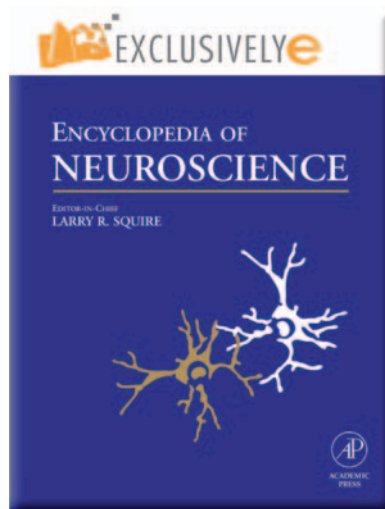


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## Amygdala: Contributions to Fear

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### History

The physiological basis for emotions has intrigued mankind for centuries. Early Greek philosophers held emotion to be a product of visceral activity – a beating heart reflecting passion and love or a clenched gut fueling jealousy and sadness. Over the course of hundreds of years, however, the study of emotion has moved from the trunk to the head. There are many factors that encouraged this shift in thinking about the localization of emotion. Perhaps the most influential one was the discovery of profound emotional changes in a man named Phineas Gage, whose brain was penetrated by an iron spike in a railway construction accident in 1848. Amazingly, Gage survived the injury to his head, but he was not the same person after recovering from the wound. Relative to his gentle demeanor prior to the accident, he angered easily, used profanity, and could not maintain interpersonal relationships after his accident. Emotions, it would appear, had their roots in the brain.

Not long after Gage's condition was described, scientists were embarking on the first neurological studies of brain function in animals. Sanger Brown and E A Shafer at the University College, London, carried one of the first studies of this kind out in 1888. They systematically examined the behavioral consequences of surgical lesions to the monkey cerebral cortex, with a focus on damage to the temporal and occipital lobes of the brain. In one case, they produced a nearly complete and bilateral lesion of temporal cortex that also included underlying structures, including the amygdala (Figure 1). The animal in this case presented with profound behavioral changes. Although its sensory and motor function and general intellectual faculties appeared to be normal, the animal's emotional behavior changed considerably after the lesion. The monkey lost fear of other, dominant monkeys and was tame in the presence of people. It also did not remember an aversive event, readily returning to interact with a monkey that had defeated it in fight, for example.

This observation of emotional changes after temporal cortical damage languished for 50 years until it was rediscovered by Kluver and Bucy in 1937. They similarly observed altered emotional behavior, particularly a loss of fear, in monkeys with temporal cortical lesions. Lawrence Weiskrantz made a key advance

