in a single learning episode and that differ in response requirements. The performance of an animal allows the inference that the memory of the animal of the specific training situations is declarative in nature. However, direct evidence for involvement of these brain systems in declarative memory must come from studies involving human subjects; these studies are also reviewed here.

Modulation of memory storage

Most studies of brain mechanisms of memory focus on the neural events mediating memory and the anatomical locus of the 'memory trace'. Equally important, however, are neurobiological systems that regulate, or modulate, long-term memory storage. Long-term memories are not made instantaneously: they consolidate over time after learning[10–12]. Recent evidence concerning memory consolidation comes from many domains of investigation, including studies of synaptic plasticity[13–15] and behavior[16–19]. Elegant demonstrations of memory consolidation in invertebrate preparations indicate that memory consolidation is evolutionarily conserved[20,21].

Post-training treatments modulate memory storage in many learning tasks. Of particular significance is the extensive evidence that memory can be selectively enhanced by post-training administration of drugs and hormones. Whether memory is enhanced or impaired by post-training treatments depends on the

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specific experimental conditions as well as the post-training treatment used[8].

Role of stress-released hormones in memory consolidation

The fact that recently formed memories are susceptible to exogenous modulatory treatments provides the opportunity for endogenous modulation of memory storage for emotional events. Stress hormones are *a priori* candidate endogenous modulators (Fig. 1). Stress-hormone systems activated by emotional situations serve the immediate adaptive needs of an organism[22]. Additionally, extensive evidence suggests they influence memory storage[8,9,23,24]. Initial studies examined the effects of post-training injections of the adrenal medullary hormone adrenaline on memory for inhibitory-avoidance training[25]. Adrenaline enhanced memory in a dose-dependent way, and the effects were, as predicted by the consolidation hypothesis, time-dependent: adrenaline enhanced memory only when administered shortly after training, that is, at the time when it would normally be released by the aversive stimulation (footshock) used in the training. Extensive research has confirmed and extended these findings. Adrenaline has comparable effects in discrimination learning and appetitively motivated tasks[8]. Adrenaline effects on memory appear to be mediated by the activation of peripheral β-adrenergic receptors[26], located on vagal afferents projecting to the nucleus of the solitary tract in the brain stem[27]. Additionally, the effects might involve the release of glucose[28].

Animal studies imply that activation of β-adrenergic receptors in humans should influence long-term declarative memory formation for emotionally arousing events. Several recent studies now support this implication. β-Adrenergic antagonists block effects of arousal (either emotionally or physically induced) on long-term declarative memory[29–31].

Emotional arousal also activates adrenocortical hormone release (cortisol in humans). The adrenocortical response is generally viewed as the 'second wave' of the autonomic response to an emotional event, following sympathetic adrenomedullary activation[24]. Most studies of adrenocortical hormones and memory have examined the impairing effects of high, sustained doses of the hormones. However, the well-known 'inverted-U' relationship between dose and retention performance suggests that lower, acute doses of corticosterone-receptor agonists should enhance memory consolidation. Several recent studies indicate that memory is enhanced by post-training peripheral[32–34] or central[35,36] (discussed later) administration of low doses of corticosterone-receptor agonists. Furthermore, adrenomedullary and adrenocortical hormones on memory interact in influencing memory storage[23,37].

To summarize, the adrenal hormones adrenaline and corticosterone appear to share two important adaptive functions in response to stressful experiences. First, they aid immediate responses to the stressful event. Second, they aid future responses by enhancing declarative memory of the arousing experience (Fig. 2).

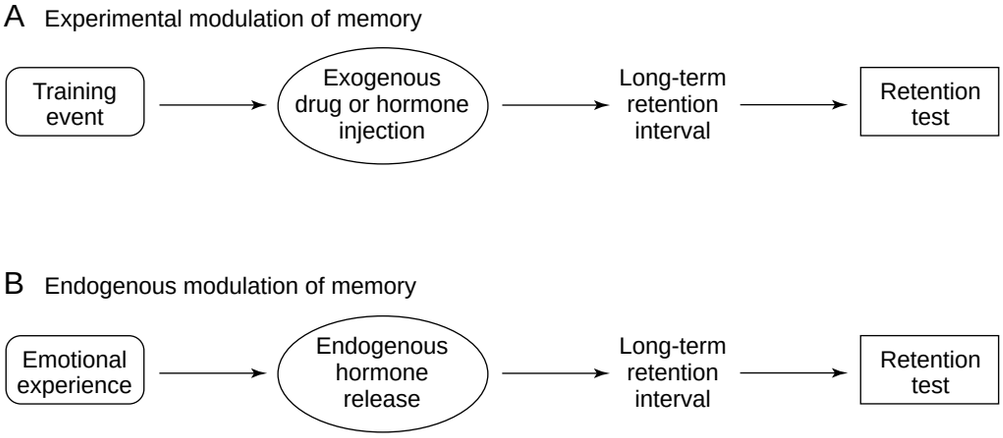

Fig. 1. ***Parallel between* (A) *experimental (exogenous) modulation of memory and* (B) *endogenous modulation of memory.*** *Post-learning treatments are assumed to modulate memory consolidation in a manner similar to the modulation normally produced by endogenous hormones released by emotional experiences.*

