Annu. Rev. Neurosci. 2000. 23:155–184

EMOTION CIRCUITS IN THE BRAIN

Joseph E. LeDoux
Center for Neural Science, New York University, New York, New York 10003; e-mail: ledoux@cns.nyu.edu

Key Words fear, memory, learning, conditioning, amygdala, limbic system

■ **Abstract** The field of neuroscience has, after a long period of looking the other way, again embraced emotion as an important research area. Much of the progress has come from studies of fear, and especially fear conditioning. This work has pinpointed the amygdala as an important component of the system involved in the acquisition, storage, and expression of fear memory and has elucidated in detail how stimuli enter, travel through, and exit the amygdala. Some progress has also been made in understanding the cellular and molecular mechanisms that underlie fear conditioning, and recent studies have also shown that the findings from experimental animals apply to the human brain. It is important to remember why this work on emotion succeeded where past efforts failed. It focused on a psychologically well-defined aspect of emotion, avoided vague and poorly defined concepts such as "affect," "hedonic tone," or "emotional feelings," and used a simple and straightforward experimental approach. With so much research being done in this area today, it is important that the mistakes of the past not be made again. It is also time to expand from this foundation into broader aspects of mind and behavior

INTRODUCTION

After decades of neglect, neuroscience has again embraced emotion as a research topic. This new wave of interest raises the question of why emotion was overlooked for so long. It is instructive to consider this question before examining what has been learned about emotional circuits, as some of the factors that led brain researchers to turn away from this topic may again hamper progress unless they can be grappled with.

Why Did Interest in Emotion Wane?

During the first half of the twentieth century, brain researchers were immensely interested in the brain mechanisms of emotional behavior. Some of the early pioneers in neuroscience worked in this area, including Sherrington, Cannon, Papez, and Hebb. Responses that occur when we defend against danger, interact with sexual partners, fight with an enemy, or have a tasty bite to eat promote the survival of individuals and their species. Emotional responses are thus inherently

0147–006X/00/0301–0155$12.00

interesting and important. So what happened? Why did research on the brain mechanisms of emotion come to a halt after midcentury?

For one thing, emotion research was a victim of the cognitive revolution. The emergence of cognitive science shifted the interest of those concerned with the relation between psychological functions and neural mechanisms toward processes (perception and memory, for example) that were readily thought of in terms of computer-like operations. From the start, cognitive scientists claimed that their field was not about emotion and other such topics (see Neisser 1967, Gardner 1987). The cognitive approach came to be the dominant approach in psychology and brain science, and research interest in emotion dwindled.

Another factor that hindered work on emotions in neuroscience was that the problem of how the brain makes emotions seemed to have been solved in the early 1950s by the limbic system concept (MacLean 1949, 1952). This appealing and convincing theory was the culmination of research on the brain mechanisms of emotion by many researchers, extending back to the late nineteenth century (see LeDoux 1987, 1991). Studies of how the brain mediates cognitive processes seemingly had a long way to go to catch up with the deep understanding that had been achieved about emotions, and researchers flocked to the new and exciting topic of cognition and the brain to begin filling the gap.

Cognitive questions also seemed more tractable than emotional ones, due in part to the dark cloud of subjectivity that hung over the topic of emotion. Although subjective experience and its relation to neural mechanisms is a potential difficulty for any area of psychology, cognitive scientists figured out how to study mental processes without having to solve the mind-body problem. They showed, for example, that it is possible to study how the brain processes (computes and represents) external stimuli without first resolving how the conscious perceptual experiences come about. In fact, it is widely recognized that most cognitive processes occur unconsciously, with only the end products reaching awareness, and then only sometimes (see Kihlstrom 1987). Emotion researchers, though, did not make this conceptual leap. They remained focused on subjective emotional experience. In spite of the fact that most research on emotions and the brain was, and still is, conducted with experimental animals, creatures in which subjective states are difficult if not impossible to prove, theoretical discussions of emotions and the brain typically reverted back to the age-old question of feelings. This approach puts the mind-body problem right smack in the middle of the path of progress.

The main lesson to be learned from this brief excursion into history is that emotion researchers need to figure out how to escape from the shackles of subjectivity if emotion research is to thrive. It is ironic that cognitive science, which led to the neglect of emotion research, may also be able to help in its resurrection by providing a strategy that allows the study of emotion independent of subjective emotional experiences. It is possible, for example, to ask how the brain processes emotional information (i.e. detects and responds to danger) without necessarily first solving the question of where conscious feelings come from. Contrary to popular belief, conscious feelings are not required to produce emotional

responses, which, like cognitive processes, involve unconscious processing mechanisms (see Öhman 1992, LeDoux 1996). If we want to understand feelings, it is likely going to be necessary to figure out how the more basic systems work. Failure to come to terms theoretically with the importance of processing systems that operate essentially unconsciously has been a major impediment to progress in understanding the neural basis of emotion. To overcome this, brain researchers need to be more savvy about the nature of emotions, rather than simply relying on common sense beliefs about emotions as subjective feeling states.

Research on emotion can also help cognitive science. A pure cognitive approach, one that omits consideration of emotions, motivations, and the like, paints an artificial, highly unrealistic view of real minds. Minds are not either cognitive or emotional, they are both, and more. Inclusion of work on emotion within the cognitive framework can help rescue this field from its sterile approach to the mind as an information-processing device that lacks goals, strivings, desires, fears, and hopes.

Once a processing approach to emotion is taken, emotion and cognition can be studied similarly: as unconscious processes that can, but do not necessarily, lead to conscious experiences. This would open the door for the integration of emotion and cognition, and such integration should be a major goal for the immediate future.

Should We Integrate the Cognitive Brain with the Limbic System?

The rise of cognitive science led to important advances in understanding the brain mechanisms of perception, attention, memory, and other cognitive processes. One might be tempted to say that the way to foster the synthesis of cognition and emotion into a new science of mind would be to put all this new information about the cognitive brain together with the definitive view of the emotional brain provided long ago by the limbic system concept. However, this would be a mistake. In spite of the fact that the limbic system concept remains the predominant view about how the brain makes emotions, it is a flawed and inadequate theory of the emotional brain.

The limbic system concept was put forth in the context of an evolutionary explanation of mind and behavior (MacLean 1949, 1952, 1970; Isaacson 1982). It built upon the view, promoted by comparative anatomists earlier in the century, that the neocortex is a mammalian specialization—other vertebrates have primordial cortex but only mammals were believed to have neocortex. And because thinking, reasoning, memory, and problem solving are especially well developed in mammals, particularly in humans and other primates that have relatively more neocortical tissue, these cognitive processes must be mediated by the neocortex and not by the old cortex or other brain areas. In contrast, the old cortex and related subcortical ganglia form the limbic system, which was said to mediate the evolutionarily older aspects of mental life and behavior, our emotions. In this

way, cognition came to be thought of as the business of the neocortex and emotions of the limbic system.

The limbic system theory began to run into trouble almost immediately when it was discovered, in the mid-1950s, that damage to the hippocampus, the centerpiece of the limbic system, led to severe deficits in a distinctly cognitive function, long-term memory (Scoville & Milner 1957). This was incompatible with the original idea that the primitive architecture of the limbic system, and especially of the hippocampus, was poorly suited to participate in cognitive functions (MacLean 1949, 1952). Subsequently, in the late 1960s, it was discovered that the equivalent of mammalian neocortex is present, though rudimentary, in nonmammallian vertebrates (see Nauta & Karten 1970). As a result, the old/new cortex distinction broke down, challenging the evolutionary basis of the assignment of emotion to the limbic system and cognition to the neocortex (Swanson 1983).

