Emotional memory and psychopathology

JOSEPH E. LEDOUX[1] AND JEFF MULLER[1,2]

[1]*Center for Neural Science, Department of Psychology, New York University, 6 Washington Place, New York, NY 10003, USA* (ledoux@cns.nyu.edu)
[2]*Clinical Psychology Program, City College, City University of New York, New York, NY, USA*

SUMMARY

A leading model for studying how the brain forms memories about unpleasant experiences is fear conditioning. A cumulative body of work has identified major components of the neural system mediating this form of learning. The pathways involve transmission of sensory information from processing areas in the thalamus and cortex to the amygdala. The amygdala's lateral nucleus receives and integrates the sensory inputs from the thalamic and cortical areas, and the central nucleus provides the interface with motor systems controlling specific fear responses in various modalities (behavioural, autonomic, endocrine). Internal connections within the amygdala allow the lateral and central nuclei to communicate. Recent studies have begun to identify some sites of plasticity in the circuitry and the cellular mechanisms involved in fear conditioning. Through studies of fear conditioning, our understanding of emotional memory is being taken to the level of cells and synapses in the brain. Advances in understanding emotional memory hold out the possibility that emotional disorders may be better defined and treatment improved.

1. INTRODUCTION

Excessive or debilitating fear and anxiety are prominent symptoms in many mental health problems. Causes of so-called anxiety disorders are poorly understood and debated. Studies of the neural basis of fear and anxiety in experimental animals may shed light on the normal processes underlying these functions and may also illuminate how pathological fear and anxiety develop and why particular anxiety phenomena, such as phobias, arise.

Classical fear conditioning has been used extensively as a means of exploring the brain mechanisms underlying fear (see LeDoux 1994; Davis 1992; Kapp *et al*. 1992; Fanselow 1994). This work has led to a delineation of the brain pathways and neural mechanisms involved in the acquisition and storage of information about real and potential dangers. With this knowledge we can begin to form hypotheses about the mechanisms that might be altered in anxiety disorders.

2. CLASSIC FEAR CONDITIONING

In fear conditioning, an innocuous stimulus, usually a light or tone, is paired with an aversive stimulus, such as an electrical shock to the feet. After conditioning, the tone or light, when presented alone, will elicit an aversive emotion reaction. The innocuous stimulus is called the conditioned stimulus or CS and the aversive stimulus the unconditioned stimulus or US.

The responses elicited by the CS are similar to those that occur in the presence of natural threats, such as the sight or sound of a predator. For example, freezing is an example of an innate response to danger seen in many species (Blanchard & Blanchard 1969; Bolles & Fanselow 1980). Rats freeze when they encounter a cat (Blanchard & Blanchard 1969). Even laboratory-reared rats that have never seen a cat, freeze when they see one for the first time. Freezing also occurs when a rat is exposed to a tone that was previously paired with a shock.

A number of responses occur together in fear (see figure 1). In addition to freezing, autonomic arousal occurs (LeDoux *et al*. 1984; Schneiderman *et al*. 1974; Smith *et al*. 1980; Cohen & Randall 1984), corticosteroid plasma levels increase (Mason 1968; van der Kar *et al*. 1991), sensitivity to pain decreases (Watkins & Mayer 1982; Helmstetter 1992), startle to unexpected, high intensity stimuli increases (Davis *et al*. 1987; Weisz *et al*. 1992) and ongoing instrumental behaviour ceases (Estes & Skinner 1941; Brady & Hunt 1951; Bouton & Bolles 1980; Smith *et al*. 1980). Other phenomena associated with fear may also occur, including piloerection, defaecation and urination, and vocalization. These various responses are highly correlated with each other.

3. CONTRIBUTION OF THE AMYGDALA AND ITS CONNECTIONS

Experiments from the late 1960s by Cohen (summarized in Cohen 1974) suggested that the amygdala was necessary for fear conditioning. Over the intervening years, much has been learned about the contribution of the amygdala, about its various nuclei and internal connections, and about its input and output pathways (see figure 2).

