Cell, Vol. 85, 469–475, May 17, 1996, Copyright ©1996 by Cell Press

Emotion: Systems, Cells, Synaptic Plasticity

Review

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The history of neuroscience in the 20th century is punctuated by periods in which the neural basis of emotion has been avidly studied and discussed. We are now in such a period, one marked by technical and conceptual advances that allow a consideration of emotional processes in terms of neuroanatomical circuits, cellular functions, and molecules. This short article will survey some of the recent advances.

Breaking Through the Consciousness Barrier

A fundamental problem in studying the mind as a function of the brain is getting past the fact that we are often consciously aware of the mental states that our own brain produces. This has historically led to the assumption that the study of the mind necessarily involves the study of consciousness. Following the rise of cognitive science, however, mental functions have been conceptualized in terms of computational processes—unconscious turnings of mental gears—rather than as subjective states. From this perspective, the exact nature of conscious states, and the relative inaccessibility of these states to empirical study (especially as brain functions), does not deter the investigation of the underlying processes. Armed with this conceptual framework, great strides have been made in understanding how we attend to and perceive objects, form memories of our experiences, imagine things that do not exist, reason and solve problems, control actions in the world, and more (see Kihlstrom, 1987; Posner, 1990).

No consensus has been reached about whether emotion can be properly regarded as being within the realm of cognitive science (see Ekman and Davidson, 1994). However, regardless of the fate of this much debated question, emotion can be studied using the same tools and conceptual framework that cognitive science has so successfully applied to other phenomena. Emotion, in other words, can be thought of in terms of computational processes (see LeDoux, 1989).

Once we take this road, the issue of whether it is possible to study emotions in animals, other than human ones, becomes moot. If emotions are not conceived of simply in terms of conscious states, then we are not restricted to studying them only in creatures whose conscious experience can be studied.

This approach may seem to obscure or sidestep what is commonly understood as the essence of emotion—for what is an emotion, if not an awareness of being in some state or situation? How can the empirical approach described here be reconciled with the pervasive experience of conscious emotional states?

The viewpoint represented in this survey is that at least some emotions can be thought of as reflecting the operation of evolutionarily old brain systems that control behaviors necessary for the survival of the individual or its species. These systems evolved to control behaviors, not to generate states of consciousness. For example, all animals defend themselves from danger. When the system that takes care of defense is operative in a brain that also happens to have consciousness, then the subjective state of mind called fear arises. It seems very likely that these behavioral control systems emerged long before self-awareness did.

If this view is correct, it means that a fundamental job of emotion researchers is to determine how the brain controls emotional responses based on the computation of the emotional significance of stimuli. And if emotional responses and conscious emotions are both products of these computations, then defining the brain mechanisms that control emotional responses also reveals important aspects of the system that generates subjective emotional states in conscious brains.

Emotions, One at a Time, in the Brain

In the past, researchers interested in the physiology of emotion have sought to find a universal brain system of emotion (MacLean, 1952). This effort culminated around mid-century in the limbic system concept, which is still widely discussed as an explanation of where our emotions come from. But in attempting to account for all emotions in one system, it actually accounts for no emotions (LeDoux, 1991). The alternative approach, which has proven to be more productive, is to track down emotional functions in the brain one emotion at a time (LeDoux, 1995). If indeed different emotions evolved for different reasons and subserve different functions with different behavioral and physiological requirements, it is also likely that they are mediated by different brain systems. It is therefore necessary to resist generalizing findings about emotional processing in the brain beyond the particular emotion under study, at least until we have some empirical justification for such generalizations.

The remainder of this review focuses on the emotion that has come to be understood best, the one we call fear. It is the product of a neural system that evolved to detect danger and produce rapid protective responses automatically (without conscious participation). This system is programmed to respond to routine dangers faced by our ancestors, but also to learn about new dangers quickly—in a single exposure. If an organism is fortunate enough to survive a novel and potentially fatal threat, the defense system learns enough from that single experience to enhance survival in future encounters with this same threat or others like it.

It is precisely this ability to learn about new dangers that has provided the most productive inroad to the study of the fear or defense system. By exploiting this natural plasticity, the experimenter can manipulate the emotional significance of stimuli and thereby lay open the dynamic workings of the defense system to investigation with a wide range of neurobiological techniques.