The limbic system itself has been a moving target. Within a few years after inception, it expanded from the original notion of "old cortex" and related subcortical forebrain nuclei to include some areas of the midbrain (Nauta 1979), and even some regions of neocortex (Kaada 1960). Several attempts have been made to salvage the limbic system by defining it more precisely (see Isaacson 1982, Swanson 1983, Livingston & Escobar 1971). Nevertheless, after half a century of debate and discussion, there are still no agreed upon criteria that can be used to decide which areas of the brain belong to the limbic system. Some have suggested that the concept be abandoned (Brodal 1982; LeDoux 1987, 1991; Kotter & Meyer 1992).

In spite of these difficulties, the limbic system continues to survive, both as an anatomical concept and as an explanation of emotions, in textbooks, research articles, and scientific lectures. This is in part attributable to the fact that both the anatomical concept and the emotional function it was supposed to mediate were defined so vaguely as to be irrefutable. For example, in most discussions of how the limbic system mediates emotion, the meaning of the term emotion is presumed to be something akin to the common English language use of the term (because no other definition is given). However, the common English use of the term emotion is at best a poor theoretical notion, for emotion is a rich and complex theoretical concept with many subtle aspects, some of which are nonintuitive and thus inconsistent with the common use of the term (for discussions see Lewis & Haviland 1992, Ekman & Davidson 1994, LeDoux 1996). On the neural side, the criteria for inclusion of brain areas in the limbic system remain undefined, and evidence that any limbic area, however defined, contributes to any aspect of any emotion has tended to validate the whole concept. Mountains of data on the role of limbic areas in emotion exist, but there is still little understanding of how our emotions might be the product of the limbic system.

Particularly troubling is the fact that one cannot predict, on the basis of the original limbic theory of emotion or any of its descendants, how specific aspects of emotion work in the brain. The explanations are all post hoc. Nowhere is this

more apparent than in recent work using functional imaging to study emotions in the human brain. Whenever a so-called emotional task is used, and a limbic area is activated, the activation is explained by reference to the fact that limbic areas mediate emotion. And when a limbic area is activated in a cognitive task, it is often assumed that there must have been some emotional undertone to the task. We are, in other words, at a point where the limbic theory has become an off-the-shelf explanation of how the brain works. However, this explanation is grounded in tradition rather than data. Deference to the concept is inhibiting creative thought about how mental life is mediated by the brain.

Although the limbic system theory is inadequate as an explanation of the specific brain circuits of emotion, MacLean's (1949, 1952, 1970) original ideas are very interesting in the context of a general evolutionary explanation of emotion and the brain. In particular, the notion that emotions involve relatively primitive circuits that are conserved throughout mammalian evolution seems right on target. Furthermore, the idea that cognitive processes might involve other circuits, and might function relatively independent of emotional circuits, at least in some circumstances, also seems correct. These functional ideas are worth holding on to, even if we abandon the limbic system as a structural theory of the emotional brain.

ESCAPING THE LIMBIC SYSTEM LEGACY: FEAR CIRCUITS

One of the main exceptions to the bleak state of affairs regarding the brain mechanisms of emotion is the body of research concerned with neural system underlying fear, especially in the context of the behavioral paradigm called fear conditioning. It has, in fact, been research on fear conditioning, and the progress that has been made on this topic, that has been largely responsible for the renaissance of interest of emotion within neuroscience. In this work, the fear system has been treated as a set of processing circuits that detect and respond to danger, rather than as a mechanism through which subjective states of fear are experienced. Through this approach, fear is operationalized, or made experimentally tractable. Some limbic areas turn out to be involved in the fear system, but the exact brain areas and the nature of their involvement would never have been predicted by the limbic system theory.

Before describing research on fear, several other approaches to the study of emotion and the brain that are not discussed further should be mentioned. One involves stimulus-reward association learning (Aggleton & Mishkin 1986, Gaffan 1992, Everitt & Robbins 1992, Ono & Nishijo 1992, Rolls 1999, Gallagher & Holland 1994, Holland & Gallagher 1999). Another involves the role of septo-hippocampal circuits in anxiety (Gray 1982), and still another involves distinct hypothalamic and brainstem circuits for several different emotions (Panksepp 1998, Siegel & Edinger 1981, Siegel et al 1999).

What is Fear Conditioning

Since Pavlov (1927), it has been known that an initially neutral stimulus [a conditioned stimulus (CS)] can acquire affective properties on repeated temporal pairings with a biologically significant event [the unconditioned stimulus (US)]. As the CS-US relation is learned, innate physiological and behavioral responses come under the control of the CS (Figure 1). For example, if a rat is given a tone CS followed by an electric shock US, after a few tone-shock pairings (one is often sufficient), defensive responses (responses that typically occur in the presence of danger) will be elicited by the tone. Examples of species-typical defensive responses that are brought under the control of the CS include defensive behaviors (such as freezing) and autonomic (e.g. heart rate, blood pressure) and endocrine (hormone release) responses, as well as alterations in pain sensitivity (analgesia) and reflex expression (fear-potentiated startle and eyeblink responses). This form of conditioning works throughout the phyla, having been observed in flies, worms, snails, fish, pigeons, rabbits, rats, cats, dogs, monkeys, and humans.

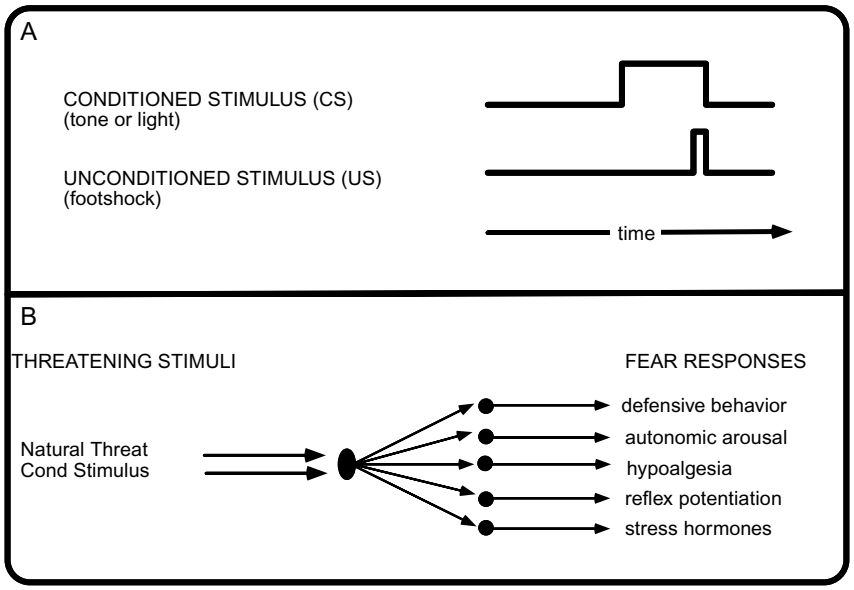

Figure 1 Fear conditioning involves the presentation of a noxious unconditioned stimulus, typically footshock, at the end of the occurrence of a relatively neutral conditioned stimulus (CS), such as a light or tone (*top*). After conditioning, the CS elicits a wide range of behavioral and physiological responses that characteristically occur when an animal encounters a threatening or fear-arousing stimulus (*bottom*). Thus, a rat that has been fear conditioned will express the same responses to a CS as to a natural threat (i.e. a cat).

