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Emotional memory systems in the brain

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The neural mechanisms of emotion and memory have long been thought to reside side by side, if not in overlapping structures, of the limbic system. However, the limbic system concept is no longer acceptable as an account of the neural basis of memory or emotion and is being replaced with specific circuit accounts of specific emotional and memory processes. Emotional memory, a special category of memory involving the implicit (probably unconscious) learning and storage of information about the emotional significance of events, is modeled in rodent experiments using aversive classical conditioning techniques. The neural system underlying emotional memory critically involves the amygdala and structures with which it is connected. Afferent inputs from sensory processing areas of the thalamus and cortex mediate emotional learning in situations involving specific sensory cues, whereas learning about the emotional significance of more general, contextual cues involves projections to the amygdala from the hippocampal formation. Within the amygdala, the lateral nucleus (AL) is the sensory interface and the central nucleus the linkage with motor systems involved in the control of species-typical emotional behaviors and autonomic responses. Studies of cellular mechanisms in these pathways have focused on the direct relay to the lateral amygdala from the auditory thalamus. These studies show that single cells in AL respond to both conditioned stimulus and unconditioned stimulus inputs, leading to the notion that AL might be a critical site of sensory–sensory integration in emotional learning. The thalamo–amygdala pathway also exhibits long-term potentiation, a form of synaptic plasticity that might underlie the emotional learning functions of the circuit. The thalamo–amygdala pathway contains and uses the amino acid glutamate in synaptic transmission, suggesting the possibility that an amino-acid mediated form of synaptic plasticity is involved in the emotional learning functions of the pathway. We are thus well on the way to a systems level and a cellular understanding of at least one form of emotional learning and memory.

INTRODUCTION

For the past several decades, the limbic system concept[53–54] has dominated thinking about the neural basis of emotion. However, during the same time, nuclei and pathways of the so-called limbic system have emerged as key components of the brain system underlying memory and other cognitive functions[56,59,77,80]. This indicates either that the limbic system concept is useful as an account of both memory and emotion or that it is not very useful as an account of either. For several reasons, detailed below, it seems that the latter is more likely and that we should look beyond the limbic system for a conceptual framework for understanding questions about the neural organization of emotion and memory.

First, those limbic areas most important for emotion are less directly involved in cognitive processes. The amygdala is a key component of the brain system involved in a variety of emotional functions[1,2,23,24,32,33,14,15,37,38,40]. Although the amygdala was in the past included, together with the hippocampus, as part of the temporal lobe memory system[56] it now appears that the amygdala is not involved in this system[57,85]. While the amygdala may contribute to some cognitive processes (see ref. 1) its contribution to cognition would seem to be considerably less than its contribution to emotion. It might even be possible to explain amygdala contributions to cognition, when they occur, in terms of the loss of the affective qualities of cognition. The survival of the limbic system concept as an account of the neural basis of emotion may be directly related to the inclusion of the amygdala in the limbic system[39].

Second, those limbic areas that have been implicated in memory and other cognitive processes seem to have less significant roles in emotion. For example, the hippocampal formation is now believed to be an essential

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component of the brain system underlying the conscious recollection of past events[80] and the processing of spatial, configural, contextual and/or relational information[59,58,73,16]. In general, damage to the hippocampus does not produce clinical alterations of emotion or interfere with emotional responsivity in experimental tasks; the hippocampus is mainly involved in emotional processes when the non-emotional (especially cognitive) aspects of the task require the hippocampus[37]. A prime example of this secondary role of the hippocampus in emotion comes from studies showing that electrical stimulation of the hippocampus is capable of modulating the expression of emotional responses elicited by hypothalamic stimulation but hippocampal stimulation itself does not elicit such responses[78]. The hippocampus thus seems to provide important inputs to emotional circuits but is not itself a primary link in those circuits. Gray's[25] hippocampal theory of anxiety would seem to be at odds with this view but it may be that contributions of the hippocampus to anxiety are more in the area of cognitions that trigger and maintain anxiety than in the emotional aspects of anxiety[37,39].

Third, the limbic system concept itself has been challenged, as there are no objective criteria that can be universally applied to decide whether a given structure belongs to the limbic system[7,37,39,82]. While areas of the limbic system, however it is defined, are involved in emotional functions, not all limbic areas are involved, emotion requires non-limbic as well as limbic areas, and non-emotional functions are also represented in the limbic system. The limbic system concept, though highly innovative and important in its time, has outlived its usefulness as an account of the neural basis of emotion and suffers from many of the same problems as an account of memory or other cognitive processes.

The best way to figure out circuits of emotion and memory is to study them empirically rather than to impose a vague anatomical concept on the functions. As described above, research in this vein suggests that the neural systems underlying memory and emotion are, at least in part, separately localizable. While these networks interact in important ways, they are sufficiently distinct that they should be considered separate systems.