Role of the amygdaloid complex in memory modulatory mechanisms

The hypothesis that the amygdala modulates declarative-memory storage is rooted in several lines of research. Early studies demonstrated that electrical stimulation of the amygdaloid complex (AC) elicits behavioral arousal (the 'orienting reflex') and activates cortical EEG (Ref. 38). It is of interest for reasons discussed below that the cortical arousal response elicited by AC stimulation is mediated by the stria terminalis (ST), a major AC pathway[38]. Goddard's research[39] was

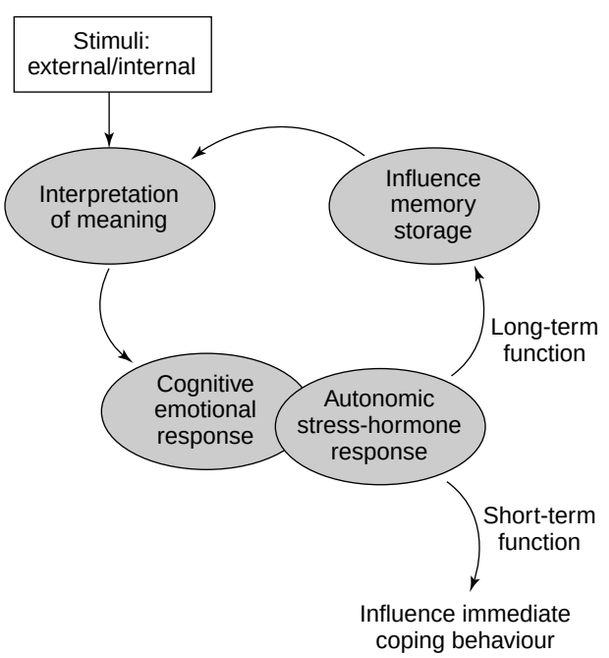

Fig. 2. ***Schematic depiction of short- and long-term functions of the stress response.*** *The sympathetic stress response serves the short-term adaptive needs of an organism to an emotionally arousing situation. Considerable evidence suggests that the sympathetic (autonomic) response also serves a long-term adaptive need: regulation of memory storage for the emotional event. The modulated memory then plays an adaptive role in the response of the organism to future situations.*

TABLE 1. Evidence for the crucial role of the basolateral amygdala in memory modulation

Procedure	Basolateral amygdaloid nucleus	Central amygdaloid nucleus	Refs
Lidocaine infusion post-learning	Modulates memory	No effect	54
Infusions of glucocorticoid agonist or antagonist into AC nuclei	Modulates memory	No effect	34
Lesions of AC nuclei, systemic dexamethasone	Blocks modulation	No effect	32
Lesions of AC nuclei, adrenalectomy	Blocks modulation	No effect	30
Lesions of AC nuclei, infusion of glucocorticoid agonist or antagonist into hippocampus	Blocks modulation	No effect	35
Lesions of AC nuclei, systemic diazepam	Blocks modulation	No effect	53
Infusion of beta-blocker into AC nuclei, systemic dexamethasone	Blocks modulation	No effect	55

the first to show that AC stimulation influences memory-consolidation processes. Electrical stimulation of the AC in rats after aversive learning severely disrupted retention. Because AC stimulation did not affect appetitively motivated learning, Goddard concluded that the AC is particularly involved with memory consolidation for aversive events (see also Ref. 40). This view does not, of course, exclude the possibility that the AC influences memory for sufficiently arousing, positively valenced experiences.

The effects of AC stimulation on memory are clearly modulatory, not simply amnesic. AC stimulation might either enhance or impair memory, depending on training conditions[41] and levels of circulating adrenaline[42,43]. Additionally, and most importantly, the evidence that lesions of the ST block AC-stimulation effects on memory suggests that the AC modulates memory storage in other brain regions activated by ST efferent projections[44].