Neuroanatomy of Fear Conditioning

Research from several laboratories combined in the 1980s to paint a relatively simple and remarkably clear picture of the neuroanatomy of conditioned fear (see Kapp et al 1992, LeDoux 1992, Davis 1992, Fanselow 1994). In short, conditioned fear is mediated by the transmission of information about the CS and US to the amygdala, and the control of fear reactions by way of output projections from the amygdala to the behavioral, autonomic, and endocrine response control systems located in the brainstem. Below, the input and output pathways, as well as the connections within the amygdala that link inputs and outputs, are described. The focus is on findings from rodents and other small mammals, as most of the work on fear conditioning has involved these species (for the contribution of the primate amygdala to fear and other emotions see Pribram et al 1979, Pribram & Melges 1969, Aggleton & Mishkin 1986, Ono & Nishijo 1992, Gaffan 1992, Rolls 1992, 1999).

Amygdala Terminology and Connections The amygdala consists of approximately 12 different regions, each of which can be further divided into several subregions (Figure 2). Although a number of different schemes have been used to label amygdala areas (see Krettek & Price 1978, de Olmos et al 1985, Amaral et al 1992), the scheme adopted by Amaral et al (1992) for the primate brain and applied to the rat brain by Pitkänen et al (1997) is followed here. The areas of most relevance to fear conditioning are the lateral (LA), basal (B), accessory basal (AB), and central (CE) nuclei and the connections between these (Figure 2). In other classification schemes, B is known as the basolateral nucleus and AB as the basomedial nucleus. The term basolateral complex is sometimes used to refer to LA and B (and sometimes AB) together. Studies in several species, including rats, cats, and primates, are in close agreement about the connections of LA, B, AB, and CE (see Pitkänen et al 1997, Paré et al 1995, Amaral et al 1992, Cassell et al 1999). In brief, LA projects to B, AB, and CE, and both B and AB also project to CE. However, it is important to recognize that the connections of these areas are organzied at the level of subnuclei within each region rather than at the level of the nuclei themselves (see Pitkänen et al 1997). For simplicity, though, for the most part we focus below on nuclei rather than subnuclei.

CS Pathways The pathways through which CS inputs reach the amygdala have been studied extensively in recent years. Much of the work has involved the auditory modality, which is focused on here.

Auditory and other sensory inputs to the amygdala terminate mainly in LA (see LeDoux et al 1990b, Romanski & LeDoux 1993, Mascagni et al 1993, Amaral et al 1992, McDonald 1998), and damage to LA interferes with fear conditioning to an acoustic CS (LeDoux et al 1990a, Campeau & Davis 1995).

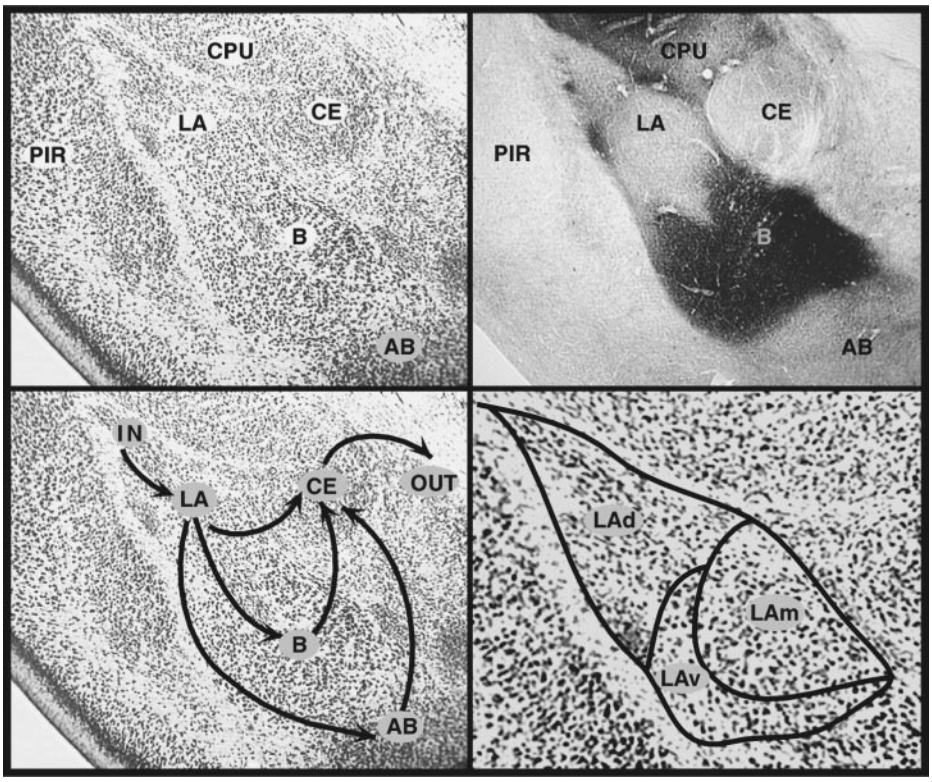

Figure 2 The amygdala consists of a number of different regions. Those of most relevance to the pathways of fear conditioning are the lateral (LA), basal (B), accessory basal (AB), and central (CE) nuclei. The piriform cortex (PIR) lies lateral to the amygdala, and the caudate-putamen (CPU) is just dorsal to it. Comparison of the Nissl-stained section (*upper left*) and an adjacent section stained for acetylcholinesterase (*upper right*) helps identify the different nuclei. The major pathways connecting LA, B, AB, and CE are shown (*lower left panel*). (*Lower right*) A blowup of the LA, emphasizing the fact that each nucleus can be divided into subnuclei. Although anatomical studies have shown that the pathways are organized at the level of the subnuclei, rather than the nuclei (see Pitkänen et al 1997), the nuclear connections (*lower left panel*) provide a sufficiently detailed approximation of the connections for the purposes of considering how the fear conditioning system is, in general, organized.

Auditory inputs to LA come from both the auditory thalamus and the auditory cortex (see LeDoux et al 1990b, Romanski & LeDoux 1993, Mascagni et al 1993), and fear conditioning to a simple auditory CS can be mediated by either of these pathways (Romanski & LeDoux 1992) (Figure 3). It appears that the projection to LA from the auditory cortex is involved with a more complex auditory stimulus pattern (Jarrell et al 1987), but the exact conditions that require the cortex are poorly understood (Armony et al 1997). Although some lesion studies have ques-