If memory and emotion are separately represented, how does the brain form memories about the emotional significance of a stimulus? Is such information stored through the hippocampal system? What is the role of the emotional system involving the amygdala? Before answering these questions, it is necessary to consider what the term "memory" refers to?

It is now widely recognized that there are many different kinds of learning and memory capacities in the brain (e.g. refs. 58, 76, 80, 84). Most typically, the term memory refers to the ability to consciously remember past experiences or previously learned information. This kind of memory, which is dependent upon the hippocampal system, is often referred to as declarative or explicit (conscious) memory[16,76,80]. There are a variety of non-declarative or implicit (unconscious) memory systems[76,80]. Each of these has its own neural representation. The one of most interest here can be referred to as an emotional memory system. This system is required for the acquisition and storage of information about the emotional significance of experiences[14,15,32,33,36–38,41]. Thus, networks involving the hippocampal formation and associated cortical areas are involved in storing declarative or explicit memory traces of experiences, regardless of whether the experiences are emotional or not. But emotional experiences also lead to storage of information through the amygdala. When memories stored through both the amygdala and hippocampus are retrieved, they have a different flavor than when only the hippocampal system is involved. This dual activation of the amygdala and hippocampus may be what gives emotional memories their special quality.

Two hypotheses can be suggested as to why amygdala activation might add subjective affect to experiences and memories. The first is an hedonic hypothesis. That is, there is something special (emotional) about the information processing performed by the amygdala. When the amygdala processes information, a central hedonic states results. This hedonic state accompanies dual activation of the amygdala and hippocampus but not activation of the hippocampus alone. The second is an anhedoic theory of emotional memory. When the amygdala circuits are activated, a host of behavioral, autonomic, and endocrine responses are either elicited (or the systems are at least readied for action), and recalled memories are charged with a degree of arousal that does not accompany activation of the hippocampal system alone. Somehow this arousal is translated into positive and negative hedonic tone, depending on the nature of the situation. These two hypotheses will be readily recognized as restatements of the centralist vs. peripheralist theories about the nature of subjective emotional experiences (see refs. 36, 74). Neither theory is acceptable or rejectable at this point. Other theories may also be possible. Failure to resolve this controversy is an embarrassment to the field but is not a stumbling block that impedes empirical research on the neural basis of emotional memory.

Thus far, I have emphasized the fact that both the amygdala and hippocampus are involved in the storage

and retrieval of information about the emotional significance of experienced emotional events. In this view, emotional experiences lead to parallel storage in emotional (amygdala-based) and non-emotional (hippocampal-based) systems. When memories are activated in this way, we have conscious knowledge of why emotion is aroused. However, it is also conceivable, if not likely, that the amygdala system can store information that is not processed by the hippocampal system. These "implicit" (unconscious) emotional memories, when activated, would lead to the same kind of aroused condition as when explicit emotional memories are activated, but in the absence of explicit (conscious) knowledge of why the arousal occurs. In such situations of emotional ambiguity, conscious systems may seek explanations for the arousal in terms of the social environment or one's own behavior[4,37,74,75].

It is obviously important to understand how the brain goes about the business of forming emotional memories and to tease apart the mechanisms involved in the establishment of explicit as well as implicit memory traces of emotional experiences. Although we are a long way from this ambitious goal, considerable progress has been made in understanding some basic facts about how memories of the emotional significance of events are stored in the brain through the amygdala and its neural connections. In the following, the approach taken by my laboratory and the major findings that have resulted will be described. Summaries of the work of other investigators who also work on this general topic can be found in recent reviews[14,15,32,33].

THE BEHAVIORAL MODEL

Our studies have involved the use of aversive classical conditioning techniques to examine the neural mechanisms through which environmental events are transformed into emotional signals in rats. We have primarily focused on the use of auditory stimuli, the meanings of which are modified by associative pairing with footshock. In the language of conditioning, the auditory stimulus is the conditioned stimulus (CS) and the footshock is the unconditioned stimulus (US). After a small number of pairings, the CS comes to elicit emotional responses (increases in arterial pressure and heart rate; freezing behavior) when presented alone (Fig. 1). These are species-typical responses that are elicited when rats are exposed to threatening stimuli, including stimuli with innately programmed significance as well as CSs that have been associated with aversive USs[5,17,18,38]. Thus, the rat does not learn the responses but instead learns the association of the CS with the US. The associative nature of the responses is demonstrated by studies comparing the responses elicited after CS–US pairings with the responses elicited after random presentations of the CS and US[65] (Fig. 1). Activation of the stored association by the CS elicits responses similar to those elicited by actual threats[5].

