The amygdala and emotion

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The amygdala complex has long been known as part of the neural circuitry critical for emotion. Beyond its role in emotional reactivity, studies of animal models and patients with amygdala damage demonstrate its importance in emotional learning, whereby cues acquire significance through association with rewarding or aversive events. Although its function in associative learning has become well established, other recent research has advanced the concept that the amygdala regulates additional cognitive processes, such as memory or attention. For example, a correspondence in the function of the amygdala has recently been shown in the modulation of memory in humans and laboratory animals. The use of animal models has progressively defined the circuitry for these functions within the amygdala and its interconnections with other brain systems, including pathways through which the amygdala modulates memory and regulates attention. These various lines of research are progressively advancing our understanding of the amygdala's role in providing linkages between affect and cognition.

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Abbreviations

CS	conditioned stimulus
SCR	skin conductance response
US	unconditioned stimulus

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Introduction

Emotion encompasses a wide range of experience and can be studied in a variety of ways, ranging from verbal descriptions to the measurement of covert physiological responses, such as heart rate. A potentially useful framework for neurobiological studies is provided by a model in which emotions are considered along two dimensions [1•]. On one dimension, emotional states range from positive (e.g. happy or confident) to negative (e.g. fear or anger). These different emotional states, in turn, are associated with different behavioral tendencies. In the case of positive emotional states, there is a tendency towards attraction or approach. In contrast, aversion and defense are associated with negative emotional states, in which withdrawal, escape and avoidance are likely to occur. A second dimension of emotion is arousal. Both positive and negative emotional states can range on this dimension from relative calm to high degrees of arousal. Consideration of these dimensions of emotion is useful in determining the neural circuits involved.

In their initial study of temporal lobe damage in non-human primates, Klüver and Bucy ([2]; see also [3]) described a loss of emotional reactivity, characterized by a relative absence of arousal and a change in behavioral responses to emotional stimuli. They observed that monkeys with damaged temporal lobes (including the amygdala, the hippocampal formation, as well as the non-limbic temporal cortex) were generally placid and approached objects that they would normally perceive as threatening. A similar pattern of hypoemotionality is commonly described in clinical case reports of human patients with amygdala damage [4]. Such effects of amygdala damage suggest a global function in the regulation of emotion. However, recent research, discussed in this review, indicates that distinct circuitry within the amygdala subserves specific aspects of emotion, differing with respect to behaviors regulated by negative and positive emotional states. Moreover, distinct circuitry underlies the control of arousal by the amygdala, providing evidence for a dissociation in the arousal and valence dimensions of emotion.

Emotion and amygdala damage in humans

Recent studies of patients with amygdala damage have indicated that the amygdala is not only important for the regulation of internal emotional states that motivate behavior expressive of those states, but may also be important for the cognitive evaluation of the emotional content of complex perceptual cues. When asked to rate the intensity of an emotion expressed in pictures of faces, a patient with bilateral amygdala damage resulting from congenital Urbach–Wiethe disease was impaired in judging the intensity of certain expressions, such as fear and surprise [5••]. This deficit was not found in patients with unilateral damage of either the left or right amygdala alone [6•]. In addition, the patient with bilateral amygdala damage had an overall tendency to endorse only prototypical expressions: that is, this patient did not perceive similarities between expressions, such as fear and surprise, that are normally endorsed for more than one emotional category by control subjects.

A difficulty in the comprehension of facial expressions was also demonstrated by a subject studied in another laboratory who had sustained bilateral amygdala damage [7•], indicating the importance of the amygdala in the processing of information about emotions conveyed by complex perceptual cues. However, intact recognition of emotions expressed in faces was recently found in two patients with bilateral amygdala lesions resulting from herpes simplex encephalitis [8•]. Importantly, these patients were tested with the identical materials used to

detect deficits in the patient with Urbach–Wiethe disease. The reasons for differences among these patients are not yet clear, but might include differences in the extent of damage outside the amygdala. An alterative view is that the cognitive evaluation of emotion is only affected by damage to the amygdala early in development, as is the case in congenital Urbach–Wiethe disease.

Studies of associative learning in humans with amygdala damage

On the basis of studies on the effects of damage to the amygdala in monkeys, Weiskrantz [9] first proposed that the amygdala has a role in emotional learning. He attributed the observed behavioral deficits to a failure to form associations through which neutral cues gain biological significance. For example, when we learn that a cue is a signal for an upcoming aversive event, the cue comes to evoke apprehension or fear. Consistent with this view, animals with lesions of the amygdala have deficits in fear conditioning.