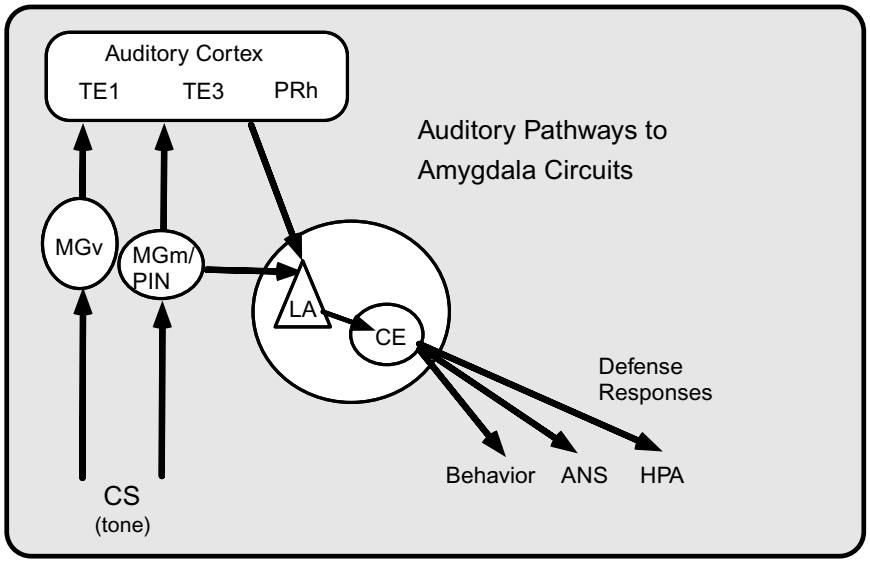

Figure 3 The neural pathways involved in fear conditioning are well characterized. When the CS is an acoustic stimulus, the pathways involve transmission to the lateral nucleus of the lateral amygdala (LA) from auditory processing areas in the thalamus [medial division of the medial geniculate body (MGm/PIN)] and cortex [auditory association cortex (TE3)]. LA, in turn, projects to the central amygdala (CE), which controls the expression of fear responses by way of projections to brainstem areas. ANS, Autonomic nervous system; CS, conditioned stimulus; HPA, hypothalamic-pituitary axis; MGv, ventral division of the medial geniculate body; PRh, perirhinal cortex; TE1, primary auditory cortex.

tioned the ability of the thalamic pathway to mediate conditioning (Campeau & Davis 1995, Shi & Davis 1998), single-unit recordings show that the cortical pathway learns more slowly over trials than does the thalamic pathway (Quirk et al 1995, 1997), thus indicating that plasticity in the amygdala occurs initially through the thalamic pathway. Recent functional magnetic resonance imaging studies in humans have found that the human amygdala shows activity changes during conditioning that correlate with activity in the thalamus but not the cortex (Morris et al 1999), further emphasizing the importance of the direct thalamo-amygdala pathway.

In addition to expressing fear responses to the CS, rats also exhibit these when returned to the chamber in which the tone and shock were paired, or a chamber in which shocks occur alone. This is called contextual fear conditioning and requires both the amygdala and the hippocampus (see Blanchard et al 1970, Phillips & LeDoux 1992, Maren et al 1997, Kim & Fanselow 1992, Frankland et al 1998). Areas of the ventral hippocampus (CA1 and subiculum) project to the B and AB nuclei of the amygdala (Canteras & Swanson 1992), and damage to these

areas interferes with contextual conditioning (Maren & Fanselow 1995, Majidishad et al 1996). Hippocampal projection to B and AB thus seem to be involved in contextual conditioning (for a comparison of the amygdala pathways involved in conditioning to a tone CS and to a context, see Figure 4).

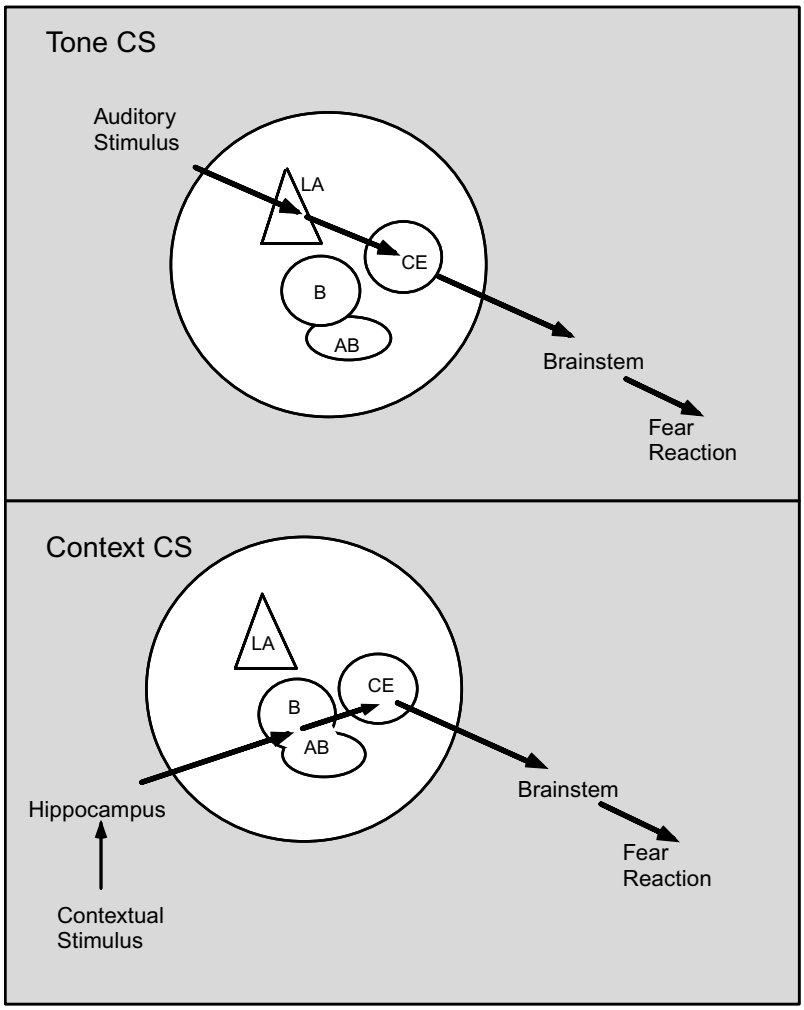

Figure 4 Conditioning to a tone [conditioned stimulus (CS)] involves projections from the auditory system to the lateral nucleus of the amygdala (LA) and from LA to the central nucleus of the amygdala (CE). In contrast, conditioning to the apparatus and other contextual cues present when the CS and unconditioned stimulus are paired involves the representation of the context by the hippocampus and the communication between the hippocampus and the basal (B) and accessory basal (B) nuclei of the amygdala, which in turn project to CE. As for tone conditioning, CE controls the expression of the responses.

US Pathways For conditioning to occur, pathways transmitting the CS and US have to converge in the brain. It is widely believed that the amygdala is a site of plasticity during conditioning, and thus of CS-US convergence. Although the US pathways have received less attention than CS pathways, some progress has nevertheless been made.

Given that LA is the site of termination within the amygdala of pathways carrying acoustic CS inputs, it is important to ask whether US inputs might also reach this area and potentially lead to plasticity in this region. Thalamic areas that receive afferents from the spino-thalamic tract (LeDoux et al 1987) project to LA (LeDoux et al 1990a) (Figure 3). Furthermore, cells in LA are responsive to nociceptive stimulation, and some of the same cells respond to auditory inputs as well (Romanski et al 1993). Thus, the substrate for conditioning (convergence of CS and US information) exists in LA, and as shown below, conditioning induces plasticity in CS-elicited responses in this area.

Cortical areas that process somatosensory stimuli, including nociceptive stimuli, project to LA and some other amygdala nuclei (see Turner & Zimmer 1984, McDonald 1998). Recent behavioral studies show that conditioning can be mediated by US inputs to the amygdala from either thalamic or cortical areas (Shi & Davis 1998), a finding that parallels the conclusions above concerning CS inputs.

The accessory basal amygdala (AB) receives inputs from the posterior thalamus (PO) (LeDoux et al 1990a), which is a terminal region of the spinothalamic tract (LeDoux et al 1987). Although AB does not receive CS inputs from auditory systems, it does receive inputs from the hippocampus (Canteras & Swanson 1992). The hippocampus, as described above, is necessary for forming a representation of the context, and these contextual representations, transmitted from the hippocampus to AB, may be modified by the US inputs to the AB.