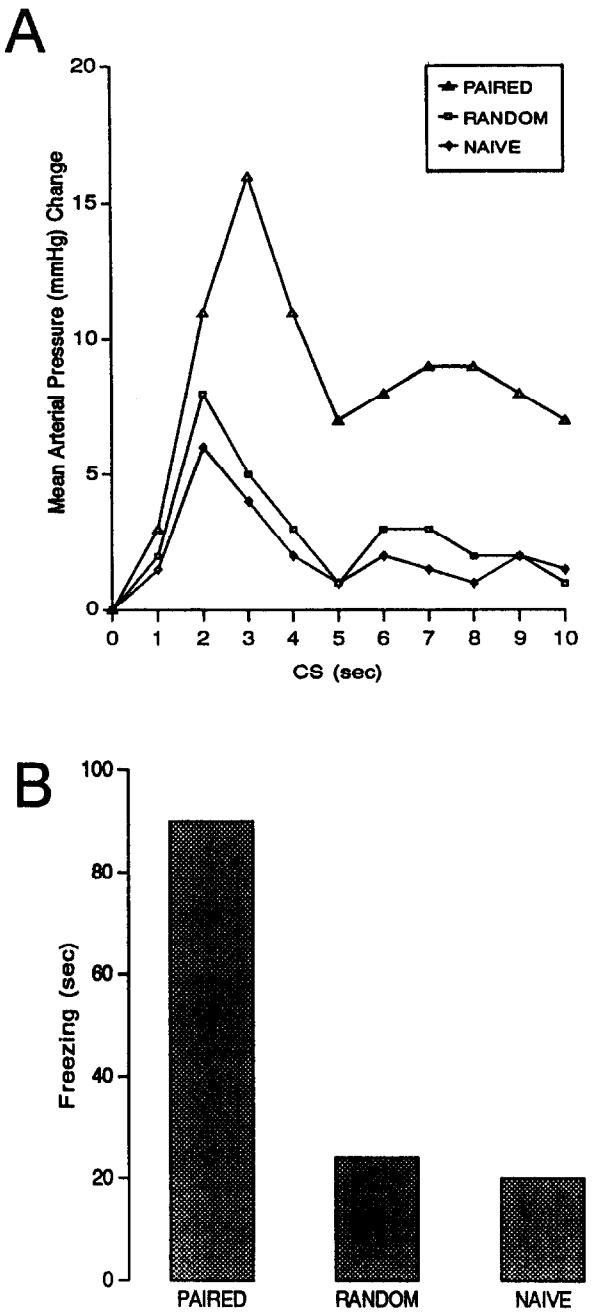

Fig. 1. Autonomic and behavioral responses elicited by an acoustic conditioned stimulus (CS). All responses were measured outside of the conditioning context (in the home cage) 24 h after conditioning or control procedure. During conditioning, the paired group experienced the 10 s CS in a paired relation with a 0.5 s footshock US, the random group experienced the CS and US in a random relation, and naive group experienced neither stimulus. During testing 3 CS alone trials was presented to measure arterial pressure responses and one 120 s CS alone trial was presented to measure freezing.

Understanding how the brain processes conditioned fear stimuli, therefore, allows to approach questions about: (1) how hardwired, innate emotional programs are activated and controlled by environmental events, (2) how novel environmental events gain access to these innate systems through learning, and (3) how information about aversive experiences in the environment are stored and used adaptively in future encounters with threatening events. Although the work involves rats, it involves an emotional system, the fear system, that is probably conserved across mammals better than any other. This no doubt explains the extremely successful use of rats in the development of drugs for the control of fear and anxiety in humans.

THE BASIC NEURAL CIRCUIT

The neural pathways involved in the association of an auditory CS with a footshock US, and thus in the elicitation of defensive responses by the CS in the absence of the US, have been identified. These will be described in terms of sensory, integrative, and motor systems.

The auditory CS is relayed through the auditory system to the thalamus. Lesions of the auditory thalamus completely eliminate the ability of the animal to associate the auditory CS with the US[51]. From the thalamus, the signal is transmitted both to the auditory cortex and to the amygdala. Lesions of the auditory cortex have no effect on conditioning[51,68], but lesions of the amygdala prevent conditioning[14,15,28,32,33,37,38,50]. These results indicate that the thalamo–amygdala pathway is a sufficient conditioning pathway, but do not indicate whether it is also a necessary pathway. Indeed, we have recently shown that neither thalamo–amygdala or thalamo–cortico–amygdala pathways are necessary and that each is sufficient as a conditioning pathway, at least for a simple, single auditory CS[67].