In practice, fear plasticity is studied using a procedure called classical fear conditioning, in which a meaningless stimulus, such as a light or tone, is paired with a noxious event, typically electric shock to the skin. As a result of this stimulus pairing, a link is formed in the

brain between the neutral and the noxious events so that the neutral stimulus, on next appearance, will elicit evolutionarily programmed defense responses. For example, after a rat has heard a tone (the conditioned stimulus, or CS) in conjunction with footshock (the unconditioned stimulus, or US), the tone will come to elicit freezing behavior, increases in blood pressure and heart rate, secretion of stress hormones, pain suppression, potentiation of somatic reflexes, induction of cortical arousal, and other responses that are also elicited if the rat is exposed to its perennial predator, a cat (See Davis, 1992; Kapp et al., 1992; LeDoux, 1994; Fanselow, 1994). In short, fear conditioning places evolutionarily shaped ways of responding to danger under the control of new threatening stimuli. These new stimuli become warning signals that allow the organism to begin protecting itself in advance of encountering the danger itself, or even to avoid the danger altogether. Fear conditioning works pretty much the same in all animals, and, at least within the vertebrates, the neural system involved seems to be pretty much the same as well.

It is worth noting that approaching the study of the fear system through the avenue of fear learning also reveals important information about how the brain supports learning and memory. Though we describe here particular brain structures and physiological changes that are specifically involved in fear learning and defense expression, the physiological mechanisms responsible for experience-driven modification of neural function within the fear conditioning circuit appear to have substantial overlap with mechanisms in other learning and memory systems of the brain, as described below. Studies of fear conditioning may therefore be useful in identifying basic mechanisms of learning and memory as well as emotion. The fact that fear conditioning is a rapidly acquired and long lasting form of memory makes it especially attractive in this regard.

An Emotional Network

The groundwork for our understanding of the neural basis of fear learning has been laid by a systematic examination of the effect of specific brain lesions on classical fear conditioning (Davis, 1992; Kapp et al., 1992; McCabe et al., 1992; LeDoux, 1994; Fanselow, 1994). Through such studies, neural circuits have been identified, components of which are essential for various aspects of fear conditioning (Figure 1A).

The amygdala and its afferent and efferent connections constitute the major elements of the fear conditioning circuitry. The central nucleus of the amygdala is essential for the expression of autonomic, humoral, and somatic fear responses elicited by learned and unlearned threats. These responses are controlled through efferent connections from the central amygdala to brainstem nuclei.

How does a natural threat, or a learned one (a CS), elicit these responses? The circuitry leading from sensory stimulation to the mobilization of the central nucleus and consequent expression of fear responses is best understood for fear conditioning with an acoustic CS and footshock US (for summary, see LeDoux, 1994; Figure 1B).