The central nucleus of the amygdala (Ce) is a key structure in the control of a variety of conditioned fear responses. Thus, lesions of the Ce interfere with

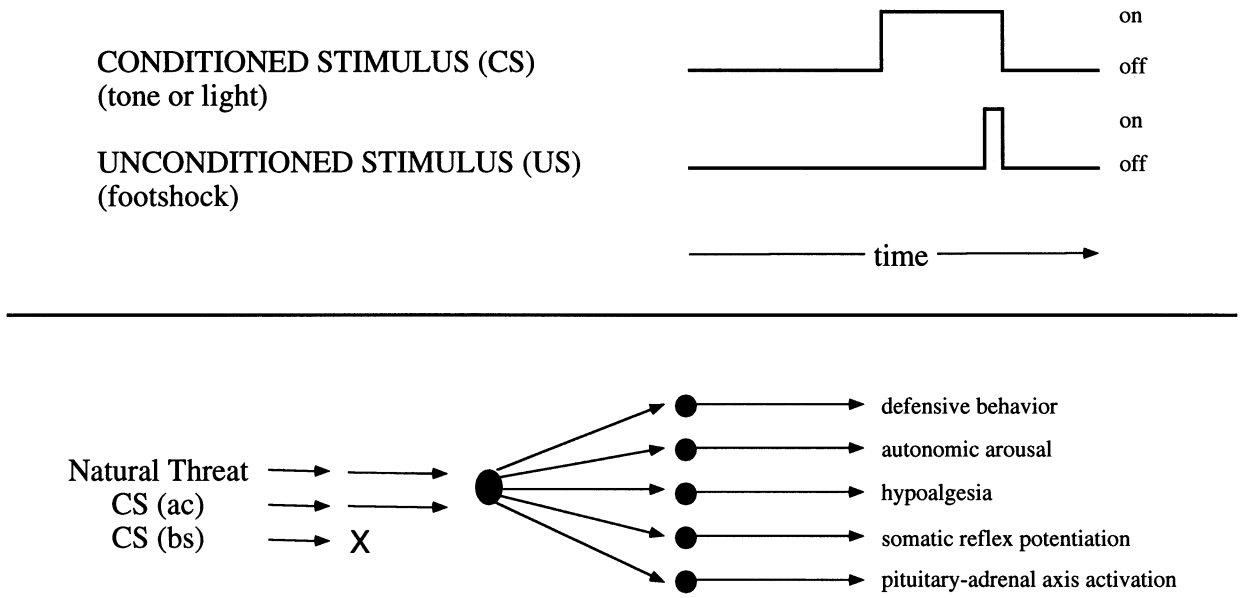


Figure 1. In fear conditioning an innocuous stimulus (the conditioned stimulus, or CS), is paired with an aversive stimulus (the unconditioned stimulus or US). Before conditioning (bc), CS presentation does not cause a fear response. After conditioning (ac), the CS elicits responses that are innate components of fear.