Anatomical tracing studies have characterized the pathways through which the auditory thalamus and auditory cortex are connected with the amygdala. The details are described in relevant publications[43–46,49,69,70]. The most important points can be summarized as follows. First, the main thalamic inputs to the amygdala originate in the medial areas of the medial geniculate body and associated regions of the posterior thalamus. These thalamic areas also projects to auditory cortex, but as part of the extralemniscal auditory system and not part of the tonotopically organized lemniscal system that makes possible veridical perceptions. The extent of sensory representation is thalamo–amygdala systems is thus relatively weak as compared to thalamo–cortical systems. Second, the projections from auditory cortex to amygdala arise not in the primary auditory cortex, but in secondary fields. The secondary fields receive direct thalamic projections as well as projections from primary auditory cortex. Third, the projections to the amygdala from both the auditory association cortex and the auditory thalamus converge in amygdala.

The lateral nucleus of the amygdala is the sensory receptive area[42–44]. It receives the convergent inputs from auditory thalamus and auditory cortex (Fig. 2). Lesions of the lateral nucleus interfere with fear conditioning[42]. In contrast, the central nucleus is the response expression area[14,15,32,33,38,47]. Lesions of this structure also interferes with conditioning. The lateral nucleus is connected with the central nucleus directly and by way of the basal (basolateral) and accessory basal (basomedial) nuclei[35,64,81] (Fig. 2). The contribution of specific intraamygdala pathways to conditioning has not been examined.

The central amygdala projects to a variety of brain-

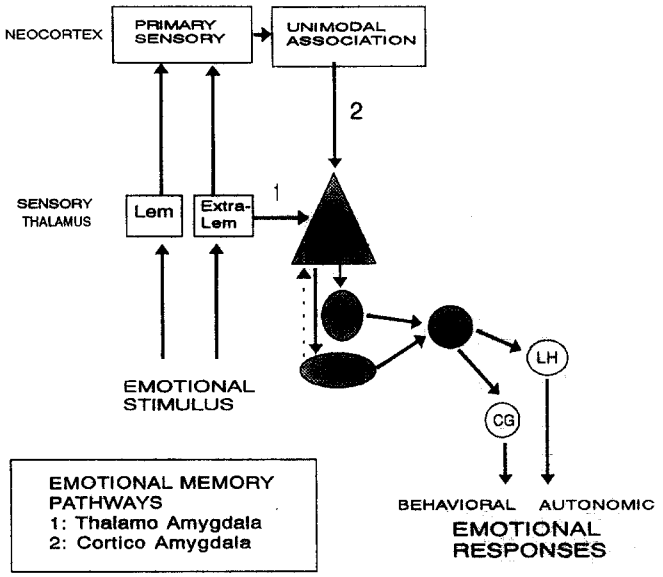

Fig. 2. Emotional memory pathways. Emotional memory, as understood through studies of fear conditioning, can be established by thalamo–amygdala and thalamo–cortico–amygdala pathways. The lateral nucleus of the amygdala (Lat Amyg) is involved in the conditioning of fear responses to modality-specific stimuli processed thorough both thalamo–amygdala and cortico-amygdala projections. Through pathway one (1), which links extra-lemniscal (Extra-Lem) sensory areas of the thalamus with Lat Amyg, undiscriminated acoustic stimuli gain access to fear control systems. More complex sensory stimuli require transmission to the cortex over the lemniscal (Lem) and Extra-Lem projections and then connections to Lat Amyg through pathway two (2). Lat Amyg projects to the central nucleus of the amygdala (Ce) by way of the basal (B) and accessory basal (AB) nuclei. Ce then has connections with brainstem areas invovled in the regulation of species typical behaviors (central gray, CG) and autonomic adjustments (lateral hypothalamus, LH).

stem areas involved in the expression of behavioral, autonomic, and endocrine responses and lesions of different projections selectively interfere with different response modalities[47]. Thus, lesions of the lateral hypothalamus interferes with the expression of autonomic but not behavioral responses, whereas lesions of the central gray region interferes with behavioral but not autonomic responses. Lateral hypothalamic lesions in primates have similar effects[79]. These findings, summarized in Fig. 2, provide an interesting contrast to studies showing that both defensive behavior and associated autonomic responses can be elicited by electrical or chemical stimulation of the central gray region[3,24]. However, the stimulation studies show the full range of responses that can be elicited when the entire system is directly activated, whereas our studies show the pathways actually used by the brain in producing defensive responses to an environmental stimulus. However, it is also possible that both behavioral and autonomic responses might be mediated by the central gray pathways in response to environmental stimuli in other situations.

Together, the various findings described above provide an input–output description of the fear conditioning pathways from sensory to motor neurons. The pathways involve transmission through the auditory system to the thalamus and then to the lateral amygdala, either directly or by way of the auditory cortex. After intraamygdala relays, the central nucleus transmits to brainstem areas involved in emotional response control. These pathways are mainly relevant for the conditioning of fear responses to simple, undiscriminated auditory stimuli like a pure tone.