The AC is crucial for memory-modulating influences of stress hormones. AC and ST lesions block the memory-enhancing effects of adrenaline and glucocorticoids, as well as those of drugs affecting opiate and GABAergic systems[8,9,33,45]. Furthermore, infusions of such drugs and hormones directly into the amygdala after training modulate memory storage[46–48].

Several findings indicate that such effects are mediated by the activation of β-adrenergic activity within the AC. The memory modulating influences are blocked by intra-amygdala infusions of β-adrenergic antagonists[48]. Additionally, footshock stimulation of the kind typically used in aversive training releases noradrenaline (NA) within the amygdala, and the release is modulated by treatments known to influence memory storage[49,50].

Fractionation of amygdala nuclei function in memory

The 'amygdala' is a heterogeneous collection of distinct nuclei. As long ago as 1915, Johnston noted that the AC 'is a complex of many diverse elements which have been brought together by mechanical forces and have no primary functional unity' (quoted by Goddard[51]). Although Johnston might have overstated the case, the evidence indicates that nuclei of the AC have different functions in learning[33,35,52].

The basolateral AC (BL) appears to be the nucleus most crucially involved in the modulation of memory storage[32–36,53] (Table 1). Electrical-stimulation experiments first suggested that the BL region influences memory consolidation[39,56]. More recent reports indicate that selective post-training inactivation of the BL with lidocaine induces retrograde amnesia whereas post-training inactivation of the central nucleus (CE) does not[54]. Other recent findings indicate that post-training infusion of a glucocorticoid agonist into the BL enhances memory, and that lesions of the BL (but not CE) block glucocorticoid-induced memory enhancement[36]. BL lesions do not block inhibitory avoidance learning or retention[32] under these conditions, thus the BL appears to be selectively involved in mediating modulatory influences on memory storage.

A recent study of c-*fos* activation in AC nuclei during olfactory learning provides further evidence consistent with a time-limited modulatory role for the BL in arousing situations. Hess and colleagues[57] examined c-*fos* expression in several AC nuclei during acquisition of a discriminated olfactory response. BL activity increased markedly when an aversive reinforcing stimulus was introduced, then decreased as the response became well learned. In another recent study, Quirk and colleagues[58] recorded from neurons in the lateral amygdala and auditory cortex during aversive conditioning and found that the acquisition of conditioned responses in the auditory cortex generally follows acquisition in the lateral amygdala. Further, cortical responses extinguish much more slowly than responses in the lateral amygdala. These electrophysiological findings are consistent with a time-limited role for the amygdala in modulating memory-storage processes in the auditory cortex[8,9].

In recent years, considerable research focused on the hypothesis that the BL might be a site where fear-based Pavlovian stimulus-reinforcement associations are formed and permanently stored[3,4]. However, as Quirk and colleagues[59] recently noted, 'the amygdala may be a permanent repository of conditioned fear memories, but this issue is not fully resolved since studies to date do not distinquish [between] effects of amygdala lesions on long-term storage and on the ability to express conditioned fear responses'.

AC modulation of memory storage in other brain regions

The evidence briefly summarized above strongly suggests that the amygdala is not the neural site of long-term memory for declarative information. It is equally evident that the amygdala, particularly the BL

nucleus, is involved in modulating memory storage processes in other brain regions. Other recent findings strongly support these implications. Packard *et al.*[60] reasoned that if the AC modulates memory in a particular brain structure, stimulation of the AC should influence formation of the type of memory thought to involve that structure. Furthermore, after modulation by AC stimulation, the memory should not be disrupted by inactivating the AC during retention testing. To examine these implications, amphetamine was micro-infused into the amygdala, hippocampus or caudate nucleus immediately after rats were trained on one of two water-maze tasks: a spatial task and a visually cued task (Table 2). The hippocampal infusion selectively enhanced retention of the spatial task and the caudate infusion selectively enhanced retention of the visually cued task. By contrast, the amygdala infusions enhanced retention of both tasks. Furthermore, inactivation of the amygdala (with lidocaine) prior to the retention tests did not block the enhanced memory. Evidence from another recent study confirms the modulatory role of the amygdala on hippocampal and caudate nucleus-based memory[61].

Evidence from many sources supports the view that influences from the AC, in particular the BL, modulate memory processes in the hippocampus and related circuitry. The BL projects prominently to the hippocampus and entorhinal cortex[62], and pharmacological stimulation of the AC functionally activates both of these regions[63] (L. Cahill, unpublished observations) (Fig. 3). Electrophysiological evidence strongly suggests that influences from the BL modulate long-term potentiation in the dorsal hippocampus[64]. Additionally, AC lesions block the memory-enhancing effect of direct hippocampal stimulation[36]. Finally, involvement of the entorhinal cortex in memory storage appears to occur after that of the AC, a finding consistent with the view that the AC modulates the entorhinal cortex[17,65].