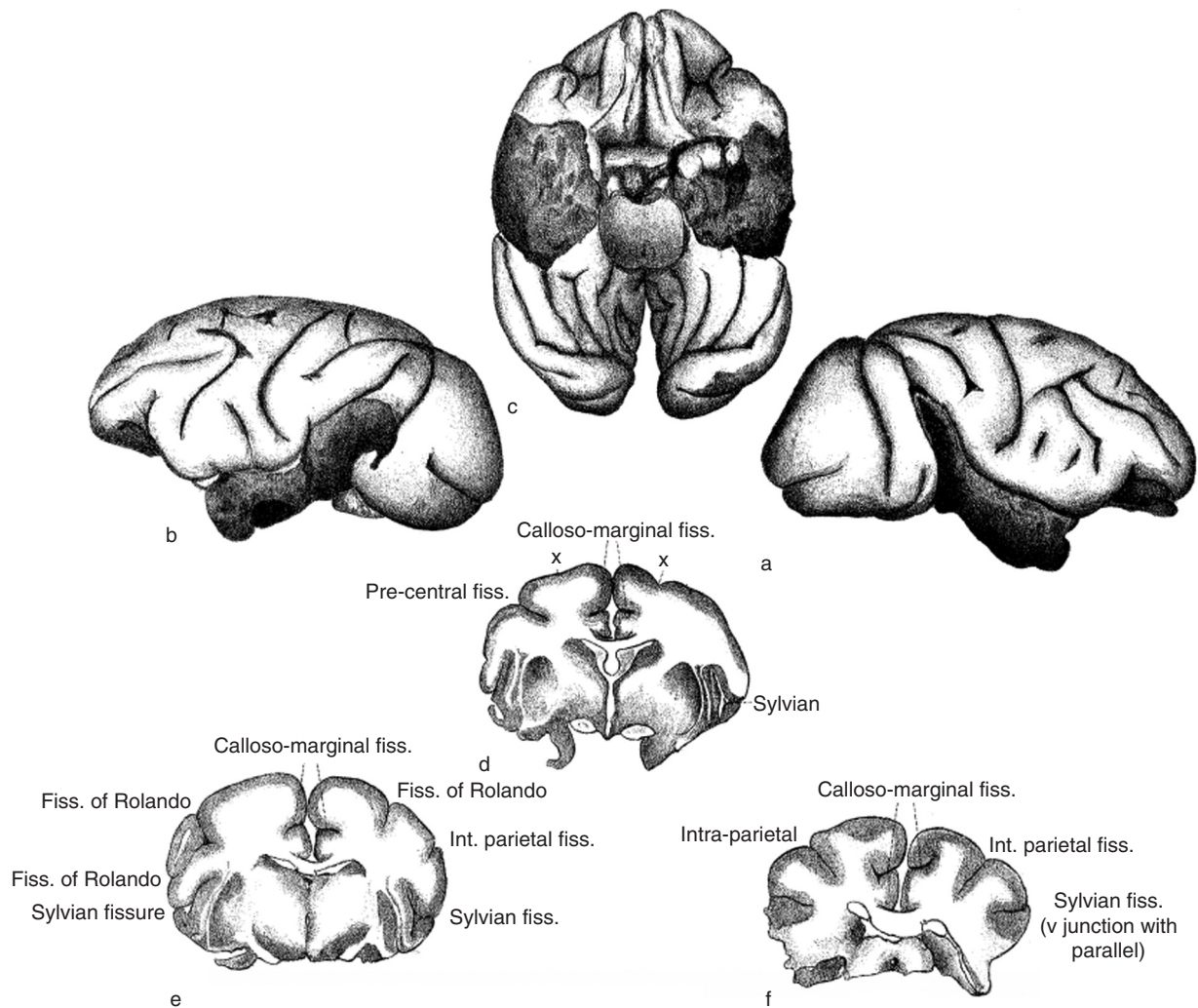
in understanding the basis for fear reductions with these lesions in 1956. He showed that the damage to the amygdala, a brain structure underlying the temporal cortex, accounted for the fear loss, and that other changes in behavior were likely the consequence of the cortical damage. Weiskrantz was also the first to suggest that the amygdala has an important role in assigning emotional value (through learning) to stimuli that predict biologically important events (including noxious events). Hence, this seminal work pinpointed a specific brain area that was critical for the genesis of an emotion – in this case, fear. To this day, the amygdala remains a focus for studying the brain mechanisms of fear.

### Anatomy of Fear

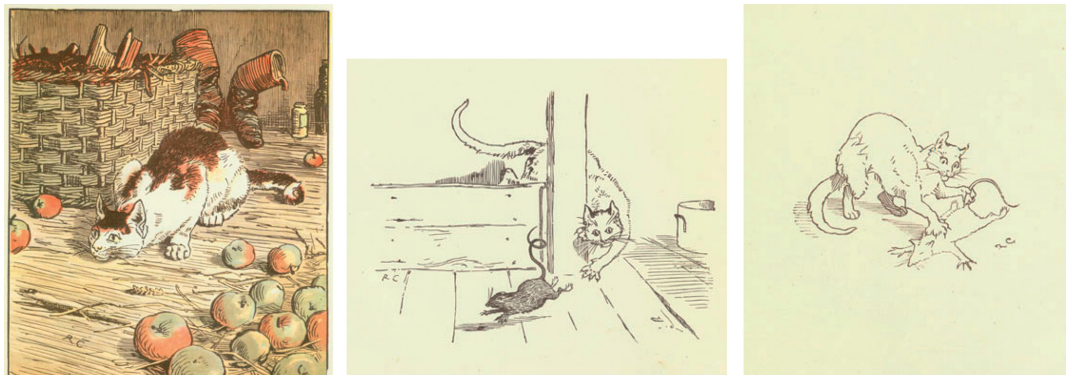
Fear is a universal emotion that not only has an obvious subjective component ('I feel afraid'), but also a unique behavioral and autonomic signature ('When I am afraid, I freeze in my tracks and my heart pounds in my chest'). The physiological and behavioral aspects of fear are readily studied in both humans and animals and these responses appear to share many similarities, among mammals at least.