Studies by Jarrel et al.[29] have shown that if a discriminated conditioning task is used, where one CS is paired with the US and another is not, the auditory cortex is required for accurate responding to the paired CS. Interestingly, auditory cortex lesions interfere with this task not by preventing responding but instead by preventing the differential responding to the paired stimulus; thus, the animals respond to both stimuli. In this situation, the fear responses are elicited through thalamo–amygdala systems, which appear unable to distinguish between the two stimuli. Studies of animals with auditory cortex lesions will provide valuable information into the limits of the thalamo–amygdala system.

Two important questions are whether this basic pattern of connectivity involving projections to the amygdala from both the sensory thalamus and sensory cortex holds for emotional conditioning in other (non-auditory) CS modalities and whether it holds for conditioning in other (non-aversive) US modalities? Although neither of these questions can be answered with the detail that is available for auditory aversive conditioning, partial answers are available. Aversive conditioning with a visual CS requires the integrity of the amygdala and does not depend on visual cortex[48]. Subcortical visual pathways to the amygdala must therefore be involved, although these have not been clearly identified at this point. Unfortunately, little information is available for appetitive conditioning tasks that are exactly comparable to fear conditioning. The only work directly relevant comes from Gallagher and Holland, showing that the central nucleus of the amygdala is involved in some aspects of aversive conditioning[22]. Some other appetitive tasks have implicated the amygdala[9,21,26,30], while others have not[10]. Thus, it seems that visual aversive conditioning is probably organized similar to auditory aversive conditioning but it is not clear whether appetitive conditioning uses similar pathways as aversive conditioning.

AN EXTENDED EMOTIONAL SYSTEM

Recently, we have begun to ask how the fear conditioning circuits involving sensory projections to the amygdala from the thalamus and cortex fit into larger cerebral networks. Thus far, we have concentrated on the question of whether the hippocampus might contribute to fear conditioning.

It has been known for some time that lesions of the hippocampal formation have no effect on the acquisition of fear reactions to a CS paired with an aversive US[66]. However, during conditioning, in addition to developing fear reactions to the CS, the animals also acquire fear reactions to the chamber in which CS–US pairings take place[5,17,18]. The hippocampus has long been thought of as play some role in spatial/contextual/configural/relational processing[16,58,59,73]. We[62] and others[34,78] therefore asked whether lesions of the hippocampus might interfere with contextual conditioning.

Hippocampal damage indeed impaired this so-called contextual fear conditioning without affecting conditioning to a CS[34,62]. Contextual fear conditioning was also interfered with by amygdala damage[62]. The amygdala is thus required for fear conditioning, regardless of the kind of CS (phasic CS, such as a tone, or continuously present CS, such as the conditioning box) associated with the US. We[62] proposed that projections from the subiculum of the hippocampal formation to the amygdala[61] are the essential pathway to the amygdala in contextual fear conditioning and that this projection functions as a high-level CS processing pathway, much as the sensory projections to the amygdala

do for phasic stimuli. An important challenge is to understand just what context is. Context differs from a standard CS in important ways. First, contextual stimuli are continuously present and are thus not explicitly paired with the US in a precise, temporal relationship. Second, contextual stimuli may not be stimuli at all but instead may be complex modailtity independent representations. The hippocampus could be involved because it is needed for attending to continuously present stimuli that have no obvious temporal parameter, because it is needed for processing modality independent information, or for a number of other reasons that are implied by one of the various theories of hippocampal function[16,58,59,73].

Our study of contextual conditioning may have revealed a general feature of cortico–amygdala function. The amygdala receives inputs from many high level association areas in the frontal and temporal lobes. These may each be playing roles in fear conditioning, but in the absence of clear tasks that are sensitive to these roles, we are unable to notice the effects of lesions of these structures. As we learn more about the functions of various cortical areas, hypotheses about the contributions of these areas to fear conditioning, and possibly to emotional processing in general, may emerge.

CELLULAR PROCESSING MECHANISMS

Once key aspects of the neural system involved in the formation of emotional memories through fear conditioning were identified, we began efforts to uncover some basic cellular mechanisms in the hope of gaining insights into the nature of information processing in these circuits. To date, this work has focused on the thalamo–amygdala system and three major issues have been researched: sensory processing capacities of single neurons, synaptic organization and neurotransmission, and synaptic plasticity.