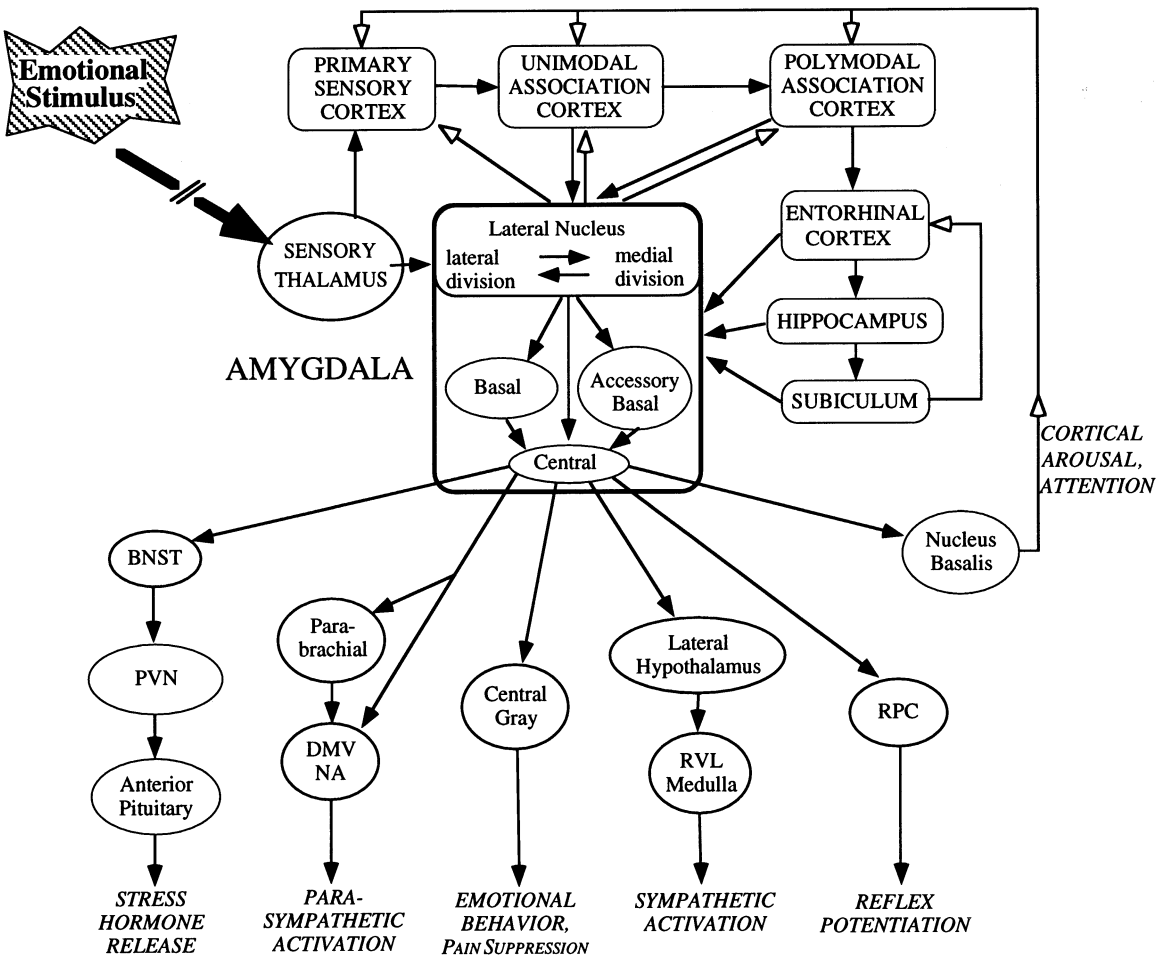


Figure 2. Fear conditioning pathways. Afferents converge on the lateral nucleus of the amygdala. The lateral nucleus projects to the basal and accessory basal nuclei which in turn project to the central nucleus, which influences various effector systems involved in the expression of emotional responses. 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; RV Medulla: rostral ventrolateral nuclei of the medulla; PVH: paraventricular nucleus of the hypothalamus.

behavioural (freezing) reactions, autonomic (sympathetic and parasympathetic) responses, stress hormone (ACTH and glucocorticoid) release, potentiation of somatic reflexes (startle and eyeblink) and changes in pain reactivity elicited by a CS (see Davis 1992; Kapp *et al.* 1992; LeDoux 1995; Fanselow 1994). Each of these responses is controlled by a separate set of output connections of Ce.

The lateral nucleus (LA) is the sensory input region of the amygdala, as has been shown by anatomical, behavioural and physiological studies (see LeDoux *et al.* 1990*a*,*b*; Bordi & LeDoux 1992; Romanski & LeDoux 1992; Campeau & Davis 1995). At least two paths from sensory areas of the thalamus to the amygdala have been identified: one direct and one by way of the sensory cortex, which in turn projects to LA. In addition, the sensory areas of the cortex projects to the perirhinal cortex, which projects to LA.

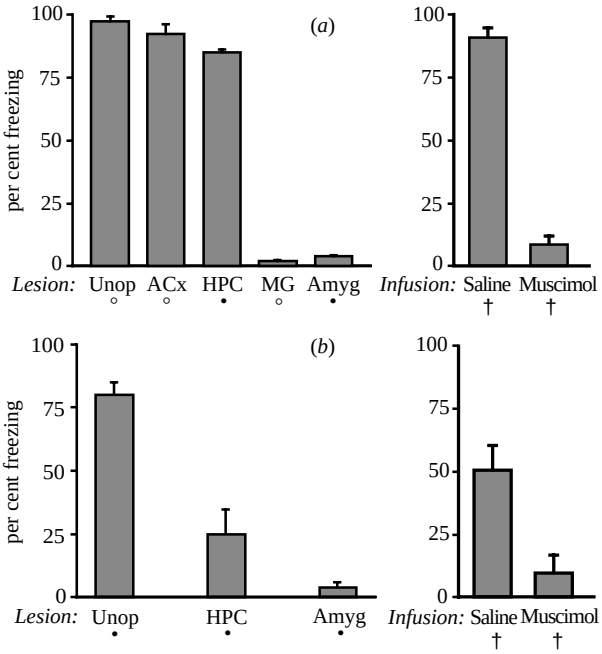
Much of our understanding of the sensory pathways involved in conditioning has involved paradigms in which an auditory CS is used. Lesion experiments coupled with anatomical tract tracing studies have established brain regions necessary for fear conditioning (see figure 3). For simple classical conditioning (one stimulus paired with shock), lesions of the auditory cortex do not interfere with conditioning, but lesions of the auditory thalamus (the medial geniculate body, MG) or auditory midbrain (the inferior colliculus) do (LeDoux *et al.* 1984). These data suggest that the acoustic CS is transmitted through the auditory system to the MG and from there to some region in addition to the auditory cortex. Antereograde labelling studies demonstrate that the MG and adjacent nuclei receiving auditory input, in addition to projecting to the auditory cortex, also sends efferents to LA (LeDoux *et al.* 1984, 1990*b*). Conditioning of fear reactions to simple acoustic stimuli can be mediated by direct projections to LA from the thalamus, and lesions of LA block fear conditioning.