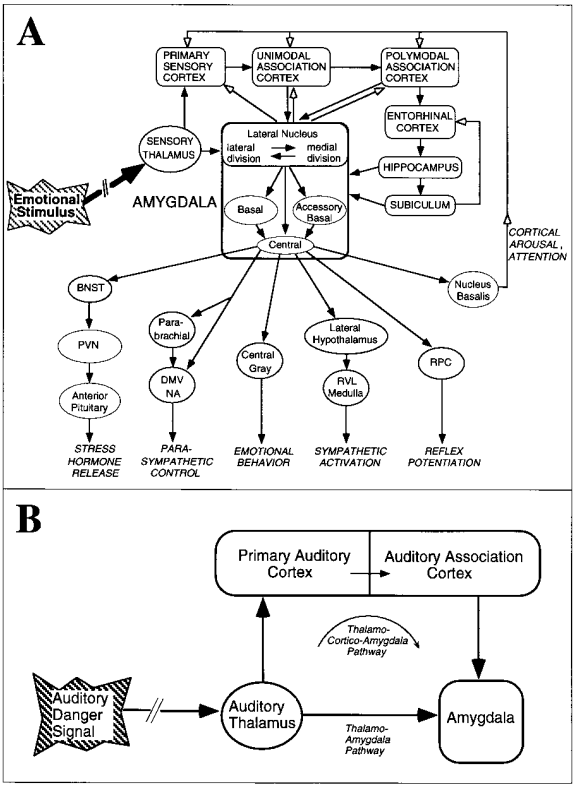

Figure 1. Schematic of a Fear Conditioning Circuit

(A) A hierarchy of incoming sensory information converges upon the lateral nucleus of the amygdala. Through intra-amygdala connections, the output of the lateral nucleus is transmitted to the central nucleus, which controls various effector systems involved in the expression of emotional responses. Forward projections are indicated by solid arrows, and feedback projections are indicated by open arrows. BNST, bed nucleus of the stria terminalis; DMV, dorsal motor nucleus of the vagus; NA, nucleus ambiguus; RPC, nucleus reticularis pontis caudalis; RVL Medulla, rostral ventrolateral nuclei of the medulla; PVH, paraventricular nucleus of the hypothalamus.

(B) Aversively conditioned auditory information is transmitted from the auditory thalamus to the lateral nucleus of the amygdala by way of two parallel pathways. The sub-cortical thalamo-amygdala pathway is monosynaptic, while the thalamo-cortico-amygdala pathway involves multiple synaptic connections.

Acoustic CS information travels through the auditory system, from cochlear receptors through the brainstem to the auditory thalamus, which then relays CS information to the amygdala by a direct monosynaptic projection, and also by an indirect pathway routed through cortical structures. Both of these pathways converge within the amygdala's sensory input structure, the lateral nucleus. It has been demonstrated that either the direct thalamo-amygdala or indirect thalamo-cortico-amygdala pathways are sufficient to support simple classical fear conditioning to a tone. Cortical input is essential, however, for conditioning to more complex acoustic events, reflecting the more finely tuned, tonotopically organized character of the thalamo-cortical projection, which allows more precise representation of the CS (McCabe et al., 1992). The direct thalamo-amygdala pathway provides faster, though less detailed, information to the amygdala. This combination of parallel CS

pathways seems well-suited for a system evolved to respond to dangerous situations where speed is of far greater importance than precise identification and evaluation of threats. It has been suggested that the faster thalamo-amygdala information may facilitate processing of CS information within the lateral amygdala and its afferent structures, both in terms of transmission speed, and perhaps also by priming neurons in these structures in preparation for the later arriving thalamo-cortical-amygdala input. Though the path of US information is less well understood, footshock and auditory information converge upon single neurons in the auditory thalamus and lateral amygdala, providing obvious opportunities for associative interactions between CS and US during conditioning.

Once auditory information enters the lateral amygdala, it is distributed throughout the amygdaloid complex through a rich network of intrinsic connections (Pitkanen et al, 1995). Unimodal auditory information enters the amygdala through the dorsal and ventral parts of the lateral division of the lateral nucleus, from which direct projections to the basal and accessory basal nuclei emanate. The lateral division also projects to the medial division, which projects to all these regions as well. The central nucleus receives projections from the medial division of the lateral nucleus, and the basal and accessory basal nuclei, and in turn, projects to the various brainstem structures which control defensive responses (Figure 1A).

So far we have described training where the occurrence of a phasic CS (tone) signals the immanence of an aversive event, and in consequence, the tone itself becomes aversive. However, more is learned during such conditioning than the predictive value of the phasic CS. The context in which training takes place—the chamber, the experimenter, and other tonically present stimuli to which the tone CS is phasically added—also acquires aversive implications when the US is delivered. This is true whether or not a phasic CS is used. Thus, when an animal is returned to a conditioning chamber in which it was shocked, the combination of sights, sounds, and smells of the experimental situation itself will reliably trigger defense responses. Recent studies have determined that contextual conditioning requires additional processing hardware: the hippocampus is also needed (Kim and Fanselow, 1992; Phillips and LeDoux, 1992). The hippocampus, with its abundance of multimodal inputs and demonstrated involvement in processing of spatial and relational information (O'Keefe, 1993; Eichenbaum et al., 1994), is well situated to provide the additional processing involved in dealing with such a highly complex stimulus as environmental context (see Figure 1A).