Fear is either innate or learned. For instance, primates appear to have an innate predisposition to learn fear of snakes. Monkeys that are born and raised in captivity exhibit fear responses to live or rubber snakes, but not to belts or toy fire trucks (none of which they have seen before). This fear response depends on observing another monkey exhibit fear in the presence of snakes. Laboratory-born deer mice can differentiate predators and nonpredators from their typical habitat, despite never having contacted those animals before. This indicates that fear systems evolved as a defensive behavior system to ward off predators found in an animal's habitat, as well accommodating rapid learning about new threats in the environment. The utility of both types of fear is obvious. Animals that can respond to threats in the environment without requiring past experience with the threat are at an obvious advantage. And rapid learning about novel threats in the environment is similarly adaptive; an animal may only have one opportunity to learn about a threat before it is mortally injured (Figure 2).

Several lines of evidence indicate that the amygdala is involved in both innate and learned fear responses. The amygdala ('almond,' Greek) is an oval-shaped collection of neurons located deep within the temporal lobe of the vertebrate brain. It is prominent in



**Figure 1** Temporal lobe lesions in a rhesus monkey. Reproduced from Brown S and Schäfer EA (1888) An investigation into the functions of the occipital and temporal lobes of the monkey's brain. *Philosophical Transactions of the Royal Society London, Series B* B179: 303–327, with permission.



**Figure 2** A cat stalking and killing a rat. Reproduced from Caldecott R (1878) *The House that Jack Built*. London: Frederick Warne & Co. Ltd. Permission obtained under the Project Gutenberg License.

mammals, but there is also a homologous structure in amphibians and reptiles, among others. In all cases, the amygdala is not a monolithic structure in the brain; it is instead a collection of anatomically and

functionally distinct nuclei with different developmental origins. It is therefore commonplace to describe the amygdala as the 'amygdaloid complex,' and to focus on particular nuclei with the amygdala.



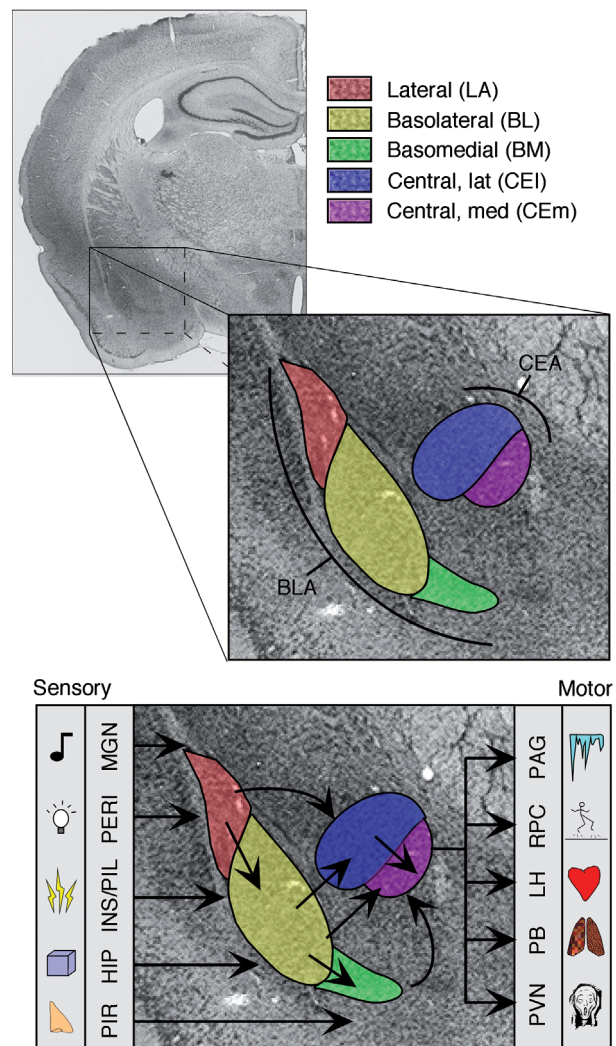
In any case, the terms amygdala and amygdaloid complex are synonymous.