Processing capacities of single neurons

The goal of this line of work has been to record from single cells in the thalamo–amygdala pathway in order to characterize the neuronal codes underlying the processing of CS and US information by these cells. As a first step, we recorded unit activity in AL in response to electrical stimulation of the auditory thalamus[13]. These studies demonstrated that cells in AL can be synaptically activated by thalamic stimulation. The initial response latencies were in the range of 4–8 ms. Next, we recorded unit activity in AL in response to stimulation with auditory CS-like events[6]. Many cells in AL were acoustically responsive and had initial onset latencies starting from 12 ms. These cells had a variety of frequency receptive field tuning functions, with some showing surprisingly narrow receptive fields for a structure outside of the auditory system. Other cells rapidly habituated to auditory stimuli. Most cells had relatively high thresholds. These properties suggest that AL neurons are hard wired to respond to auditory stimuli in three ways that are particularly relevant to emotional coding: first, the short latencies are consistent with direct transmission from the thalamus (thalamic cells respond to auditory stimuli in 7–10 ms and thalamo–amygdala transmission takes 4–8 ms) and may allow the amygdala to produce rapid emotional responses to acoustic events; second, the high thresholds suggest that AL cells may serve as intensity filters, allowing the amygdala produce defensive, protective reactions to loud stimuli; third, the rapidly habituating cells may be novelty detectors. Learning in this system then could involve a lowering of threshold, while maintaining the same receptive field; modification of the receptive field; or reduction in habituating tendencies. Recent work shows that most of the acoustically responsive cells are also responsive to somatosensory stimulation[71]. These physiological studies thus suggest clues into the nature of processing in the thalamo–amygdala system. Future work will be aimed at determining how CS–US interactions in the amygdala might account for emotional learning and memory, as expressed behaviorally.

Synaptic plasticity

Long-term potentiation (LTP) has been used extensively to study synaptic plasticity in the hippocampus and other areas of the nervous system[8,52,83]. LTP involves the delivery of high frequency electrical stimuli to a fiber system and recording of synaptic responses in a terminal region. LTP occurs when the synaptic response to a fixed stimulus is increased after high frequency tetanization. Tetanization of the thalamo–amygdala pathway produces an increase in a field potential recorded in AL[12]. This is indicative of an amplified synaptic response. LTP has also been elicited in AL by stimulation of cortico-amygdala pathways[11].

Many questions remain unanswered about thalamo–amygdala LTP[41]. However, at a minimum it shows that the circuit is plastic. An important step would be to show that stimulation of CS and US inputs to AL can produce LTP. This would provide a realistic model of synaptic plasticity in a circuit with a well-defined learning and memory function and could help to further our understanding of the relation of LTP to memory as well as our understanding of how emotional memories are formed. Such studies will have to await the identification of the US pathway to AL.

Synapses and transmitters

Considerable progress has been made in identifying the kinds of synapses formed and the neurotransmitter used by thalamo–amygdala projections. Dual labeling light microscopic studies have been performed to determine possible transmitter substances present in the cells of origin of the thalamo–amygdala projection. The dual labeling involved retrograde transport to selectively label the cells of origin of the thalamo–amygdala projection and immunocytochemistry to determine the presence of the transmitter substance[45]. Such studies show that the excitatory amino acid glutamate is a likely candidate transmitter. Electron microscopic studies have shown that the thalamo–amygdala projection mainly forms asymmetric synapses in AL[46]. Since asymmetric synapses are usually indicative of excitatory transmission, these findings are consistent with the presence of the excitatory substance glutamate in the cells of origin. Most of the terminals contact dendritic spines or the distal shafts of dendrites. Further electron microscopic studies demonstrated that many terminals in AL contain glutamate immunoreactivity[19]. The glutamate-labeled terminals, like thalamo–amygdala terminals, tend to contact dendritic spines and at least some of the thalamo–amygdala terminals contain glutamate immunoreactivity[20]. Moreover, intraventricular or iontophoretic injections of excitatory amino acid antagonists interferes with the synaptic responses recorded in amygdala after thalamic stimulation[63].