Following upon these animal studies, two recent studies of patients with amygdala damage have assessed conditioned autonomic responses [10•,11••]. Consistent with earlier observations, both studies found that patients with amygdala damage (either unilateral or bilateral) were impaired in acquisition of a conditioned skin conductance response (SCR) when a normally neutral cue (the conditioned stimulus or CS) had been paired with a mildly aversive event (loud noise) that served as the unconditioned stimulus (US). However, the patients accurately recollected many facts about the task and had normal reactions to the aversive US, as indicated by both intact unconditioned responses (i.e. increased SCR evoked by the noise presented alone) and their evaluations of the loud noise as 'irritating' and 'unpleasant'. Although these verbal and physiological signs of emotional reactivity survived damage to the amygdala, neutral cues failed to become associated with the aversive properties of the loud noise. These studies demonstrate that the amygdala is also important for emotionally-based learning in humans.

The modulation of memory after amygdala damage

A recent study of a patient with amygdala damage [12•] has supported the notion that the strength of memories can be modulated by the amygdala complex, an idea derived from research with laboratory animals [13]. A patient with amygdala damage was tested in a task that shows modulation of memory by emotional arousal. As originally devised, the test material consists of a brief narrated slide show in which the identical material is shown to different groups of subjects accompanied by either an emotionally provocative narrative or a neutral narrative in the middle phase of the story. Control subjects demonstrate superior memory for items shown under the condition of emotional arousal relative to subjects tested in the non-emotional neutral condition, a phenomenon that is blocked by a beta-adrenergic antagonist [14]. By confining the neutral and emotional narratives to different phases of the slide show, a within-subject version of this task was used for testing the patient with bilateral amygdala damage. This patient had normal retention of the non-emotional phase of the story but failed to show enhanced memory for the material presented in the emotional phase, despite a self-assessed normal emotional reaction to that component of the narrative [12•]. Thus, the modulation of memory, attributable in normal subjects to the induction of emotional arousal, is lacking after amygdala damage.

These recent studies in humans are in agreement with observations in laboratory animals showing impairments in classical conditioning tasks and the modulation of memory after damage to the amygdala. The parallels are significant because brain damage in clinical cases is often not isolated to the amygdala complex, and consequences of clinical conditions for brain function outside this structure are difficult to exclude. Although much of the relevant comparison data comes from studies of rodents, it is likely that the current direction of research with clinical subjects may serve as an impetus for further studies in non-human primates, where selective brain manipulations can be made to provide a detailed account of the relevant neural systems in the primate brain. An important advance in this effort is the recent introduction of selective neurotoxic lesions of the amygdala for neuropsychological investigations in monkeys [15•].