Of the ten or so amygdaloid nuclei, there are two major contributors to the fear response: the basolateral complex (including the lateral, basolateral, and basomedial nuclei) and the central nucleus (Figure 3). The basolateral complex receives considerable sensory information from subcortical and cortical areas. It in turn projects heavily to the central nucleus, which sends axons to other brain areas involved in generating specific fear responses, such as freezing (immobility), tachycardia, and stress hormone release. Damage to either the basolateral complex or the central nucleus can impair fear responses under a variety of conditions.

### Innate Fear

Caroline and Robert Blanchard at the University of Hawaii first demonstrated that rats with amygdala lesions lose their innate fear of cats. Normal rats exhibited fear, particularly freezing behavior, in the presence of a cat. This response was markedly reduced by damage to the amygdala. However, the lesions, like those used in the early monkey studies, damaged both neurons in the amygdala, as well as axons passing through the amygdala from one brain area to another. More selective lesions of the amygdala, or reversible inactivation of amygdala neurons, suggest that the amygdala may not be as important in generating innate fear responses as once believed. For example, neurotoxic lesions (that spare axons) or reversible inactivation of neurons in the amygdala do not prevent fear (freezing behavior, in this case) to a predator odor (trimethylthiazoline, a component of fox feces). In primates, neurotoxic lesions of the amygdala do reduce fear responses to real or artificial snakes, but these effects are not nearly as pronounced as those produced by lesions that also damage axons. Similarly, humans with amygdala damage exhibit normal autonomic responses, such as a galvanic skin response, to aversive stimuli. Another brain area that may be involved in innate fear responses is the hypothalamus. Rosen and colleagues have shown that molecular markers for neuronal activity are increased in the rat hypothalamus, but not the amygdala, after exposure to a predator (a cat).

In sum, large lesions that encompass both neurons and axons passing through the amygdala produce profound disturbances in innate fear reactions, although more selective manipulations of amygdaloid neurons within discrete nuclei produce only mild impairments (if any) in innate fear responses. Indeed, rats with amygdala lesions exhibit normal fear reactions in a number of tests of fear and anxiety, such as the open field (which measures locomotor activity in



**Figure 3** Anatomy of the amygdala. The amygdaloid nuclei can be roughly divided into two subsystems. These include the lateral, basolateral, and basomedial nuclei, which together form the basolateral complex (BLA) and the central nucleus (CEA). The BLA receives and integrates sensory information from a variety of sources. These include the medial and ventral divisions of the thalamic medial geniculate nucleus (MGN, auditory), the perirhinal cortex (PERI, visual), the insular cortex (INS, gustatory and somatosensory), the thalamic posterior intralaminar nucleus (PIL, somatosensory), the hippocampal formation (HIP, spatial and contextual), and the piriform cortex (PIR, olfactory). Intra-amygdaloid circuitry conveys the conditioned stimulus–unconditioned stimulus association to the CEA, where divergent projections to the hypothalamus and brain stem mediate fear responses such as freezing (periaqueductal gray, PAG), potentiated acoustic startle (nucleus reticularis pontis caudalis, RPC), increased heart rate and blood pressure (lateral hypothalamus, LH), increased respiration (parabrachial nucleus, PB), and glucocorticoid release (paraventricular nucleus of the hypothalamus, PVN). For simplicity, all projections are drawn as unidirectional connections, although in many cases these connections are reciprocal.

a brightly lit novel environment) or the elevated-plus maze (in which animals avoid well-lit arms that are elevated above the floor in favor of dark and enclosed arms).