Although the auditory cortex need not be intact for simple fear conditioning to occur, neural activity is modified in the auditory cortex during such conditioning (Weinberger 1995). Further, auditory cortex lesions do disrupt fear conditioning when the direct connections from the MG to the amygdala have been destroyed (Romanski & LeDoux 1993). Although not necessary, cortico-amygdala projections are certainly sufficient in mediating simple fear conditioning.

Physiological evidence from the auditory thalamus suggests possible differences in the function of two pathways. Direct projections from the auditory thalamus originate in the medial regions of the auditory thalamus (called the medial subdivision of the medial geniculate or MGm and the posterior intralaminar nucleus or PIN), where cells tend to be broadly tuned to respond to a relatively large range of auditory frequencies, rather than in the ventral MG (MGv), which has cells with narrow tuning (and thus with a greater capacity to precisely represent auditory events) (Bordi & LeDoux 1994*a*,*b*).

The suggestion that there are distinct functions arising from differences in the frequency tuning within the two pathways is consistent with some behavioural data. Discrimination learning (one tone, the CS+, paired with shock, and the other CS−, not), is interfered with by post-training auditory cortex damage (Jarrell *et al.* 1987). With such lesions, both the CS+ and CS− elicit fear responses, whereas non-lesioned animals learn to respond only to the CS+. Certainly, a possible explanation is that when the auditory cortex is lesioned, behavioural performance depends on the broadly tuned medial MG cells. As a result, the animal tends to overgeneralize the fear reaction, responding to stimuli other than the CS+. However, another study found that pre-training lesions of the auditory cortex did not alter stimulus generalization responses, which were tested after single frequency tone CS–US pairings (Armony *et al.* 1997). Thus, the further elucidation of the functions of the two pathways remains an important area of future research.

The indirect pathway from the thalamus to the cortex to the amygdala introduces additional synapses, and thus the cortical path would be expected to be a slower route. The direct pathway permits rapid but imprecise processing of danger; the cortical pathway allows precise but slower processing. The direct thalamic path to the



Sources: ° Romanski & LeDoux, 1992 • Phillips & LeDoux, 1992 † Muller et al., 1997

Figure 3. Effect of fear conditioning (tone–shock pairing) in rats. Observations were made following CS presentation without the US. Freezing, the cessation of all non-respiratory movement, was used as a measure of fear. Data is summarized from previous work as indicated. (*a*) Effects on conditioning to a tone. *Left panel*: effects of pre-training electrolytic lesions. Only auditory thalamus and amygdala lesions disrupted fear conditioning to the tone. *Right panel*: pre-training inactivation of the basolateral amygdala by muscimol, a GABAa agonist, disrupted fear conditioning. (*b*) Effects on conditioning to the context. *Left panel*: hippocampal and amygdaloid lesions disrupted context conditioning. *Right panel*: pre-training inactivation of the basolateral amygdala by muscimol disrupted context conditioning. Abbreviations: Unop, unoperated controls; ACx, auditory cortex; HPC, dorsal hippocampal formation; MG, medial geniculate; Amyg, amygdala complex.

amygdala may be advantageous in situations where rapid responses to potential dangers are important.

Whether the amygdala has a role in the acquisition, in contrast to the expression, of fear learning is difficult to assess using permanent lesions. Temporary disruption of the amygdala's functioning can address the acquisition question. Infusions before training into the lateral and basal nuclei of the amygdala of a glutamate antagonist specific for the NMDA receptor disrupt acquisition but not expression of previous learning (Miserendino *et al*. 1990; Fanselow & Kim 1994). Similarly, inactivation of the lateral and basal nuclei with a GABAa agonist disrupts acquisition without abolishing later acquisition, after the amygdala's function has recovered (Muller *et al*. 1997). (See figure 3.)