In view of its widespread efferent projections, the AC can potentially modulate memory processes in many brain regions, although this idea has not as yet been systematically examined. For example, it is possible that the AC could modulate memory-storage processes in the neocortex via projections to various cortical regions[66]. The orbitofrontal cortex is particularly interesting in this respect: evidence from recent human-brain imaging studies suggests that the AC and orbitofrontal cortex interact functionally during emotionally arousing situations[67,68].

The AC might also modulate cortical-memory processes indirectly, via activation of diffusely projecting nuclei. For example, Weinberger and colleagues suggested that the modulatory action of cholinergic agents on learning-related plasticity in the cortex might stem from influences from the AC on the nucleus basalis[69]. It is known that stumulation of the BL activates the cortical EEG, and that this effect depends crucially on the activity of the nucleus basalis[38,70,71]. The AC might also modulate cortical memory-storage processes indirectly via projections to the locus coeruleus[72].

The AC and emotionally influenced, long-term declarative memory in humans

There has been controversy concerning the role of the AC in declarative memory[73,74]. Scoville and Milner[73] examined memory in ten patients (including H.M.) who had received medial temporal-lobe surgery, often including removal of the AC, and concluded that 'Removal of the amygdala bilaterally does not appear to cause memory impairment'. A recent study investigating a rare patient with AC damage concluded that, although the AC is important for classical conditioning of autonomic responses, it is not involved with declarative memory[75]. However, the animal research reviewed above suggests that the AC should not be involved in declarative-memory formation in all circumstances; rather, it should be important for the enhanced long-term declarative memory associated with emotional events. This hypothesis receives support from recent studies of memory in rare patients with selective AC lesions, and from brain-imaging studies of emotionally influenced memory in healthy subjects.

Several studies report that long-term, emotionally influenced memory is impaired in patients with selective AC damage[76–78], and that memory for relatively unemotional material is normal in these patients. Importantly, the emotional reactions of the patients to the emotional material appear normal. One patient even spontaneously described to the investigators her strong negative reaction to a particular highly aversive stimulus, yet failed to demonstrate enhanced recall of this stimulus[78]. Considered together with other evidence of normal emotional reactions in patients with AC damage[79], these findings suggest that the AC in humans might not be critical for an emotional reaction *per se*, but for processes translating an emotional reaction into enhanced long-term recall[67]. However, it should be noted that several other recent studies also implicate the human AC (especially the left AC) in emotional responsiveness to various aversive stimuli[68,80–82].

TABLE 2. Amygdala modulation of hippocampus-dependent and caudate-nucleus-dependent memory

Infusion	Retention spatial task	Cued task
Hippocampus	Enhanced	No effect
Caudate nucleus	No effect	Enhanced
Amygdala	Enhanced	Enhanced

Rats were subjected to one of two types of water-maze training, a spatial task or cued task, and the effect on memory of a post-training infusion of d-amphetamine into different brain areas was assessed. From Ref. 60.

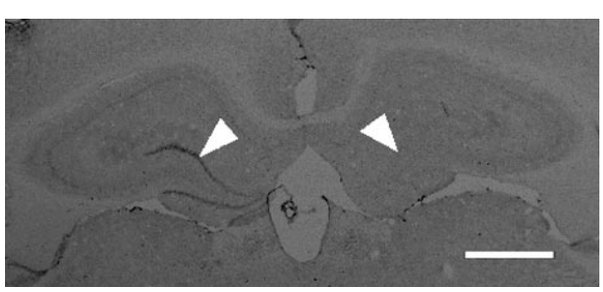

Fig. 3. ***An example of functional activation of the hippocampus after stimulation of the amygdaloid complex.*** *A rat received an injection of the excitatory amino acid NMDA into the left amygdaloid complex (AC) and a simultaneous infusion of vehicle into the right AC. Immunochemical procedures for identifying Fos protein were then performed. Note the striking activation of the dentate gyrus (arrows) ipsilateral to the NMDA-injected amygdala (left side) compared to the vehicle injected side. Scale bar, ~1 mm.* Modified from Ref. 63.