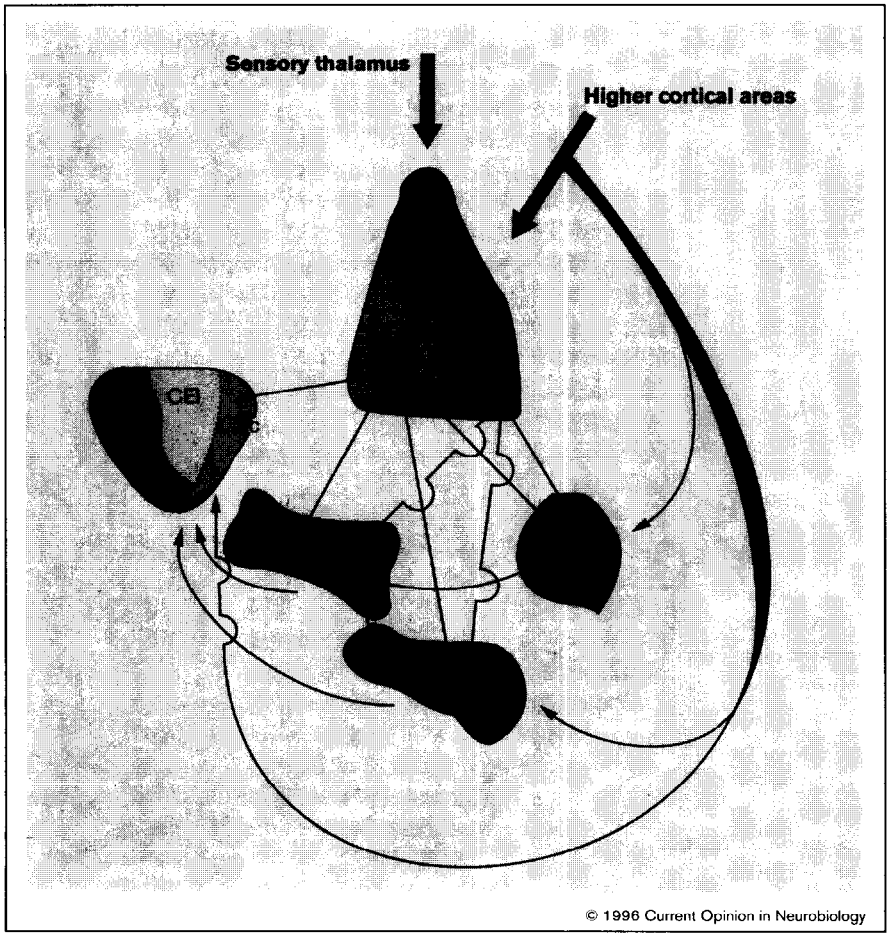
Studies of fear conditioning in the rat

A neural systems analysis of the amygdala circuitry used in emotional learning continues to progress in several models of fear conditioning. Cues that signal an impending aversive event elicit freezing, potentiate startle reactivity, and produce characteristic autonomic responses in rodents. The amygdala complex has proven to be critical for the acquisition of this full range of conditioned fear behaviors [16,17•,18•,19••,20,21••]. The relevant pathways afferent and efferent to the amygdala, as well as component circuits within the amygdala complex, are becoming better defined [22•,23•,24••,25•,26••].

The nuclei of the amygdala complex illustrated in Figure 1 are critical for fear conditioning in the rat [22•,23•]. Indeed, these components of the amygdala share a common function in fear conditioning to either visual or auditory cues. Acquisition of fear to such cues was examined in rats that sustained either selective neurotoxic lesions of the basolateral complex (including lateral and basal nuclei) or lesions of the central nucleus [21••]. Each lesion produced an entirely comparable impairment in fear conditioning that was not limited to a particular sensory modality.

Considerable progress is also being achieved in the study of neural plasticity within this circuitry. As indicated in Figure 1, the lateral nucleus provides a relay for sensory

Figure 1



Nuclei of the amygdala complex critical for fear conditioning in the rat. Displayed are pathways for inputs that serve as a basis for fear conditioning, which can be established via direct subcortical thalamo-amygdala or indirect thalamo-cortico-amygdala processing. AB, accessory basal nucleus; Bmc, basal nucleus (magnocellular division); Bpc, basal nucleus (parvicellular division); CEc, central nucleus (capsular division); CEl, central nucleus (lateral division); CEm, central nucleus (medial division); Ll, lateral nucleus (lateral division); Lm, lateral nucleus (medial division). Adapted from [22•].

information from subcortical structures. A particularly interesting report by Rogan and LeDoux [24••] has shown that long-term potentiation achieved by stimulation of the thalamo-amygdala projection also enhances the evoked potential recorded in the lateral amygdala from a naturally transduced auditory input. Thus, the processing of cues commonly employed in classical conditioning tasks can be enhanced by a plasticity mechanism isolated to a particular pathway into the amygdala.

Until quite recently, renditions of the neural circuitry for fear conditioning focused on a limited set of subcortical pathways to and from the amygdala. Given that de-cortication does not abolish such learning [27], only a consideration of subcortical circuitry was deemed necessary. Subsequent studies have shown, however, that fear conditioning can be established via direct subcortical thalamo-amygdala or indirect thalamo-cortico-amygdala processing; these two routes have equipotentiality with respect to learning. In the well studied case of fear conditioning with auditory cues, fear conditioning is only abolished after removal of the entire auditory thalamus, including the origin or inputs to cortex and to the amygdala [28].

