Mechanisms of emotional arousal and lasting declarative memory
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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.


The evidence summarized here supports the view that specific hormonal and brain systems activated by emotional arousal regulate long-term memory storage. Much evidence for this view comes from animal studies involving human subjects; these studies are 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. Recent evidence concerning memory consolidation comes from many domains of investigation, including studies of synaptic plasticity and behavior. Elegant demonstrations of memory consolidation in invertebrate preparations indicate that memory consolidation is evolutionarily conserved.
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
specific experimental conditions as well as the post-training treatment used.

**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. Additionally, extensive evidence suggests they influence memory storage. Initial studies examined the effects of post-training injections of the adrenal medullary hormone adrenaline on memory for inhibitory-avoidance training. 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. Adrenaline effects on memory appear to be mediated by the activation of peripheral β-adrenergic receptors, located on vagal afferents projecting to the nucleus of the solitary tract in the brain stem. Additionally, the effects might involve the release of glucose.

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. Emotional arousal generally viewed as the ‘second wave’ of the autonomic response to an emotional event, following sympathetic adrenomedullary activation. 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 or central administration of low doses of corticosterone-receptor agonists. Furthermore, adrenocortical and adrenocorticoid hormones on memory interact in influencing memory storage.

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).

**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. Goddard’s research was...
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 amnestic. AC stimulation might either enhance or impair memory, depending on training conditions41 and levels of circulating adrenaline. 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 efficient projections41. 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 systems8,9,33,45. Furthermore, infusions of such drugs and hormones directly into the amygdala after training modulate memory storage8,9,42.

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 antagonists8. 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 storage8,9,42.

**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). Although Johnston might have overstated the case, the evidence indicates that nuclei of the AC have different functions in learning.19,20,22,33

The basolateral AC (BL) appears to be the nucleus most crucially involved in the modulation of memory storage20,22,33 (Table 1). Electrical-stimulation experiments first suggested that the BL region influences memory consolidation20,22,33. 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.42 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.42 BL lesions do not block inhibitory avoidance learning or retention42 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 colleagues43 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 colleagues44 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.44

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.45 However, as Quirk and colleagues44 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 distinguish 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. 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.

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, and pharmacological stimulation of the AC functionally activates both of these regions (L. Cahill, unpublished observations) (Fig. 3). Electrophysiological evidence strongly suggests that influences from the BL modulate long-term potentiation in the dorsal hippocampus. Additionally, AC lesions block the memory-enhancing effect of direct hippocampal stimulation. 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.

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. 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.

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. It is known that stimulation of the BL activates the cortical EEG, and that this effect depends crucially on the activity of the nucleus basalis. The AC might also modulate cortical memory-storage processes indirectly via projections to the locus coeruleus.

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

There has been controversy concerning the role of the AC in declarative memory. Scoville and Milner 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 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, 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. Considered together with other evidence of normal emotional reactions in patients with AC damage, 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. 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.

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. Immunohistochemical 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.

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<tr>
<th>Infusion</th>
<th>Retention spatial task</th>
<th>Cued task</th>
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<tr>
<td>Hippocampus</td>
<td>Enhanced</td>
<td>No effect</td>
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<td>Amygdala</td>
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TABLE 2. Amygdala modulation of hippocampus-dependent and caudate-nucleus-dependent memory

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 6-amphetamine into different brain areas was assessed. From Ref. 60.
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\(^a\). 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 emotion-ally 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. AC activity while viewing the relatively neutral films and the emotional films did not correlate with subsequent recall of those films. AC activity while viewing the emotional films and long-term recall of those films and AC activity while viewing the 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.

Finally, another recent PET study\(^b\) reports that viewing (and presumably forming memories of) emotionally arousing events 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.

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 dur-ing and after an emotionally arousing event and appears to regulate declarative-memory storage pro cesses 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.

FIG. 5. Hypothetical memory-modulatory mechanism for emotion-ally arousing events. Experiences can be stored in various brain regions with little or no involvement of other stress-hormone activation at 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.

**Selected references**