CE receives nociceptive inputs from the parabrachial area (Bernard & Besson 1990) and directly from the spinal cord (Burstein & Potrebic 1993). Although the CE does not receive inputs from sensory areas processing acoustic CSs, it is a direct recipient of inputs from LA, and from B and AB. US inputs to CE could be involved in higher-order integration. For example, representations created by CS-US convergence in LA or context-US convergence in AB, after transfer to CE, might converge with and be further modified by nociceptive inputs to CE.

Output Pathways CE projects to brainstem areas that control the expression of fear responses (see LeDoux et al 1988, Kapp et al 1992, Davis 1992). It is thus not surprising that damage to CE interferes with the expression of conditioned fear responses (Kapp et al 1979, Hitchcock & Davis 1986, Iwata et al 1986, van der Kar et al 1991, Gentile et al 1986). In contrast, damage to areas to which CE projects selectively interrupts the expression of individual responses. For example, damage to the lateral hypothalamus affects blood pressure but not freezing responses, and damage to the peraqueductal gray interferes with freezing but not blood pressure responses (LeDoux et al 1988). Similarly, damage to the bed nucleus of the stria terminalis has no effect on either blood pressure or freezing

responses (LeDoux et al 1988), but it disrupts the conditioned release of pituitary-adrenal stress hormones (van der Kar et al 1991). Because CE receives inputs from LA, B, and AB (Pitkänen et al 1997), it is in a position to mediate the expression of conditioned fear responses elicited by both acoustic and contextual CSs (Figure 4).

Intraamygdala Pathways From the findings described above, it would appear that information about a simple CS (such as a tone paired with shock) is directed toward CE (where response execution is initiated) by way of pathways that originate in LA. Although LA projects to CE directly, and by way of B and AB, the direct projection from LA to CE seems to be sufficient because lesions of B and AB have no effect on simple fear conditioning to a tone (Majidishad et al 1996). An alternative was recently proposed by Killcross et al (1997). They argued that a direct projection to CE that bypasses LA can mediate conditioning. However, fibers from auditory areas terminate mainly in LA (see above). Moreover, auditory response latencies in LA are shorter than in CE (both before and after conditioning) (see next section below), which suggests that CE depends on LA for its inputs. These facts aside, though, it is important to point out that the task used to rule out LA as a way station to CE involved hundreds of training trials, whereas the tasks used to implicate LA have involved tens of trials (see Nader & LeDoux 1997). It is possible that the additional training trials used in the Killcross study allowed the brain to learn in a way that is not normally used when fewer trials are given. At most, a direct pathway to CE would be an alternative rather than the main route of transmission through the amygdala.

Physiological Plasticity in the Amygdala Related to Fear Conditioning

With the basic elements of the circuitry understood from lesion studies, researchers have turned to questions about the nature of the plasticity within the amygdala that might underlie fear learning. Fear plasticity in the amygdala has been studied in three closely intertwined ways. First, single-unit recordings have been made in areas of the amygdala implicated in fear conditioning by lesion studies. Second, long-term potentiation (LTP), an experimentally advantageous but artificial form of plasticity, has been studied in these same areas. Third, drugs that block LTP have been infused into amygdala areas where LTP is believed to occur, and effects on the acquisition of conditioned fear behavior assessed. These approaches are summarized below. In addition, evidence regarding the molecular basis of fear learning is described.

Unit Recordings Pathway tracing and lesion studies suggest that LA is the sensory gateway to the amygdala, and thus the first possible site in the amygdala where cells processing the CS might be modified by association with the US in fear conditioning. As already noted, some cells in LA are responsive to both CS

and US inputs. Further, CS-elicited responses in LA cells are modified after pairing with the US (Quirk et al 1995, 1997) (Figure 5). Conditioned plasticity also occurs in the auditory cortex (Weinberger 1995, 1998; Quirk et al 1997). However, the response latencies in LA within trials (<20 ms) and the rate of acquisition (one to three trials) are best explained in terms of direct auditory thalamo-amygdala transmission, rather than cortico-amygdala transmission, because conditioned responses in the auditory cortex occur later both within and across trials (Quirk et al 1997). Plasticity in the auditory thalamus (Weinberger 1995, 1998) could contribute to LA plasticity. Plasticity has also been observed in B (Maren et al 1991, Uwano et al 1995) and CE (Pascoe & Kapp 1985) during aversive conditioning, but the acoustic responses latencies both before and after conditioning are longer than in LA. LA thus seems to be both the initial point of sensory processing and the initial site of plasticity in the amygdala.

Long-Term Potentiation LTP is a physiological procedure pioneered in studies of the hippocampus (Bliss & Lomo 1973) and is believed to engage the cellular mechanisms similar to those that underlie natural learning (see Lynch 1986, Bliss & Collingridge 1993). The most extensively studied form of LTP occurs in the CA1 region of the hippocampus and involves the interaction between presynaptic glutamate and two classes of postsynaptic receptors (Nicoll & Malenka 1995). First, glutamate binds to AMPA receptors and depolarizes the postsynaptic cell. The depolarization allows glutamate to bind to the N-methyl-D-aspartate (NMDA) class of receptors. Calcium then flows into the cell through the NMDA channel and triggers a host of intracellular events that ultimately result in gene induction and synthesis of new proteins (Dudai 1989, Huang et al 1996, Kandel 1997). These then help stabilize the changes over long periods of time.

There have been a number of studies of LTP in the amygdala, mostly involving in vitro brain slices and pathways carrying information from the cortex to LA and B (Chapman et al 1990, Chapman & Bellevance 1992, Gean et al 1993, Huang & Kandel 1998). These studies have led to mixed results regarding the possible role of NMDA receptors in cortico-amygdala LTP, with some studies finding effects (Huang & Kandel 1998) and some not (Chapman & Bellevance 1992). Recent in vitro studies indicate that LTP in the thalamo-amygdala pathway requires postsynaptic calcium but the calcium does not enter through NMDA receptors (Weisskopf et al 1999). Instead, calcium entry appears through L-type voltage-gated calcium channels. These channels have also been implicated in a form of LTP that occurs in the hippocampus (Cavus & Teyler 1996). It has also been shown that prior fear conditioning leads to an enhancement in synaptic responses recorded subsequently in vitro from amygdala slices (McKernan & Schinnick-Gallagher 1997). The receptor mechansisms underlying this form of plasticity have not been elucidated.