Another brain structure involved in fear conditioning is the ventromedial prefrontal cortex, which is implicated in extinction, the process by which a CS loses its ability to trigger defense responses after repeated presentation of the CS alone. Extinction provides a means by which experience can modify established conditioned responses to meet the exigencies of a changing environment. Lesions of the ventromedial prefrontal cortex prolong the extinction process (see LeDoux, 1995).

The circuitry described here, derived primarily from work with rodents, has found parallels in studies of fear conditioning in many other species including birds and primates (for review, see LeDoux, 1994). The presence of this system in such disparate species identifies it as an evolutionarily old, successful solution to the problem of fear learning that has been conserved through natural selection. The recent discovery of neuropathologies that involve specific damage to the amygdala has made it possible for detailed studies of the neural basis of fear conditioning to be extended to humans. As in all other species studied, damage to the amygdala has been found to interfere with fear conditioning in humans (Bechara et al., 1995; LaBar et al, 1995).

Synaptic Organization And Plasticity

The identification of brain structures and circuits involved in various aspects of fear conditioning sets the stage for more detailed investigation of the neural mechanisms driven by environmental danger. It is widely believed that learning induces changes in the transmission properties of neurons active during training episodes, and that memories are embodied in the persistence of these and/or consequent changes. A wide range of tract-tracing and electrophysiological techniques has been used to study synaptic organization and function in critical loci of the thalamic, necortical, and hippocampal input pathways to the amygdala. We will focus here on experimental findings that have direct bearing on experience-dependent plasticity in these pathways.

Studies in a number of systems have implicated excitatory glutamatergic transmission and NMDA receptor function in memory formation (see Staubli, 1995). In the thalamo-amygdala pathway, glutamate is present in presynaptic neurons and in the post synaptic terminal region (see LeDoux, 1995; Figure 2). Further, both NMDA and AMPA receptors are prevalent in the terminal areas (Farb et al., 1995), and electrophysiological evidence has confirmed the role of glutamatergic transmission in this circuit (Li et al., 1995).

Clues regarding the nature of the changes in neuronal function that occur in the course of fear conditioning have been provided by the demonstration that amygdala-petal pathways of the fear conditioning circuit are susceptible to induction of long term potentiation of synaptic efficacy (LTP). LTP refers to a heterogenous class of artificial phenomena generally characterized by a long lasting increase in electrically evoked post-synaptic potential (when measured intracellularly) or population field response (when measured extracellularly) after delivery of the induction stimulation (typically, high frequency electrical stimulation of afferents; see Bliss and Collingridge, 1993; Malenka and Nicoll, 1993). The classic form of LTP is dependent upon glutamatergic transmission, and specifically upon NMDA receptor function, and has been widely discussed as a possible element in the physiology of learning and memory. LTP has been produced in pathways to the amygdala originating in the auditory thalamus (Clugnet and LeDoux, 1990), neocortex (Chapman et al., 1990), and hippocampus (Maren and Fanselow, 1995).

As in other brain systems, NMDA receptor function is a mechanistic link between LTP and the plasticity