Integration of the signals from the direct and cortical pathways could take place in LA. The cortico-amygdala and thalamo-amygdala projections converge onto the same region within LA (LeDoux *et al*. 1991*a*) and even on to the same neurons (Li & LeDoux 1996), suggesting that the monosynaptic arrival of inputs in the amygdala from the acoustic thalamus might influence the processing of inputs arriving later over multisynaptic cortico-amygdala pathways (LeDoux 1992).

As inputs come into the amygdala by way of LA and outputs leave by way of Ce, there must be communication between these regions. Indeed, LA projects to Ce both directly and by way of the basal (basolateral) and accessory basal (basomedial) nuclei (Price *et al*. 1987; Pitkänen *et al*. 1995; Savander *et al*. 1996). At this point, the contribution of specific intraamygdala pathways is not understood.

In addition to developing fear reactions to the specific stimulus paired with the shock, animals also learn to fear the various stimuli that just happen to be present. This is readily demonstrated by placing a rat back in a chamber in which it previously received tone-shock pairings. The rat will often begin to freeze when placed in the chamber, suggesting that it has been conditioned to the apparatus where the tone and shock were paired, as well as to the tone itself. Lesions of the hippocampus have no effect on simple or discrimination fear conditioning, but disrupt contextual conditioning (Phillips & LeDoux 1992; Kim & Fanselow 1992; Selden *et al*. 1991). This is consistent with the long-held belief that the hippocampus plays an important role in situations in which the interrelation of various stimuli is important (O'Keefe & Nadel 1978; Nadel & Willner 1980; Eichenbaum *et al*. 1992; Sutherland & Rudy 1989). Damage to the amygdala abolishes conditioning to both a discrete CS and to contextual stimuli, and projections from the hippocampus to the amygdala may be involved.

These observations of neural connectivity, electrophysiological activity of neurons and behavioural effects of lesions provide a description, from sensory to motor neurons, of the structures and pathways underlying auditory fear conditioning. The circuitry involves transmission of inputs through the early stages of the auditory system to the acoustic thalamus. Projections from the auditory thalamus to LA directly or by way of auditory cortex transmits CS information to the amygdala in simple conditioning, but projections through cortex are required for differential conditioning. Projections to LA and possibly other amygdala regions from the hippocampus may be involved in contextual conditioning. LA projects to Ce, both directly and by way of intra-amygdala connections. Efferent to Ce, the pathway diverges, with different projections mediating different responses. These findings contribute to a circuit description of specific brain nuclei and pathways, complete with input, output and integrative processing sites. However, other brain areas certainly also contribute, possibly modulating activity in these pathways. Obvious examples include the various chemically specific brainstem pathways that project diffusely to the amygdala and the rest of the forebrain.

4. CELLULAR AND SYNAPTIC MECHANISMS OF FEAR CONDITIONING

One model of the synaptic changes underlying learning is long-term potentiation (LTP), in which a post-synaptic response to a given pre-synaptic input is enhanced after a train of high frequency stimuli. LTP can be induced in LA by stimulation in the auditory thalamus (Clugnet & LeDoux 1990; Rogan & LeDoux 1995) or by stimulation of cortical projections to LA (Chapman *et al*. 1990). LTP has also been demonstrated in the amygdala by stimulation of projections from the hippocampal formation (Maren & Fanselow 1995). In addition, the evoked responses recorded in LA from an auditory tone are enhanced after LTP induction by the same method of MG stimulation (Rogan & LeDoux 1995). Presumably the auditory stimulus is transmitted through a subset of the fibres that were potentiated. Natural information processing is thus affected by LTP (see figure 4). If something like LTP occurs naturally during learning, clearly the brain can make use of it to respond more effectively to external events.

Findings from the classic model systems (especially the hippocampal formation) in which LTP is studied, have implicated the neurotransmitter glutamate and two of the major classes of glutamate receptors, NMDA and AMPA, in LTP induction and maintenance (Madison *et al*. 1991; Malenka & Nicoll 1993; Bliss & Collingridge 1993; Cotman *et al*. 1988). Blockade of NMDA receptors in the amygdala prevents fear conditioning (Miserendino *et al*. 1990; Fanselow & Kim 1994), suggesting that an NMDA-dependent form of synaptic plasticity in the amygdala might contribute to fear conditioning. Although NMDA receptors have not yet been implicated in LTP in the sensory input pathways to LA, studies of the anatomy and physiology of synaptic transmission in the input pathways to LA provide the foundation for understanding the role of NMDA receptors in synaptic plasticity in this region in both LTP and natural learning (fear conditioning).