LTP has also been studied in vivo in the thalamo-amygdala pathway using recordings of extracellular field potentials (Clugnet & LeDoux 1990, Rogan & LeDoux 1995, Rogan et al 1997). These studies show that LTP occurs in fear

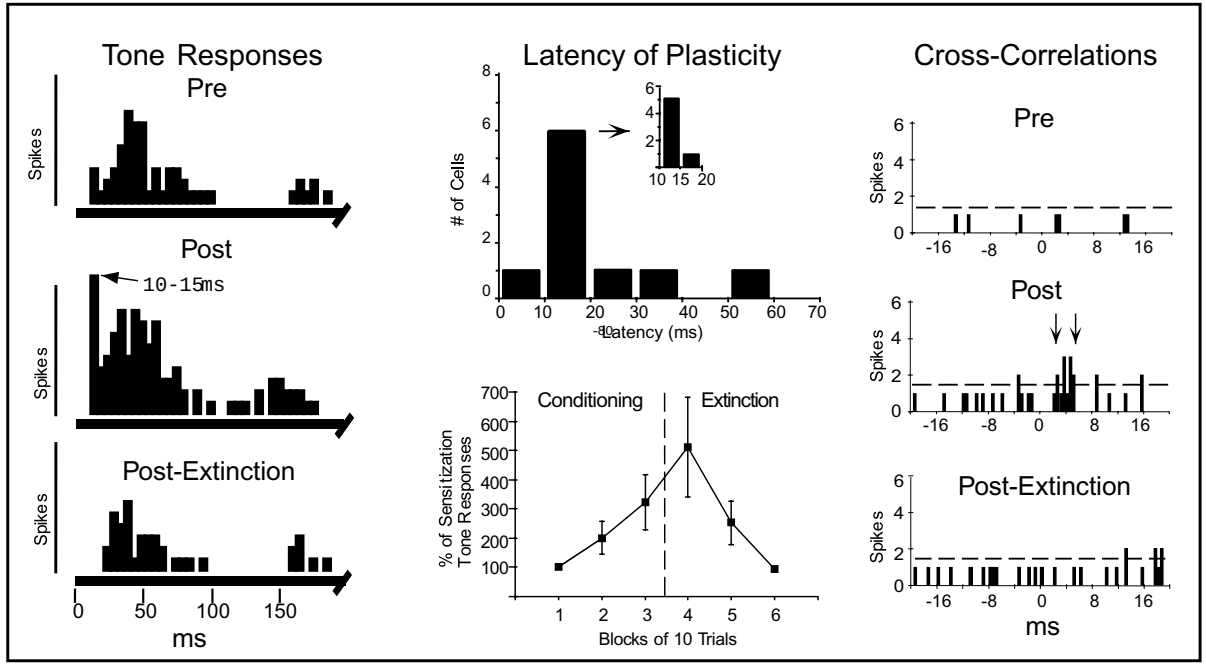

Figure 5 During fear conditioning, cells in the lateral amygdala (LA) of rats show plasticity (increased firing rates) during exposure to a conditioned stimulus tone. (*Left*) Some cells are responsive to tones prior to conditioning (Pre), but their rate of firing increases after conditioning, esepcially the earliest latency response (10–15 ms after tone onset). This early plasticity goes away after extinction. From simultaneously recorded cells, it can be seen that conditioning also leads to an increase in the synchrony of firing, such that cells that were not correlated before conditioning become so afterward (*right panel*). In some cases (not shown), the synchrony remained even after extinction, which suggests that long-term memory may be in part encoded by connections between cells rather than just in the rate of firing. Based on Quirk et al (1995).

processing pathways, that the processing of natural stimuli similar to those used as a CS in conditioning studies is facilitated following LTP induction, and that fear conditioning and LTP induction produce similar changes in the processing of CS-like stimuli (Figure 6). Although exploration of mechanisms are difficult in these in vivo studies, they nevertheless provide some of the strongest evidence to date in any brain system of a relation between natural learning and LTP (Barnes 1995, Eichenbaum 1995, Stevens 1998). LTP has been found in vivo in the hippocampal-amygdala pathway, which is believed to be involved in context conditioning (Maren & Fanselow 1995).

Infusion of Drugs that Block LTP The fact that blockade of NMDA receptors with the drug D,L-2-amino-5-phosphonovaerate (APV) prevents LTP from occurring in the CA1 region of the hippocampus inspired researchers to attempt to prevent fear conditioning by infusion of APV into the amygdala. Initial studies were promising (Miserendino et al 1990). Infusion of APV prior to learning blocked fear conditioning, but infusion proior to testing had no effect. NMDA receptors thus seemed to be involved in the plasticity underlying learning and not in the transmission of signals through the amygdala. However, subsequently both in vivo (Li et al 1995, 1996; Maren & Fanselow 1996) and in vitro (Weisskopf & LeDoux 1999) studies have suggested that NMDA receptors make significant contributions to synaptic transmission in pathways that provide inputs to the amygdala. Furthermore, several studies have found that blockade of NMDA receptors affects both the acquisition and the expression of fear learning (Maren et al 1996, Lee & Kim 1998), which is more consistent with the transmission rather than the plasticity hypothesis, but others have confirmed that acquisition could be affected independently from expression (Gewirtz & Davis 1997).

The contribution of NMDA receptors to fear conditioning and its underlying plasticity, as opposed to synaptic transmission in amygdala circuits, remains unresolved. Given the relatively weak contribution of NMDA receptors to transmission in the cortical input, perhaps the disruption of fear learning is explained by a combination of different effects on the two pathways: blockade of transmission and plasticity in the thalamic pathway, and blockade of plasticity in the cortical pathway. It is also possible that behaviorally significant plasticity occurs downstream from LA input synapses in the amygdala, and that the effects of APV infusions is on this plasticity rather than on the plasticity at input synapses. Additional work is needed.

Intracellular Signaling Mechanisms Some progress has been made in elucidating intracellular signals that underlie long-term memory. These mechanisms are best worked out in invertebrates, but many of the details also seem to apply to hippocampal LTP and spatial learning (Kandel 1997, Huang et al 1996). The general view is that the molecular cascade starts with the influx of calcium during action potentials. The rise in calcium then triggers several kinases and transcription factors, including calmodium-activiated kinase II, mitogen-activated protein