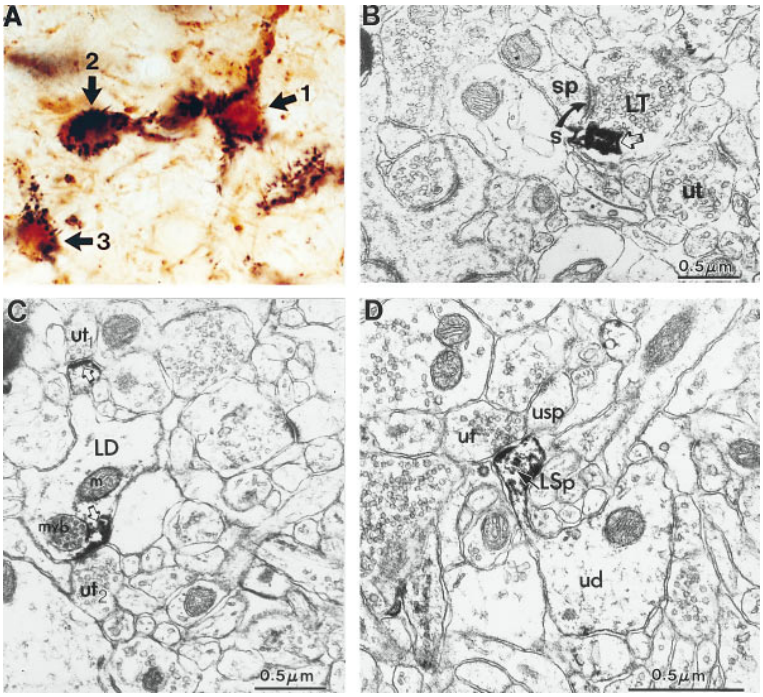

Figure 2. Glutamate in Thalamic Cells that Project to the Lateral Amygdala and Glutamate Receptors in Postsynaptic Spines in the Lateral Amygdala

(A) High-power photomicrograph of the acoustic thalamus illustrates cells dually-labeled for glutamate and the retrograde tracer WGA-HRP following injection of WGA-HRP in the lateral amygdala (arrows 1–3). Immunoreactivity for glutamate appears as the brown reaction product while the WGA-HRP histochemical reaction product appears as black crystals. Based on LeDoux and Farb (1991).

(B) An electron micrograph shows an axon terminal in the lateral amygdala that contains WGA-HRP (arrow) anterogradely transported from the acoustic thalamus. The labeled terminal (LT) forms an asymmetric synaptic contact (s, curved arrow) with a dendritic spine (sp). Asymmetric synapses are indicative of excitatory transmission. An unlabeled terminal (ut) is shown for comparison. Based on LeDoux et al. (1991).

(C) Electron micrograph showing the distribution of NMDAR1-immunoreactiviity within dendritic processes of the lateral amygdala. An axon terminal (ut_1) forms an asymmetric contact with an NMDAR1-labeled dendritic spine. Another axon terminal (ut_2) forms an asymmetric contact with an NMDAR1-labeled dendritic shaft. Open arrows indicate the presence of the NMDAR1 reaction product. Mitochondria (m) can be seen within the labeled dendrite (LD). Based on Farb et al. (1995).

(D) Electron micrograph shows an axon terminal (ut) forming an asymmetric synaptic contact on a dendritic spine immunoreative for the AMPA receptor subunit GluR2/3 (LSp). The dendritic shaft (ud) is unlabeled. An unlabeled spine (usp) is shown for comparison. Based on Farb et al. (1995).

underlying fear conditioning. Intra-amygdala blockade of NMDA receptor function during training with an acoustic CS disrupts acquisition of fear conditioning, but injections after training and before testing are ineffective in blocking the expression of conditioned fear (Miserendino et al, 1990; Kim et al., 1991; Figure 3). NMDA receptor mediated processes in the amygdala thus appear to be involved in plasticity during fear conditioning and could mediate amygdala dependent LTP (Figure 3). However, studies showing the involvement of NMDA receptors in routine synaptic transmission in the amygdala (Li et al., 1995) suggests that the plasticity results should be cautiously interpreted.

Nevertheless, evidence relating LTP with learning is primarily correlative and resoundingly inconclusive (for review, see Barnes 1995; Staubli, 1995). This is true in the hippocampus, where LTP has been most exhaustively studied, as well as the amygdala. However, the amygdala studies, especially the studies of the thalamo-amygdala pathway, have the advantage of being performed in well defined circuits that have been specifically implicated in a well characterized form of behavioral learning. As a result, LTP induction in pathways determined to be involved in fear conditioning can be viewed as a means of uncovering endogenous mechanisms that are potentially capable of supporting learning-related changes in natural information processing. Recent studies have in fact shown the processing of an auditory stimulus by the thalamo-amygdala pathway is enhanced for long periods of time by induction of LTP in the pathway (Rogan and LeDoux, 1995; Figure 4). This kind of mechanism, and its placement in a pathway known to be involved in learning, conforms to several theoretical expectations of the kind of mechanisms needed for induction of plasticity after brief episodes of tone-shock pairing. Whether these mechanisms are in fact activated during fear conditioning is not known. Such a demonstration would help to close the gap between LTP and natural learning.