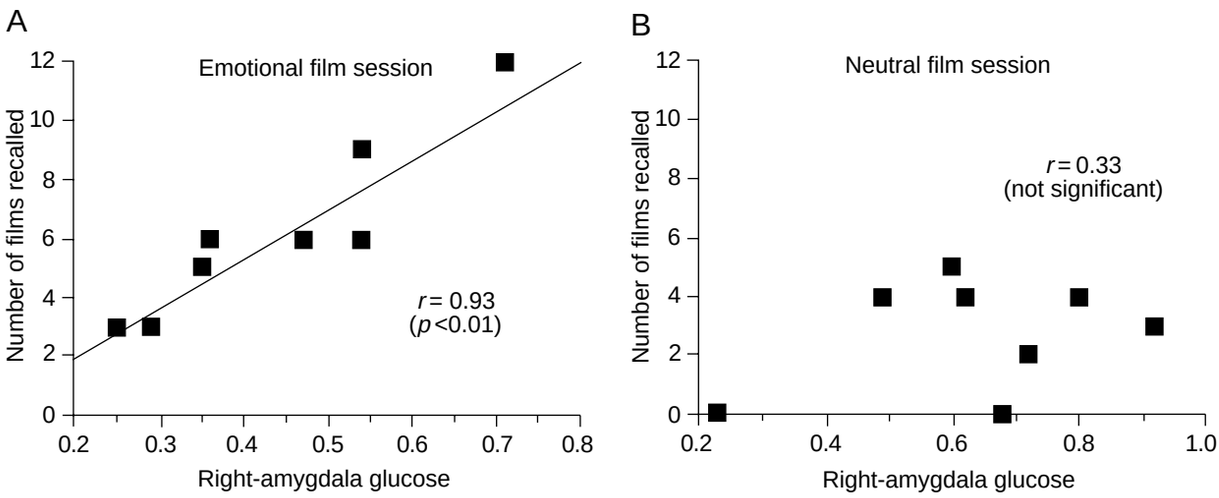

Fig. 4. ***Amygdala activity in healthy humans selectively correlated with the formation of declarative memory for emotionally arousing information.*** *Correlations between* **(A)** *glucose utilization in the right amygdaloid complex (AC) of healthy subjects while viewing a series of relatively emotionally arousing films and long-term recall of those films and* **(B)** *glucose utilization in the right AC of the same subjects while viewing a series of relatively emotionally neutral films and long-term recall of those films.* Modified from Ref. 67.

A recent positron emission tomography (PET) study of glucose activity in human AC provides additional support for the hypothesis that the AC is selectively involved with long-term memory for emotionally arousing events[67]. Subjects in this study received two PET scans (separated by several days): one while viewing a series of emotionally arousing (negative) films, the other while viewing a series of relatively emotionally neutral films. Free recall tests assessed memory for the films three weeks after the second PET session. Activity in the right AC while viewing the emotional films correlated highly (r = +0.93) with retention of those films. AC activity while viewing the neutral films did not correlate with subsequent recall of those films (Fig. 4). Consistent with studies of patients with AC lesions, these PET findings suggest that the AC mediates the influence of emotional arousal on long-term declarative memory[67].

Finally, another recent PET study[83] reports that viewing (and presumably forming memories of) emotionally arousing films activates the AC, but recall of previously learned emotional events does not, findings again consistent with a time-limited role of the human AC in influencing declarative-memory formation for emotional events.

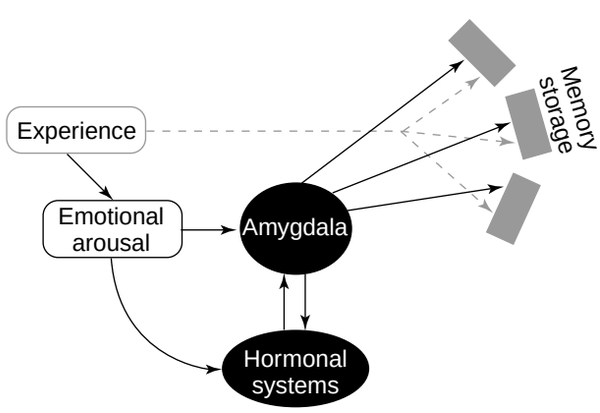

Fig. 5. ***Hypothetical memory-modulatory mechanism for emotionally arousing events.*** *Experiences can be stored in various brain regions with little or no involvement of either stress-hormone activation or the amygdaloid complex (AC). During periods of emotional arousal, stress-hormone systems interact with the AC to modulate memory-storage processes occurring in other brain regions.*

Concluding remarks

An impressively broad array of experimental evidence either directly supports, or is consistent with the hypothesis that stress-hormone systems and the AC are key components of an endogenous memory modulating system. Generally inactive in unemotional learning situations, this system is activated during and after an emotionally arousing event and appears to regulate declarative-memory storage processes in other brain regions (Fig. 5). This mechanism aids in the selection of long-term memories on which, according to William James, our mental ship rides.

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