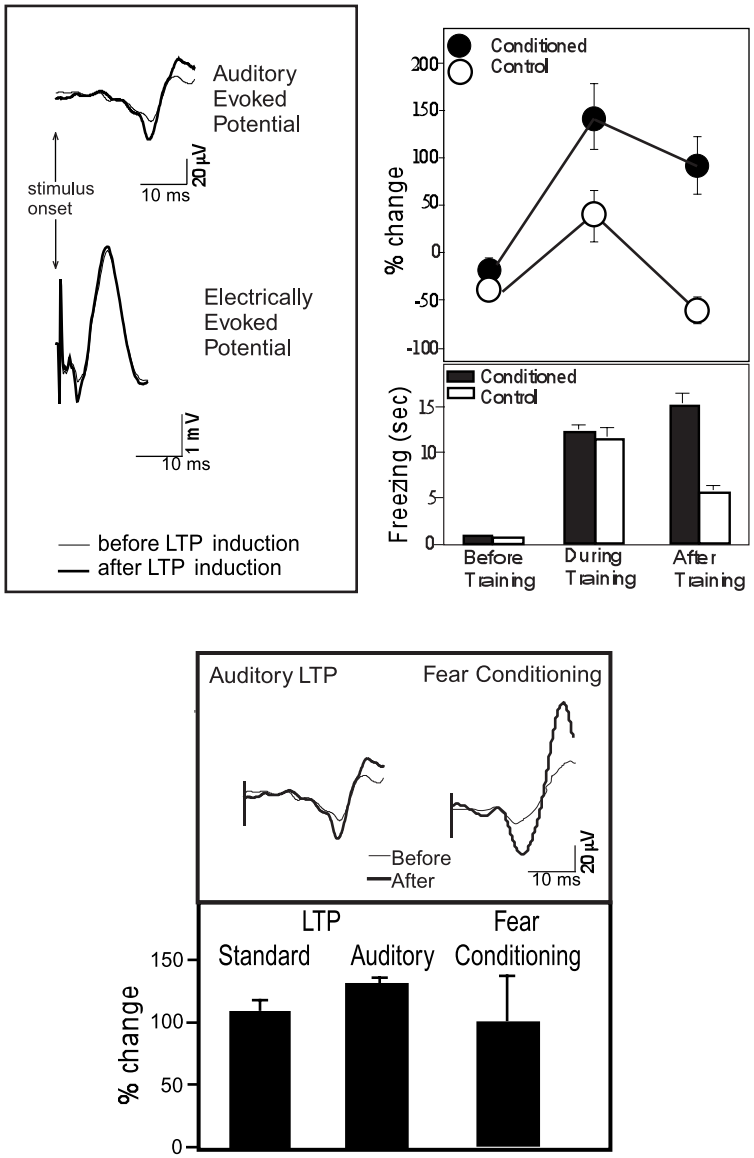

Figure 6 Following high-frquency electrical stimulation of the thalamo-amygdala pathway, low-frequency electrical stimulation of the same pathway or external auditory stimulation elicits a larger evoked potential with a sharper slope than before (*upper left*). This pathway thus shows long-term potentation (LTP), which can be measured by electrical stimulation or natural stimulation of the inputs to the amygdala. Similar changes in auditory-evoked potentials are elicited following fear conditioning (*bottom*). The enhancement of the evoked response by fear conditioning is further illustrated (*upper right panel*). (*Caption continues at bottom of next page.*)

(MAP) kinase, cAMP-dependent kinase, protein kinase C, and cAMP response element binding protein (CREB). These act, possibly in concert, to induce genes and initiate synthesis of new proteins. Many of these same intracellular signals have been implicated in fear conditioning through studies of genetically altered mice (Bourtchouladze et al 1994, Mayford et al 1996, Abel et al 1997). However, recent studies have also turned to the use of specific blockers of various signaling pathways in the brain (Bourtchouladze et al 1998, Atkins et al 1998, Josselyn et al 1998, Schafe et al 1999). For example, Schafe et al (1999) recently found that interference with MAP kinase, protein kinase A, and protein synthesis disrupted long-term (but not short-term) memory of both tone and contextual fear conditioning (Figure 7).

But Is the Amygdala Necessary?

In spite of a wealth of data implicating the amygdala in fear conditioning, some authors have recently suggested that the amygdala is not a site of plasticity or storage during fear conditioning (e.g. Cahill & McGaugh 1998, Vazdarjanova & McGaugh 1998). They argue instead that the amygdala modulates memories that are formed elsewhere. It is clear that multiple memory systems exist in the brain (see Squire et al 1993, Eichenbaum 1994, McDonald & White 1993), and that the amygdala does indeed modulate memories formed in other systems, such as declarative or explicit memories formed through hippocampal circuits or habit memories formed through striatal circuits (Packard et al 1994). However, evidence for a role of the amygdala in modulation should not be confused with evidence against a role in plasticity (Fanselow & LeDoux 1999). That the amygdala is indeed important for Pavlovian fear conditioning is suggested by studies showing that inactivation of the amygdala during learning prevents learning from taking place (e.g. Muller et al 1997, Helmstetter & Bellgowan 1994). Furthermore, if the inactivation occurs immediately after training, then there is no effect on subsequent memory, showing that the effects of pretraining treatment is on

Before conditioning, the auditory-evoked potential elicted by the conditioned stimulus (CS) in the lateral amygdala did not differ in groups that were to be given paired conditioning trials or unpaired presentations of the CS and the unconditioned stimulus. The responses separated during conditioning and remained different after training. (*Bottom*) Behavioral conditioned fear learning in the same animals. The groups do not differ before conditioning. During training both groups "freeze." Freezing in the control group during training was not due to the formation of a conditioned fear memory because as soon as training was terminated the response decreased. Only the paired group showed training-induced enhancement of the auditory-evoked response and of fear behavior. The similarity of the behavioral responses during training, a time when the neural responses differed, indicates that the response after training is unlikely to be due to nonspecific factors related to the expression of the behavior. Based on Rogan & LeDoux (1995) and Rogan et al (1997).

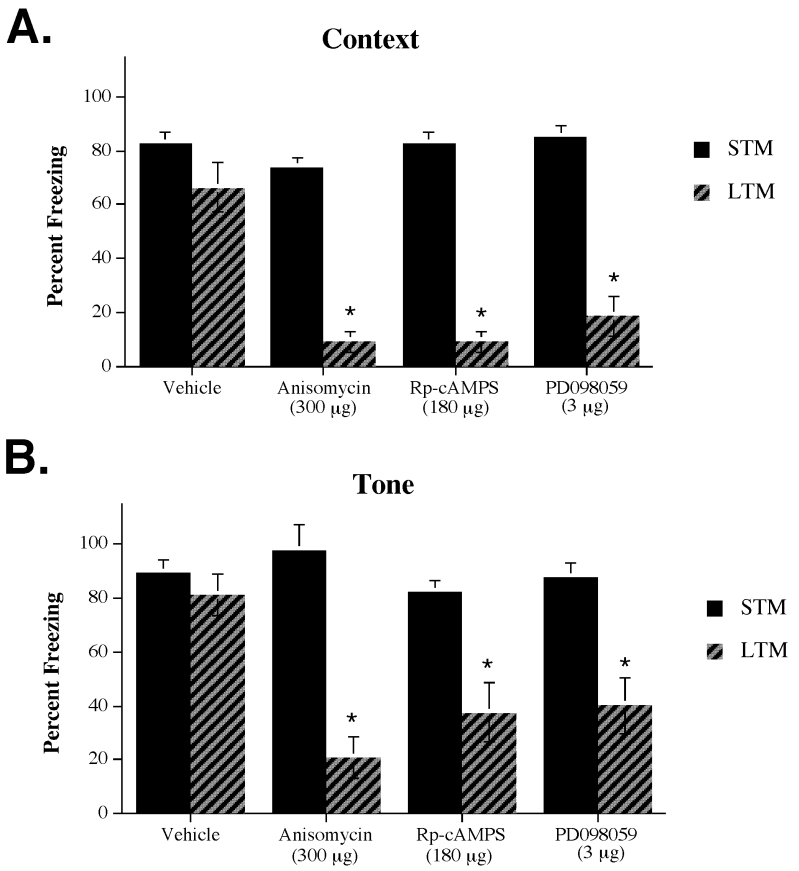

Figure 7 Blockade of protein synthesis (with anisomycin), protein kinase A (with Rp-cAMPS), or mitogen-activated protein kinase (with PD098059) interferes with the expression of long-term memory (LTM), but not short-term memory (STM), for fear conditioning in rats. Drugs were administered intraventricularly immediately after conditioning, and fear respones were tested 24 h later while the rats were drug free. Based on Schafe et al (1999).

learning and not on processes that occur after learning (Wilensky et al 1999). The amygdala thus seems to be essential for Pavlovian fear conditioning and does not modulate its own learning.

Two additional points should be noted. First, although plasticity in the amygdala appears to be required for Pavlovian fear conditioning to occur, the site of long-term memory storage is not known. It is possible that the storage is in the amygdala itself or, alternatively, that the storage is distributed and involves inter-

actions between the amygdala and cortical or other areas. Second, plasticity within the amygdala is probably not required for learning cognitive aspects of fear, as suggest by Cahill & McGaugh (1998). This would explain why humans with amygdala damage are able to lead fairly normal lives in spite of the fact that they have certain deficits in processing danger signals (see below).