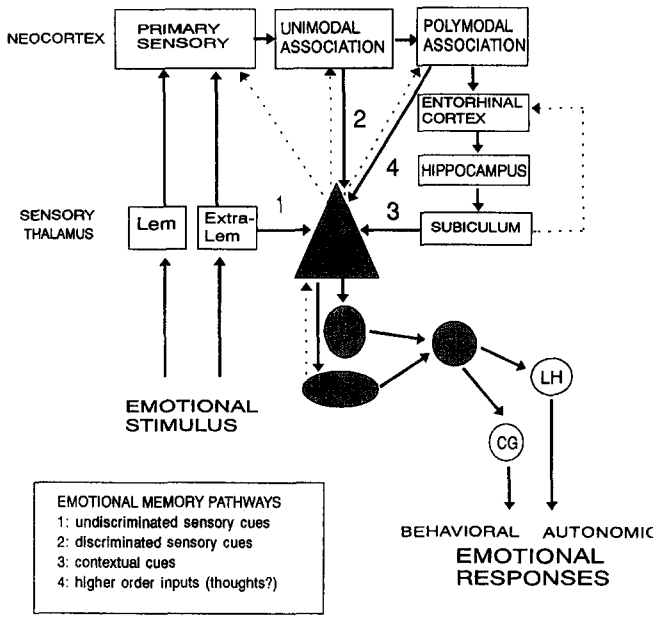

Fig. 3. Extended emotional memory pathways. Thalamo–amygdala projections (Pathway 1) are involved in conditioning to simple (undiscriminated) modality-specific inputs, whereas cortico-amygdala projections (Pathway 2) are required for conditioning to stimuli that must be disriminated on the basis of perceptual fearture. Lat Amyg also receives inputs from the subiculum, a major output of the hippocampal formation (Pathway 3). Hippocampo–amygdala projections have been implicated in contextual conditioning. Complex association cortex (e.g. multimodal areas of the frontal lobes) also project to Lat. Amyg. (Pathway 4). These connections may be involved in the formation of emotional memories on the basis of complex cognitions (thoughts). AB, accessory basal (basomedial) nucleus of the amygdala; B, basal (basolateral) nucleus of the amygdala; Ce, central nucleus of the amygdala; CG, central gray; Extra-Lem, extralemniscal areas of sensory thalamus; Lem, lemniscal areas of sensory thalamus; LH, lateral hypothalamic area.

These studies thus begin to characterize the morphological and physiological bases of neurotransmission in the thalamo–amygdala projection. Such information provides initial clues to the local circuit organization of the projection and suggests hypotheses for additional physiological and behavioral studies. Given the role of glutamate in synaptic plasticity in the hippocampus[8,52,83] and the observation that blockade of excitatory amino acid transmission in the amygdala interferes with fear conditioning[14], we begin to see the possibility of a cellular understanding of fear conditioning, a possibility that was once believed to be mainly obtainable in simple, invertebrate preparations[31].

EMOTION AND MEMORY: CONCLUSIONS

The emotional memory system revealed by this research is depicted in Fig. 3. This Figure emphasizes the extensive degree of parallel processing that takes place, even in this highly oversimplified illustration of the relevant pathways. For purposes of this discussion, consider three kinds of inputs that reach the amygdala in an emotional learning situation. First, the amygdala receives multiple inputs about the CS: inputs from auditory thalamus and various stages of auditory association cortex. These provide the amygdala with various levels of CS representation. The representations vary in temporal and spatial domains, with faster representations being less complete. Second, the amygdala receives inputs from the US pathway, the origin of which is still unknown. These make conditioning possible by modifying the neural processing in any or all of the various levels of CS representation. Third, the amygdala receives inputs from the hippocampal formation about the context in which conditioning is taking place. This contextual representation may also interact with the US in the amygdala to make contextual conditioning possible. Alternatively, the context representation may instead simply modulate the CS–US representation at the level of the amygdala, allowing the extent of fear expressed and conditioned to be adjusted to the context.