### Learned Fear

As John Watson showed in the early 1920s, fear is readily learned. He conditioned the infant 'Little Albert' to fear white rats by pairing a noxious, loud noise each time he presented the boy with the rat. Albert, who had no fear of the rat before Watson's intervention, quickly came to be upset and scared by the animal, crying and reeling from it when Watson placed it in his lap (Figure 4). In this case, Albert learned to associate, through classical or Pavlovian conditioning, the white rat and loud noise. Not surprisingly, fear conditioning has become a standard model for understanding how fear is learned in animals and humans.

In the laboratory, fear conditioning proceeds by exposing animals to an innocuous stimulus (conditioned stimulus; CS) that is followed by a noxious event (unconditioned stimulus; US). After as little as a single conditioning trial, animals come to exhibit a learned fear response (conditional response; CR) to the CS. This fear response includes autonomic and behavioral components, and is easily quantified.

An enormous body of work indicates that the amygdala is critical for fear conditioning. In rats, lesions of either the basolateral complex or the central nucleus of the amygdala severely impair both learning and remembering conditional fear responses. Amazingly, lesions of the amygdala disrupt very old fear memories, up to 1-year-old memories in rats. The involvement of these amygdaloid nuclei in fear learning holds for many different stimuli (e.g., tones, lights, places, and odors) and responses (e.g., freezing, heart rate, analgesia, and acoustic startle). And like rats, humans with amygdala lesions (from either surgical interventions for epilepsy or from an amygdala-damaging genetic condition) show deficits in fear conditioning.

The inability of animals and humans with amygdala damage to learn new fears or remember old fears is not simply a problem with expressing fear. As mentioned previously, many fear responses survive amygdala damage. In fact, deficits in learning fear responses can be reproduced with temporary inactivation of

the amygdala during the conditioning experience. And interfering with cellular events in the amygdala that are involved in synaptic plasticity shortly after a conditioning experience can impair memory formation even if the amygdala is functioning normally at the time the aversive event is experienced.

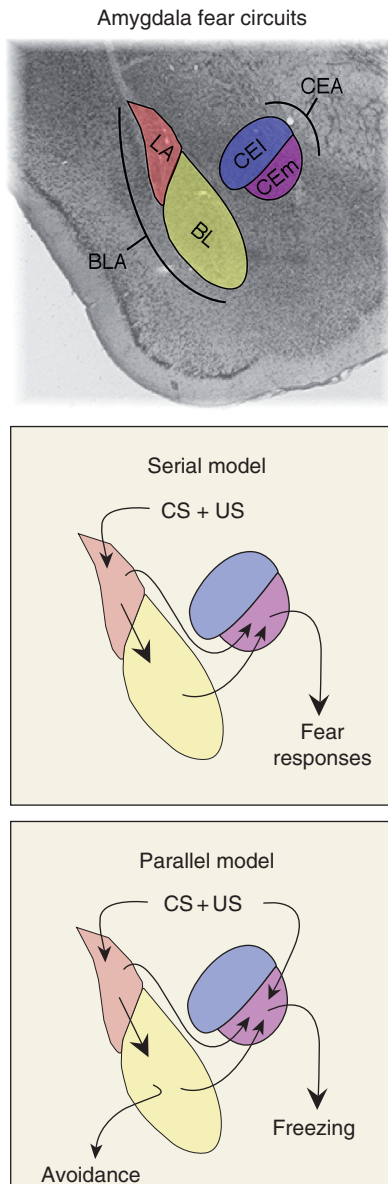
The critical region of the amygdala necessary for associating the CS and the US during fear conditioning is under debate. Considerable data suggest that CS and US convergence occurs in the basolateral complex (particularly the lateral nucleus), suggesting that it is where learning occurs in the amygdala (Figure 5). However, sensory information also reaches the central amygdala, and recent work suggests that it may be more important than previously recognized for learning new fears. Indeed, the two structures might work in parallel to mediate different aspects of what is learned during an aversive event.