Learning-induced alterations in single unit activity have been observed throughout the fear conditioning circuit, including the auditory thalamus and cortex (Weinberger, 1995), and various amygdala subnuclei (For review, see Quirk et al., 1995). Neurons in each of these structures not only exhibit increased firing rates to the CS after conditioning, but also show receptive field plasticity (see Figure 5). That is, the frequency preferences of cells can be shifted towards the CS at the expense of the previously preferred frequencies. Conditioned re-tuning of receptive fields is a powerful and underutilized approach to studies of learning induced plasticity (Weinberger, 1995).

A recent study involving measurement of single unit activity from multiple cells simultaneously in the lateral amygdala has revealed that conditioning of unit activity is characterized by an increase in the firing rate of the shortest latency responses, an effect that points to the primacy of the short latency thalamo-amygdala pathway in fear conditioning (Quirk et al, 1995). The time course of this effect parallels behavioral indices of conditioning, with respect to both speed of acquisition and extinction. These changes are only characteristic of the dorsal part

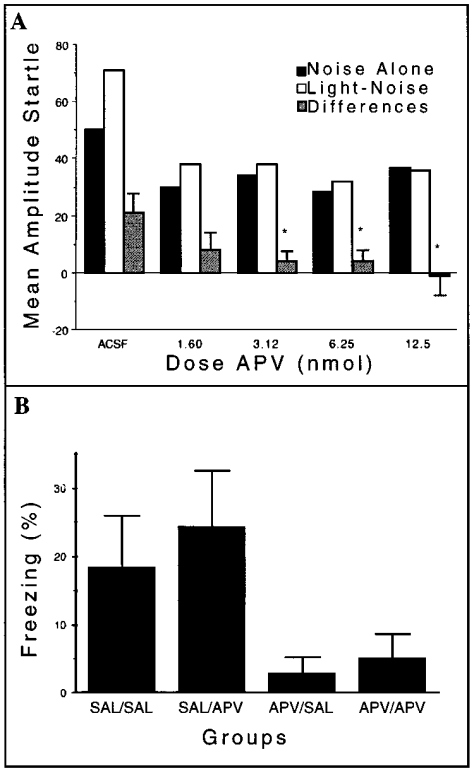

Figure 3. Disruption of NMDA Receptor Function in the Amygdala Blocks Fear Conditioning

(A) Rats were classically conditioned to fear a visual cue (light). One week later, their startle response to a loud noise was measured in the presence or absence of the light. Fear potentiated startle was reduced by intra-amygdala administration of the NMDA receptor antagonist APV during fear conditioning, in comparison to animals receiving infusion of artificial cerebral spinal fluid (ACFS). Adapted from Davis (1992).

(B) Rats received either saline (SAL) or APV through intra-ventricular cannulae immediately before conditioning and immediately before testing. Rats receiving APV before training displayed less freezing behavior during testing. Pre-testing infusion of APV did not alter performance during testing. Adapted from Kim et al. (1991).

of the lateral nucleus, which receives auditory inputs from the thalamus. Conditioning also leads to acquisition of increased functional coupling of spontaneous action potentials between cells. In some cells, this conditioned coupling is not reversed with extinction. These conditioned cell assemblies may reflect the long term memory of fear conditioning. The post-extinction persistence of conditioned functional coupling in the lateral amygdala (or between cells in the lateral amygdala and other regions) may reflect a substrate for the phenomenon of fear recovery, whereby fully extinguished conditioned responses can reappear at full strength after certain types of stressful stimulation—a phenomenon that occurs in human phobias and may explain the indelibility of emotional memory.

A simple neural network model incorporating essential elements of the fear conditioning circuitry has been constructed (Armony et al., 1995; Figure 6). The model is anatomically constrained, and incorporates empirical measurement of auditory response properties of cells in the thalamo-amygdala and thalamo-cortico-amygdala pathways. This model permits rigorous examination of the information processing capabilities and behavioral output of this circuit, and has proved to capture the main features of conditioning-induced receptive field retuning (see Figure 5A) as well as CS frequency-specific behavioral changes.