As glutamate and its receptors are suspected to be responsible for both LTP and natural fear conditioning, it is important to demonstrate that synapses involved in fear conditioning are glutamatergic. This has been shown in the pathway from the medial geniculate body to the amygdala, a pathway that exhibits LTP. The cells of origin of this pathway in the thalamus, as determined by retrograde transport from LA, can also

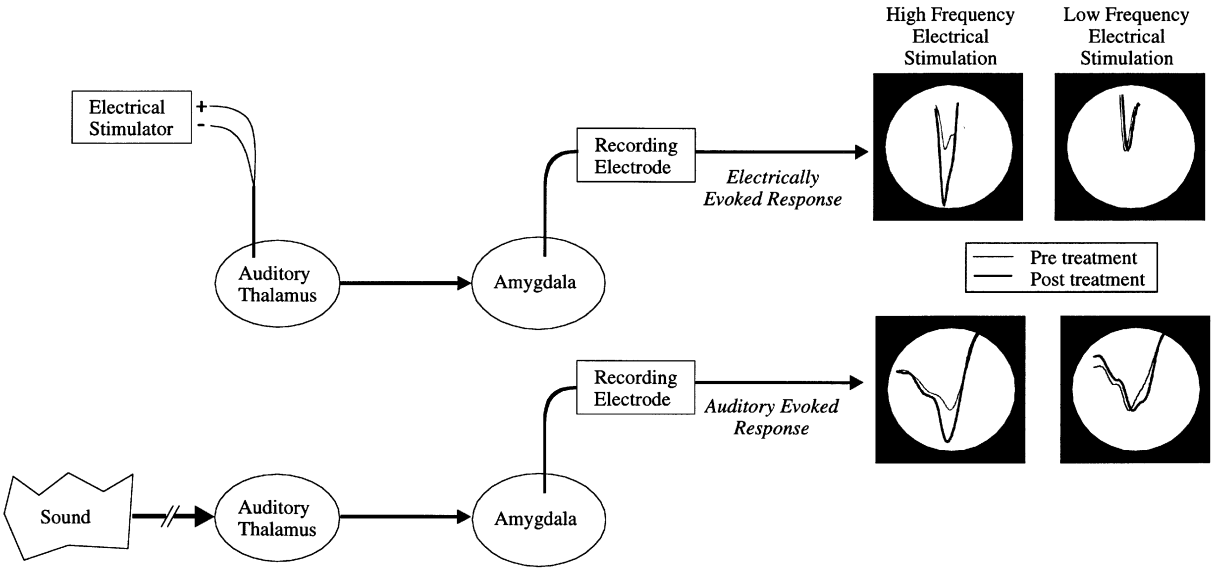


Figure 4. LTP induction increases auditory responses in the lateral nucleus of the amygdala. Field potentials were evoked in the lateral amygdala by electrical stimulation of the MGm and PIN, and by tone presentation. High frequency electrical stimulation in the MGm and PIN resulted in long lasting enhancement of auditory-evoked responses (top), and also produced long lasting enhancement of auditory-evoked responses (bottom). Low frequency electrical stimulation did not change responses to auditory or electrical stimuli.

be labelled by a glutamate marker (LeDoux & Farb 1991). In addition, these thalamo-amygdala projections mainly form asymmetric synapses (which indicates excitatory transmission) on dendritic spines in LA (LeDoux *et al*. 1991*b*). Many terminals in LA that originate in the auditory thalamus contact spines that are immunoreactive for NMDA and AMPA receptors (Farb & LeDoux 1994; Farb *et al*. 1995). Finally, physiological studies have shown that blockade of either NMDA or AMPA receptors interferes with transmission through this pathway (Li *et al*. 1995), suggesting that information flow in this pathway depends on both types of receptors (Li *et al*. 1995). This differs somewhat from the classic picture of NMDA receptors that has emerged from studies of hippocampal circuits, where NMDA receptors have been shown to be crucial for synaptic plasticity but not for routine synaptic transmission (e.g. Bliss & Collingridge 1993). In contrast to the thalamo-amygdala pathway, and like hippocampal circuits, transmission from the auditory cortex to LA is interfered with by AMPA but not NMDA blockade (Li & LeDoux 1996). Glutamate and its receptors thus play somewhat different roles in the transmission of auditory signals to LA from thalamic versus cortical areas.