As is the case for auditory information, perhaps multiple pathways are equipotential for a variety of events (both CS and US) that depend on the amygdala for their association. The thalamic nuclei that target the amygdala (medial division of the medial geniculate, the posterior intralaminar nucleus, and the suprageniculate nucleus) are sources of auditory, somatosensory and visual information that might serve as a basis for learning associations between CSs (such as simple tones or lights) and USs (such as footshock). However, other routes for input provided by an aversive stimulus, such as footshock, must be adequate to support learning in fear conditioning tasks, otherwise removal of the direct thalamo-amygdala projections would be sufficient to abolish learning in fear conditioning with auditory cues. In addition, Campeau and Davis [25•] recently reported that thalamic lesions that disrupt fear conditioning to an auditory CS did not impair fear conditioning when a visual CS was used. An important feature of this study was the within-subject design for comparing the effects of lesions on conditioning to cues in different sensory modalities. The modality-specific impairment they observed also indicates that the identified origin of thalamic input to the lateral nucleus of the amygdala is not essential for encoding the properties of the

US that support conditioning, otherwise learning would have been generally affected because the same US was used in auditory and visual versions of the task.

One important objective in defining the neural circuitry for any particular instance of learning is to provide a framework for the identification of sites and mechanisms where changes in neural function occur as a basis for learning. This neural systems approach has met with considerable success in invertebrate organisms with less complex information processing systems. The use of simple cues in studies of mammals, however, may not simplify the neural circuitry that is capable of mediating learning, as the equipotentiality of multiple pathways for simple auditory cues indicates. Somewhat paradoxically, the use of more complex stimuli may constrain the circuits that can provide adequate input to the amygdala complex for learning. For example, considerable interest has focused on the role of the amygdala in contextual fear conditioning in rodents [20,29]. As distinct from fear that comes to be evoked by discrete cues, context conditioning refers to the fear that can be conditioned to more complex configurations of cues, such as those that define a particular environment. It appears that contextual fear conditioning is dependent on information processed by the hippocampus that is provided to the amygdala. On the basis of such evidence, Maren and Fanselow [26••] recently reported that stimulation of the hippocampal formation at the origin for the hippocampal projection to basolateral amygdala potentiated a short latency component of the evoked field potential in the basolateral amygdala. Damage to this circuitry alone was also sufficient to impair behavioral conditioning to the context.

In addition to providing the amygdala with highly processed information, limbic/cortical connectivity may be important for storage or retrieval of long-term information. It is now recognized that the parahippocampal region of cortex in the monkey, which includes the perirhinal, parahippocampal and entorhinal cortices, forms an important part of the medial temporal lobe memory system [30]. While much recent research has emphasized that these areas form an interface between the neocortex and hippocampus, they are also highly interconnected with the amygdala complex. Considerable parallels exist in the neuroanatomical principles that define this cortex in primate and rodent brains, including connectivity with the amygdala complex [31•]. Damage to perirhinal cortex in rats can impair fear conditioning; when lesions are made after, but not before training, deficits in the expression of fear conditioning are observed [32]. The effect of post-training perirhinal damage on fear conditioning might represent a cross-species homology for the role of perirhinal cortex in information storage or retrieval.

Specialized function of amygdala subsystems in associative learning

Although the study of fear conditioning supports the concept of a common function subserved by a set of amygdala nuclei (lateral, basal and central), other evidence indicates that these components of the amygdala comprise subsystems that serve different functions. One clear functional distinction comes from studies of taste/odor potentiation learning. Several studies have shown that damage limited to the basolateral amygdala abolishes taste potentiation of odor conditioning, even though animals with these lesions exhibit no impairment in learning simple associations to either taste or odor alone [33,34•,35•]. Unlike simple associations, the potentiation phenomenon depends on the formation of an association between the taste and odor cues in order for odor conditioning to occur. Importantly, damage to the central nucleus was shown to be without effect in these studies. The pathways and interconnections with basolateral amygdala through which taste/odor potentiation is acquired have not yet been defined, but are not likely to include the central nucleus.

Other examples of amygdala functions dependent on basal/lateral nuclei, which are unaffected by central nucleus damage, come from studies of appetitive learning [36]. It might be tempting to speculate that direct innervation from the basolateral amygdala to the ventral striatum, including the nucleus accumbens, provides a substrate for learning that is supported by motivational/emotional conditions of a positive valence, whereas learning based on negative affective states such as fear are supported by an amygdala processing system that includes the central nucleus.