Beyond Fear

Much progress has been made in understanding the neural basis of fear and fear learning. This progress is not only important for our understanding of emotion as a normal function of the brain, but can also be expected to contribute fundamentally to a more detailed understanding of the etiology of a wide range of psychopathologies. Several lines of evidence suggest that many of the most common psychiatric disorders involve, in varying degrees, the fear system of the brain. Included are phobias, panic attacks, posttraumatic stress syndrome, obsessive-compulsive disorder, and generalized or free-floating anxiety. Clearly, if studies of fear only contributed to our understanding of the fear system, our

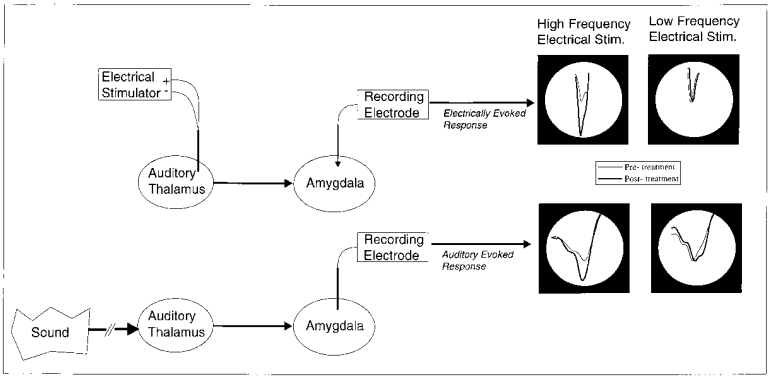

Figure 4. Induction of LTP in the Thalamo-Amygdala Pathway Enhances Auditory Responses in the Lateral Nucleus of the Amygdala

Field potentials were evoked by auditory stimulation of the lateral amygdala and by electrical stimulation of the medial division of the medial geniculate nucleus and posterior intralaminar nucleus (MGm/PIN), which contain the cells of origin of the direct thalamo-amygdala projection. High frequency electrical stimulation of the MGm/PIN resulted in long-term potentiation of electrically-evoked responses (top), and also produced long lasting enhancement of auditory-evoked responses (bottom). Low frequency electrical stimulation did not alter processing of auditory or electrical stimuli in this pathway. Field potentials were quantified by slope and amplitude measurements.