Other single unit recording studies have shown that neurons in several amygdala regions undergo changes in physiological responsivity during fear conditioning (see Quirk *et al*. 1995; Uwano *et al*. 1995; Kapp *et al*. 1992). Although it is important to understand the changes occurring in these and other (Weinberger 1995) areas, efforts have focused on LA and its sensory inputs, as LA is the first nucleus where processing occurs within the amygdala for auditory stimuli. Recent studies have shown cells in LA increased their responses to a tone after the tone had been paired with a shock (Quirk *et al*. 1995). This is a demonstration that physiological response properties of cells in LA are modified by conditioning. Interestingly, the greatest change in responsivity was in the shortest latency responses (10–15 ms after tone onset). These short latency changes are consistent with direct transmission from the auditory thalamus, suggesting that the thalamo-amygdala pathway is potentiated to a greater extent than the cortico-amygdala pathway. Using a statistical technique to test the correlation between the firing of pairs of cells at various temporal intervals, putative functional coupling was also examined. Increased correlation in the firing of LA cells during the time when no tone was present (spontaneous firing) was found. Thus, LA cells express their learning experiences by responding as quickly as possible and by firing more synchronously than they did before training (see figure 5).

These studies thus begin to characterize the morphological and physiological bases of neurotransmission in the sensory input pathways to the amygdala. Such information provides initial clues to the local circuit organization of the projection and suggests hypotheses for additional physiological and behavioural studies aimed at uncovering the cellular foundations of emotional learning.

5. IMPLICATIONS FOR PSYCHOPATHOLOGY

Although our understanding of the detailed organization of the neural systems mediating fear conditioning has been achieved through research on experimental animals, recent studies suggest that similar systems are involved in human fear conditioning (LaBar 1995; Bechara *et al*. 1995). How can this information help us understand psychopathological fear in humans?

The classic approaches to the conceptualization and treatment of anxiety disorders are derived from Freud's psychoanalytic theory and Watson's behavioural theory of anxiety (Freud 1915; Watson & Rayner 1920; Dollard & Miller 1950). Though vastly different in