It must be recognized that this basic scheme is only

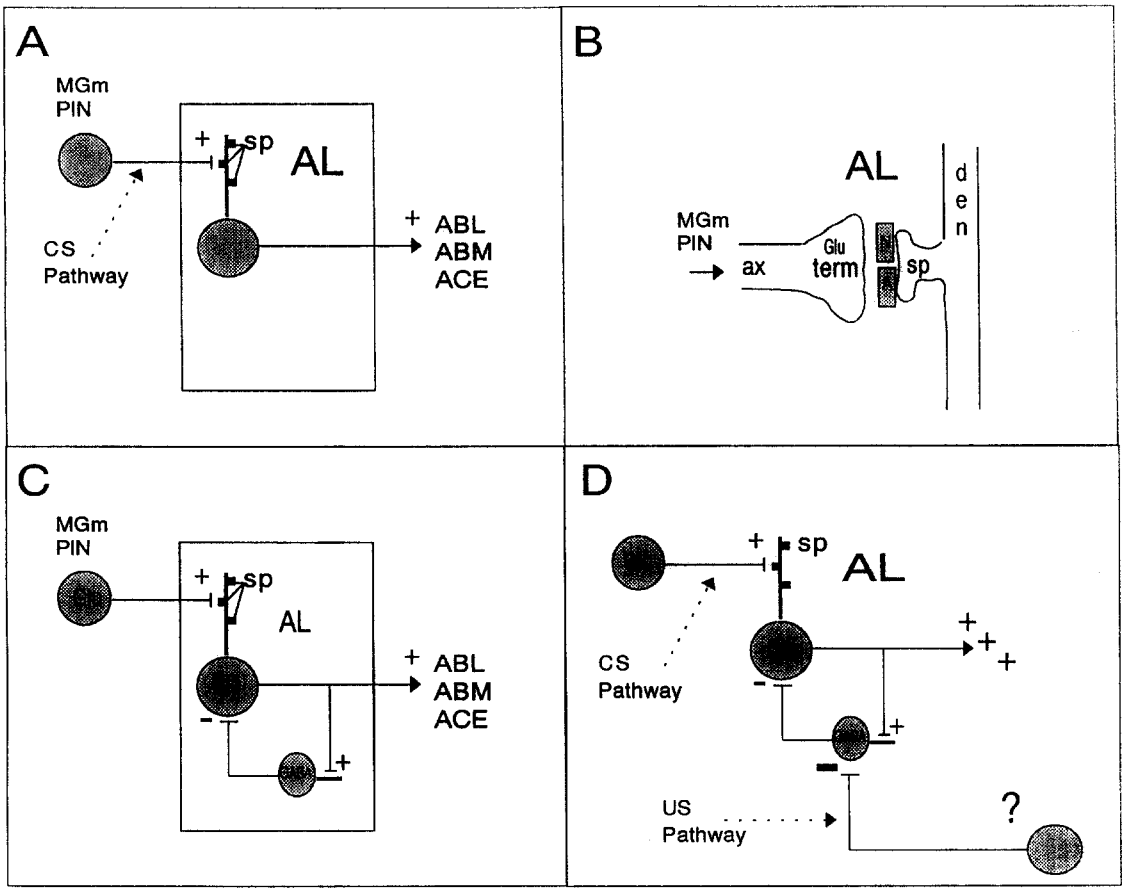

Fig. 4. Synaptic mechanisms in the lateral nucleus of the amygdala (AL). A: auditory conditioned stimulus (CS) pathway from the auditory thalamus (medial areas of medial geniculate body, MGm/PIN) to AL. The pathway forms asymmetric (excitatory) synaptic contacts with the dendritic spines of projection neurons. Projection neurons send their axons to the basal (basolateral, ABL), accessory basal (basomedial, ABM), and central (Ce) nuclei of the amygdala. B: thalamo-amygdala axon (ax) terminals (term) arising in MGm/PIN appear to use glutamate (Glu) as a neurotransmitter. Glu interacts with NMDA (N) and AMPA (A) postsynaptic receptors. C: recurrent collateral ihnibition in AL. Excitatory inputs to AL terminate on projection neurons that give rise to excitatory projections to target areas but also give rise to local collateral projections to GABA inhibitory interneurons. These then contact the projection neuron and inhibit its further activation. D: one way in which the unconditioned stimulus (US) might mediate conditioning is by removing the influence of the inhibitory interneuron in the recurrent collateral feedback loop. This would allow the CS to exert a stronger excitatory impact on target areas. Many other hypotheses are possible. The origin of the US pathway is unknown.

part of the story. It is surely an important part, but some of the factors not accounted in much detail are the following. First, the system contains many reciprocal and back projections, so that most of the areas that project to the amygdala also receive projections from it as well. This allows for highly complex interactions not only between the amygdala and each of its inputs but also between the inputs by way of the amygdala. Thus, the amygdala is a site where information from auditory cortex can be integrated with information from hippocampus and prefrontal cortex. Second, the amygdala is but one of several possible sites of plasticity in the circuit. Plasticity occurs in most of the areas in this circuit during auditory fear conditioning and conditioning expressed at the level of behavior reflects the integration of these various plastic changes. Third, the amygdala is also reciprocally interconnected with the hypothalamus and basal forebrain systems involved in motivational control and basal motivational states may have important influences on emotional system functioning. For example, a hungry animal may be less fearful than a satiated one. Finally, the amygdala also receives inputs from a variety of diffuse projecting systems within the brain and from the periphery that allow the modulation of all of the processing described so far. Such modulation can have powerful effects on long-term storage[55]. All of these aspects, and many more, need to be accounted for.

We have thus come a long way towards an understanding of the neural system underlying fear conditioning and have made some progress at the cellular level as well. It is important to keep in mind, though, that fear conditioning is a very elemental kind of emotional learning. In this respect, two important chal-

lenges face us. The first is to convert the fear conditioning system into a more general understanding of emotional memory, one which accounts for more complex kinds of fears and their learning, as well as one that extends from fear to other emotions. The second is to integrate the emotional memory system into a more general understanding of memory. Progress in these areas will require the joint efforts of researchers now working on topics that are often perceived as separated. But now that so much progress has been made in some of the individual areas, the way is paved for beginning the difficult task of integration across areas.

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