Given the importance of the amygdala in learning and remembering fearful experiences, it is not surprising that the amygdala becomes active during fear conditioning. In humans, this has been revealed using functional magnetic resonance imaging. Blood flow in the amygdala increases when people view fearful facial expressions or when they are presented with conditioned stimuli that predict aversive unconditioned stimuli. In rats, amygdala activation is observed in the activity of single neurons. In both the basolateral complex and central nucleus, amygdala neurons increase their activity (fire more action potentials) to a newly learned fear stimulus. This activity is closely tied to what the animal has learned about the fear stimulus, and is not simply related to a state of fear itself.

The identification of the amygdala as a key brain area for emotional learning has allowed an unprecedented analysis of the molecular events involved in fear memory formation. Learning is believed to alter synaptic communication in the amygdala, possibly by inducing phenomena such as long-term potentiation, a long-lasting enhancement of synaptic transmission. In line with this possibility, drugs that prevent



**Figure 4** John B Watson conditions fear in 'Little Albert.' Reproduced from Watson JB (1920) *Experimental Investigation of Babies*. Chicago: Stoelting, with permission.



**Figure 5** Different models for information processing in the amygdala during fear conditioning. BLA, basolateral complex; LA, lateral nucleus; BL, basolateral nucleus; CEA, central amygdala; CEI, central lateral nucleus; CEM, central medial nucleus; US, unconditioned stimulus; CS, conditioned stimulus. Reprinted from *Neuron*, Vol. 47, Maren S, Synaptic mechanisms of associative memory in the amygdala. 783–786, Copyright 2005, with permission from Elsevier.

long-term potentiation also impede fear learning when they are injected into the amygdala. Hence, fear memories appear to be represented as long-lasting synaptic changes among amygdala neurons.

### Pathological Fear

The ability to engage the fear system and associated defensive behaviors after a threat is clearly adaptive.

However, fear can also be pathological under some conditions, and excessive fear is at the root of many disorders of fear and anxiety, including panic disorder, posttraumatic stress disorder, and specific phobias, to name a few. In posttraumatic stress disorder, for example, a severe trauma yields a persistent and intrusive state of fear that has debilitating effects on the affected individual.

Pathological fear in posttraumatic stress disorder and other anxiety disorders is often associated with elevated activity in the amygdala. There is some evidence that elevated amygdala activity is the consequence of a loss of cortical inhibition. For example, prefrontal cortical activity is often inversely correlated with amygdala activity in patients with anxiety disorders.

Clinical interventions for anxiety disorders are varied, but many involve behavioral procedures, including exposure therapy to reduce fear in a controlled setting. In its essence, exposure therapy is an extinction procedure in which a fear stimulus is presented without its aversive consequence, in a safe environment. After fear conditioning, CRs can be extinguished by presenting the CS without the US for several trials. Importantly, there is considerable evidence that this procedure does not erase the fear memory, but rather results in new learning (e.g., CS is safe) that inhibits the fear memory. The persistence of the fear memory after extinction is demonstrated by the renewal of the fear when a CS is presented outside of the environment where extinction was performed, and by the spontaneous recovery of fear responses as time passes after the end of extinction training.

The new learning that accompanies extinction also requires the amygdala. Pharmacological manipulations in the amygdala that impair fear conditioning also impair extinction learning. Moreover, drugs that enhance the activity of amygdala neurons can facilitate extinction under some conditions. This may be an important complement to behavioral interventions for treating anxiety disorders.

In addition to the amygdala, there are other brain areas implicated in the suppression of pathological fear. Another medial temporal lobe structure, the hippocampus, is important for learning and remembering the places in which fear and extinction memories are established. The prefrontal cortex exhibits inhibitory control over the amygdala and may be involved in promoting extinction memory when there is conflict between safety and danger signals. It is clear that a wide network of neurons is engaged in both learning new fears and suppression of old ones.

*See also:* Amygdala: Structure and Circuitry in Primates; Amygdala: Structure and Circuitry in Rodents and Felines; Aversive Emotions: Molecular Basis of



Unconditioned Fear; Emotion; Neuroimaging; Extinction; Anatomy; Genetics of Human Anxiety and Its Disorders; Panic Disorder as an Emotional Disorder; Pharmacology of Fear Extinction; Phobia and Human Evolution; Prefrontal Cortex: Structure and Anatomy.

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