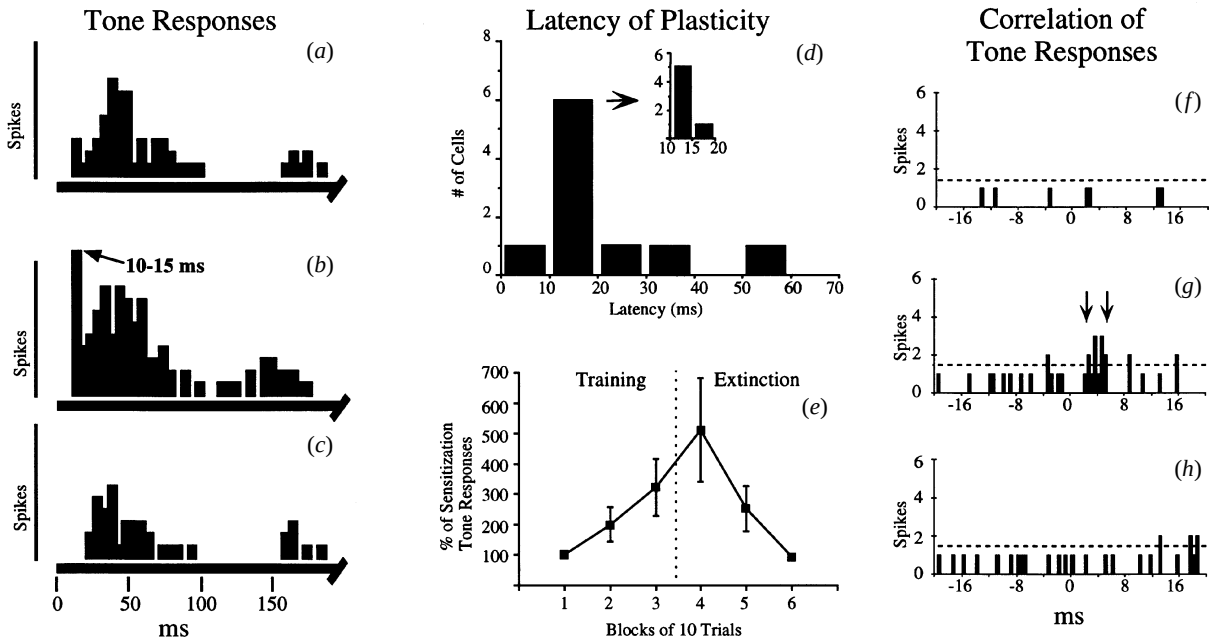


Figure 5. Unit Recordings. Left: time histogram of a lateral amygdala neuron's action potentials during presentation of a tone at three points during training: before pairing with footshock (*a*), early extinction (*b*), and following 30 extinction trials (*c*). The horizontal bar indicates the start of a 5 kHz tone. Bin width is 5 ms. Note the increased number of early responses (<15 ms) in the 'test' observation. Centre: (*d*) 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. (*e*) Line graph (bottom) shows the change in tone responses for 16 neurons in the lateral nucleus that significantly conditioned. Tone responses (from the first 70 ms of the tone) at different points in training are expressed as a percentage of sensitization responses. Right: cross-correlation between the spike trains of 2 simultaneously recorded lateral amygdala neurons at different points during training. (*f*) Pre-pairing with footshock; (*g*) early extinction; (*h*) following 30 extinction trials). Data taken during spontaneous activity (in the absence of the tone). The time of one neuron's firing is defined as 0; the time of the other's firing is shown in relation to time 0. Training induced a significant peak at +3 ms.

many ways, both approaches posit an acquired source of anxiety. During an aversive experience, associations are formed between painful stimuli and other information being processed at the time. Trauma is understood as an intense aversive experience. Traumatic learning, and the memories formed as a result of such experiences, as we have seen, involve the processing of external signals by the amygdala. The basic mechanisms of traumatic learning are revealed by studying how emotional memories are formed in rats during fear conditioning.

However, it has often been said that fear conditioning is inadequate as an explanation of how anxiety disorders are learned (e.g. Seligman 1969). In particular, it seems that human anxiety disorders are more resistant to extinction than laboratory conditioned fears. While the classical conditioned fear responses of animal models can be extinguished rather straightforwardly, the anxiety of human pscyhopathologies, including phobias, obsessive–compulsive disorders, and depression, is much more difficult to treat. A discrete episode of fear conditioning in an adult animal may be a poor model of much of the suffering with which humans cope. It appears that in humans, the accumulation of repeated, small injuries, most importantly early in life, in interactions with care-givers, is a tremendously important factor in moderate levels of psychopathology and may predispose an individual to be more susceptible to developing the symptoms associated with classic single episode traumas.

One candidate brain region where information about past experience can be brought together with current perceptions to make decisions based on emotional input is the medial prefrontal cortex. This area of the brain projects to the amygdala and to various amygdala target areas in the brainstem and may be involved in the modulation of processing within the amygdala and the control of responses by the amygdala. In the famous case of Phineas Gage (Damasio *et al.* 1994) damage to this area resulted in debilitating social and emotional deficits. In one animal experiment, conditioned fear reactions in rats can be made highly resistant to extinction when the medial prefrontal cortex is damaged (Morgan *et al.* 1993). It is thus possible that medial prefrontal cortex activity plays a role in pathological fear. In particular, it is possible that early alterations in the medial prefrontal cortex predispose some humans to develop pathological fear and anxiety under conditions that leave less enduring emotional scars on others.

Conscious recall of some past experience requires that the temporal lobe memory system be intact (Squire *et al.* 1993). This system involves the hippocampus and related cortical areas. When this system is damaged, new conscious memories cannot be formed, but other kinds of learning that do not involve conscious recollection, so-called implicit forms of learning, are undisturbed. Fear conditioning is an implicit form of learning. It can take place in the absence of the hippocampal memory system. Normally, in a traumatic situation, we form both implicit and explicit memories through these two

systems. However, if for some reason the hippocampus is not fully functional, it is possible to form unconscious emotional memories without any conscious content. Memory formed from trauma early in life may be an example of implicit-only memory. The absence of explicit memories from infancy may be explained by insufficient development of the hippocampal system. There is evidence that the hippocampus develops somewhat later than the amygdala (Jacobs & Nadel 1985). So, it is conceivable that early trauma might result in the formation of emotional memories for situations that are not consciously recalled. In addition, it is known that intense stress can alter the normal functions of the hippocampus. (Diamond & Rose 1994; McEwen & Sapolsky 1995.) As a result, it is possible that even adults with an otherwise intact hippocampus could fail to form conscious memories of a trauma, while at the same time forming unconscious emotional memories. It is important to point out that these unconscious emotional memories formed by the amygdala and related brain areas can never be converted into conscious memories. Conscious memories depend on the hippocampal memory system. If this system does not form a conscious memory of some situation it is not possible to later retrieve a conscious memory.

In conclusion, it is clear that studies of fear conditioning have begun to make important contributions to our understanding of how emotional memories are learned and stored in the brain. However, much work remains. For example, human thoughts are intimately interrelated with emotional activity. Now that a model system for rapid, implicit emotional evaluation and learning has been identified, it will be possible to turn to studies of the interaction of this system with other systems of the brain responsible for cognitive processing and conscious experience.

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