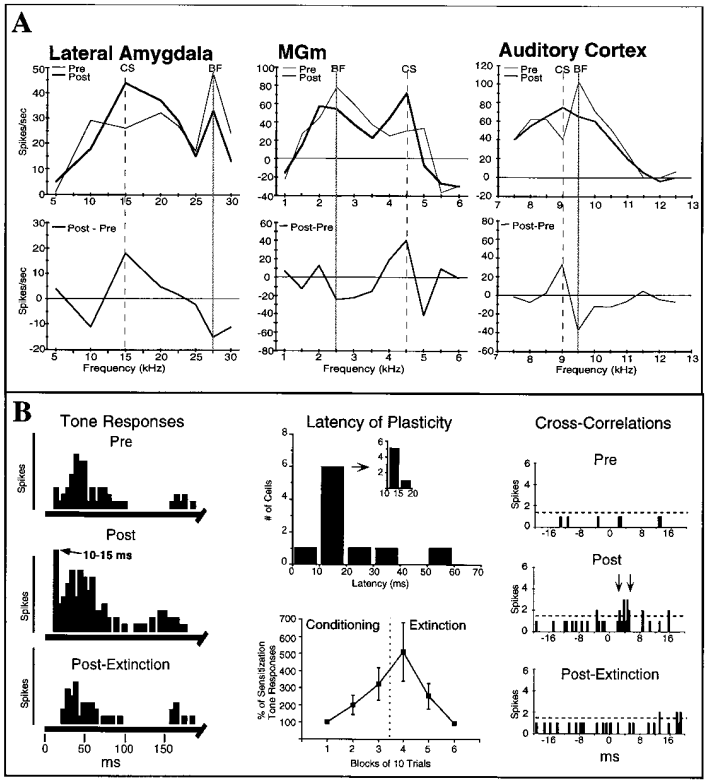

Figure 5. Conditioned Unit Activity in the Fear Conditioning Circuit

(A) Retuning of auditory receptive field (RF) properties of single neurons in the lateral amygdala, medial division of the medial geniculate nucleus (MGm), and auditory cortex after fear conditioning. Before conditioning with an acoustic CS, the neuron's auditory receptive field (Pre), and best frequency (BF) was determined. Fear conditioning with a CS of a frequency different than the neuron's BF was then performed. In each case pictured here, the post-training receptive field (Post) shifted towards the CS frequency. The bottom half of each figure depicts the Post-Pre difference plots, showing relative decreases in firing to the pretraining-BF, and increased firing to the CS frequency after training. Right panel adapted from Bakin and Weinberger (1990); center panel adapted from Edeline and Weinberger (1992); left panel adapted from Armony et al. (1995).

(B) The left panel is a post-stimulus time histogram showing the tone response of a lateral amygdala neuron at three points during training: sensitization (pre), early extinction (post), and following 30 extinction trials (post-ext). The horizontal bar indicates the start of a 5 kHz tone. Bin width is 5 ms. Note the increase in early responses (less than 15 ms) following training. The center panel histogram shows the latency of the earliest significant conditioned response for 10 neurons in the lateral amygdala. Note the preponderance of conditioned responses prior to 15 ms following tone onset. Below, a learning curve showing the change in tone responses for 16 LA neurons that significantly conditioned. Tone responses (first 70 ms of tone) at different points in training are expressed as a percentage of sensitization responses. The right pane shows cross-correlations between the spike trains of two simultaneously recorded lateral amygdala neurons at different points during training, during spontaneous activity. Training induced a significant peak at 3 ms suggesting a change in the efficacy of intra-amygdala synaptic connections. Adapted from Quirk et al., (1995).

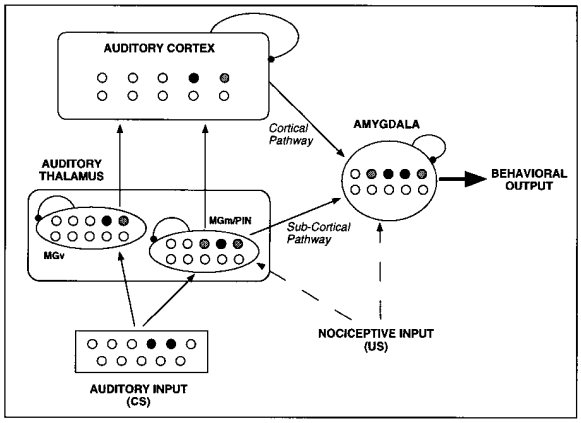

Figure 6. Diagram of the Network Used to Run Simulations of Fear Conditioning

Each module of self-inhibitory, nonlinear units represents a relevant structure in the fear conditioning circuit. A typical pattern of activation is schematized by representing unit activity with gray shadings (solid bullet, maximum activation; open bullet, zero activation). Connections between modules are feedforward and excitatory, and are a simplification of the corresponding pathways in the actual rat brain. The strengths of these connections are adjusted during learning through an extended Hebbian rule. Dashed arrows indicate excitatory, nonmodifiable connections. The model captures the main features of conditioning-induced receptive field retuning (see Figure 5A) as well as CS frequency-specific behavioral changes. Adapted from Armony et al. (1995).

efforts would be well spent. There is reason to believe, however, that some of these findings will have application to other emotions as well. For example, studies of many emotional processes seem to lead to the amygdala, including those that fall in the category of positive as well as negative affect (see Aggleton, 1992). At present, these emotions are far less well understood than fear, but the basic information about amygdala anatomy and physiology derived from the study of fear should contribute to the study of these other amygdala-based emotional systems.

Explorations of fear have laid a foundation for pursuing the neural basis of emotion, breaking through some of the mystery of this most celebratedly mysterious aspect of the mental terrain. As we noted at the beginning of this review, emotion research has waxed and waned in neuroscience over the decades. It may well be that this cyclical pattern has ended—the advances made in this most recent, and most vigorous, period of emotion research have solidly grounded this field. Emotion is now, and is likely to continue to be, a thriving area of research in neuroscience.

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