A very recent study, however, challenges this view and indicates that central and basolateral amygdala may also have distinctive and dissociable roles in aversive conditioning. Killcross, Everitt and Robbins (AS Killcross, BJ Everitt, TW Robbins, *Soc Neurosci Abstr* 1995, 21:1667) used a novel conditioned punishment procedure in which a behavioral measure of classically conditioned fear could be examined concurrently with instrumental avoidance learning. Neurotoxic lesions of lateral/basal nuclei produced a marked and persistent impairment in avoidance conditioning, but only transiently impaired classically conditioned suppression to the CS associated with aversive footshock. The opposite pattern of behavior was seen in rats with selective neurotoxic lesions of the central nucleus; that is, the lesioned rats displayed a marked and persistent impairment of classically conditioned behavior, but intact acquisition of avoidance learning. Because learning the CS/US association was important for both the classically and instrumentally conditioned behaviors, it appears that rats with central nucleus damage are capable of acquiring such associations and can express that learning

in the form of voluntary behavior (avoidance) as long as the lateral/basal nuclei are intact. By the same token, the CS/US association can be acquired by rats with basolateral amygdala damage and expressed in the form of behavioral suppression, as long as the central nucleus is spared. These results provide an indication of more distributed learning within the amygdala fear conditioning system than previously recognized, suggesting that there may exist multiple representations of the CS/US association within this circuitry. This concept seems at odds with the traditional serial processing scheme of information flow through the lateral/basal region to the central nucleus (shown in Figure 1), but it is consistent with recent anatomical findings that cortico-amygdala input is more widely distributed to components of this circuitry than formerly appreciated [31•].

Selective damage of the amygdala central nucleus produces the interesting finding of a dissociation of the motivational and arousal components of associative learning, at least in appetitive conditioning. Rats with selective neurotoxic lesions of the central nucleus have a pronounced deficit in the acquisition of conditioned orienting behavior to both auditory and visual cues that are used as CSs during conditioning [37]. In the same appetitive conditioning procedure, the CS which fails to acquire conditioned orienting, nonetheless acquires reinforcing/motivational value because rats will learn behaviors directed to the location of food (US) delivery [38••]. That aspect of associative learning is also evident in second-order conditioning. In the second-order conditioning procedure, a stimulus, which initially served as the CS during conditioning, is then used in place of food to support learning to a new CS. Learning to the new CS shows that the original CS gained reinforcing/motivational value. After central nucleus damage, second-order conditioning is acquired normally by rats that fail to learn a conditioned orienting response.

Additional studies have shown that a deficit in conditioned orienting after central nucleus damage appears to be a signature of a more extensive impairment in the processing of cues in associative learning. In a variety of circumstances in which normal animals enhance processing of target cues, rats with central nucleus lesions fail to show this modulation of attention [38••]. Such findings are consistent with the view that the amygdala regulates alerting and arousal functions [39]. Although much emphasis has usually been placed on projections from amygdala central nucleus to brainstem output systems, new evidence supports a role for central nucleus connectivity with the forebrain in the regulation of arousal and certain aspects of information processing. For example, central nucleus innervation of a component of the basal forebrain cholinergic system, which in turn innervates cortex, and of substantia nigra dopamine neurons, which in turn innervate dorsolateral striatum, are important substrates for conditioned orienting behavior and the increased processing of cues based on learning ([40••]; JS Han, RW McMahan, PC Holland, M Gallagher, *Soc Neurosci Abstr* 1995, 21:1224). Additional pathways from the amygdala that influence neural mechanisms/plasticity in the forebrain are likely to provide a route for the modulation of memory [14]. These pathways and functions of the amygdala are separable, at least to some degree, from those that provide a substrate for the positive or negative value that cues acquire in emotional learning.

Conclusions

Current research has progressed considerably beyond the initial concept that amygdala damage leads to hypoemotionality and impairment in emotional learning. The neural circuits within the amygdala complex that subserve these functions are being defined. Different output pathways from the amygdala have been delineated that mediate specific aspects of learning connected with positive and negative emotional states. Moreover, the arousal dimension of emotional states has been shown to be somewhat separable from that encoding emotional valence. In addition, specific output pathways related to the arousal dimension of emotional experience contribute to the regulation other cognitive functions, such as attention and the modulation of memory. Building on this progress, future work will continue to give greater definition to the multiple functions of the amygdala complex in associative learning.

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