THE HUMAN AMYGDALA

Over the past several years, there has been an explosion of interest in the role of the human amygdala in fear. Deficits in the perception of the emotional meaning of faces, especially fearful faces, have been found in patients with amygdala damage (Adolphs et al 1995, Calder et al 1996). Similar results were reported for detection of the emotional tone of voices (Scott et al 1997). Furthermore, damge to the amygdala (Bechara et al 1995) or areas of temporal lobe including the amygdala (LaBar et al 1995) produced deficits in fear conditioning in humans. Functional imaging studies have shown that the amygdala is activated more strongly in the presence of fearful and angry faces than of happy ones (Breiter et al 1996) and that subliminal presentations of such stimuli lead to stronger activations than do freely seen ones (Whalen et al 1998). Fear conditioning also leads to increases in amygdala activity, as measured by functional magnetic resonance imaging (LaBar et al 1998, Buchel et al 1998), and these effects also occur to subliminal stimuli (Morris et al 1998). Additionally, when the activity of the amygdala during fear conditioning is cross correlated with the activity in other regions of the brain, the strongest relations are seen with subcortical (thalamic and collicular) rather than cortical areas, further emphasizing the importance of the direct thalamao-amygdala pathway in the human brain (Morris et al 1999). Other aspects of emotion and the human brain area are reviewed by Davidson & Irwin (1999), Phelps & Anderson (1997), Cahill & McGaugh (1998).

CLINICAL IMPLICATIONS

Although it is clear that studies of acute fear responses elicited by conditioned fear stimuli cannot account for all aspects of fear and fear disorders, there is growing enthusiasm for the notion that fear learning processes similar to those occurring in fear conditioning experiments might indeed be an important factor in certain anxiety disorders. For example, fear conditioning models of posttraumatic stress disorder and panic disorder (Pitman & Orr 1999, Goddard et al 1998) have been proposed recently by researchers in these fields.

Earlier in this century, the notion that conditioned fear contributes to phobias and related fear disorders was fairly popular. However, this idea fell out of favor because laboratory fear conditioning seemed to produce easily extinguishable fear, whereas clinical fear is difficult to treat. The notion arose that fear disorders

involve a special kind of learning, called prepared learning, where the CS is biologically significant rather than neutral (Seligman 1971, Marks 1987, Öhman 1992). Although preparedness may indeed contribute, there is another factor to consider. In studies of rats, Morgan et al (1993; but see Gewirtz & Davis 1997) found that easily extinguished fear could be converted into difficult-to-extinguish fear in rats with damage to the medial prefrontal cortex. This suggested that alterations in the organization of the medial prefrontal regions might predispose certain people in some circumstances (such as stressful situations) to learn fear in a way that is difficult to extinguish (treat) under normal circumstances. These changes could come about because of genetic or experiential factors, or some combination.

COGNITIVE-EMOTIONAL INTERACTIONS IN THE BRAIN FROM THE PERSPECTIVE OF FEAR CONDITIONING

One of the key issues for the coming years is to integrate research on emotion and cognition. As already noted, this will not be achieved by simply linking research on the limbic system with research on the cortex. An approach that offers more anatomical precision on the emotion side is needed. Studies of fear conditioning provide a framework for beginning such an endeavor. Although this bottom up approach focused on fear may seem needlessly tedious, it is possible that once other emotions are understood in sufficient anatomical detail, some general principles that apply to other emotions will emerge. For the time being, it is best to restrict the discussion to fear circuits and their interactions with cognitive systems. Thus, in this section we consider how fear processing by the amygdala is influenced by and can influence perceptual, attentional, and memory functions of the cortex.

The amygdala receives inputs from cortical sensory processing regions of each sensory modality and projects back to these as well (Amaral et al 1992, Turner et al 1980, McDonald 1998). As shown above, these projections allow the amygdala to determine whether danger is present in the sensory world. But in addition to processing the significance of external stimuli, the amygdala can also influence sensory processing occurring in cortical areas. The amygdala only receives inputs from the late stages of cortical sensory processing, but it projects back to the earliest stages (Turner et al 1980, Amaral et al 1992). Thus, once the amygdala is activated by a sensory event from the thalamus or cortex, it can begin to regulate the cortical areas that project to it, controlling the kinds of inputs it receives from the cortex. The amygdala also influences cortical sensory processes indirectly, by way of projections to various "arousal" networks, including the basal forebrain cholinergic system, the brainstem cholinergic system, and the locus cerouleus noradrenergic system, each of which innervates widespread areas of the cortex (e.g. Aston-Jones et al 1996, Gallagher & Holland 1994, Holland & Gallagher

1999, Kapp et al 1992, Weinberger 1995). Thus, once the amygdala detects danger, it can activate these arousal systems, which can then influence sensory processing. The bodily responses initiated by the amygdala can also influence cortical areas, by way of feedback either from proprioceptive or visceral signals or hormones (e.g. McGaugh et al 1995, Damasio 1994). Amygdala regulation of the cortex by either direct or indirect routes could facilitate the processing of stimuli that signal danger even if such stimuli occur outside the attention field (Armony et al 1996, 1998; Armony & LeDoux 1999).

In humans, damage to the amygdala interferes with implicit emotional memories but not explicit memories about emotions, whereas damage to the medial temporal lobe memory system interferes with explicit memories about emotions but not with implicit emotional memories (Bechara et al 1995, LaBar et al 1995). Although explicit memories with and without emotional content are formed by way of the medial temporal lobe system, those with emotional content differ from those without such content. The former tend to be longer lasting and more vivid (see Christianson 1989, Cahill & McGaugh 1998). Lesions of the amygdala or systemic administration of a beta-adrenergic antagonist prevent this amplifying effect of emotion on declarative memory (Cahill & McGaugh 1998), which suggests that the amygdala can modulate the storage of explicit memories in cortical areas. At the same time, the medial temporal lobe memory system projects to the amygdala (Amaral et al 1992). Retrieval of long-term memories of traumatic events may trigger fear reactions by way of these projections to the amygdala.

Although there has been relatively little work on the role of the amygdala in cognitive-emotional interactions, the importance of the amygdala as a bridge between emotion and attention was pointed out over thirty years ago (e.g. Pribram & Melges 1969). Given the extensive connections between the amygdala and cortical areas, this topic is begging for research.

WHAT ABOUT FEELINGS?

Consciousness is an important part of the study of emotion and other mental processes. Although we are far from understanding what consciousness is, a number of theorists have proposed that it may be related to working memory, a serially organized mental workspace where things can be compared and contrasted and mentally manipulated (Baddeley 1992). A variety of studies of humans and nonhuman primates point to the prefrontal cortex, especially the dorsolateral prefrontal areas—as well as the anterior cingulate and orbital cortical regions—as being involved in working memory (Fuster 1998, Goldman-Rakic 1996, Braver et al 1997, Carter et al 1998). Immediately present stimuli and stored representations are integrated in working memory by way of interactions between prefrontal areas, sensory processing systems (which serve as short-term memory buffers, as well as perceptual processors), and the long-term explicit (declarative) memory system involving the hippocampus and related areas of the temporal lobe.

In the case of an affectively charged stimulus, such as a trigger of fear, the same sorts of processes will be called upon as for stimuli without emotional implications, but in addition, working memory will become aware of the fact that the fear system of the brain has been activated (Figure 8). This additional information, when added to perceptual and mnemonic information about the object or event, could be the condition for the subjective experience of an emotional state of fear (LeDoux 1996).

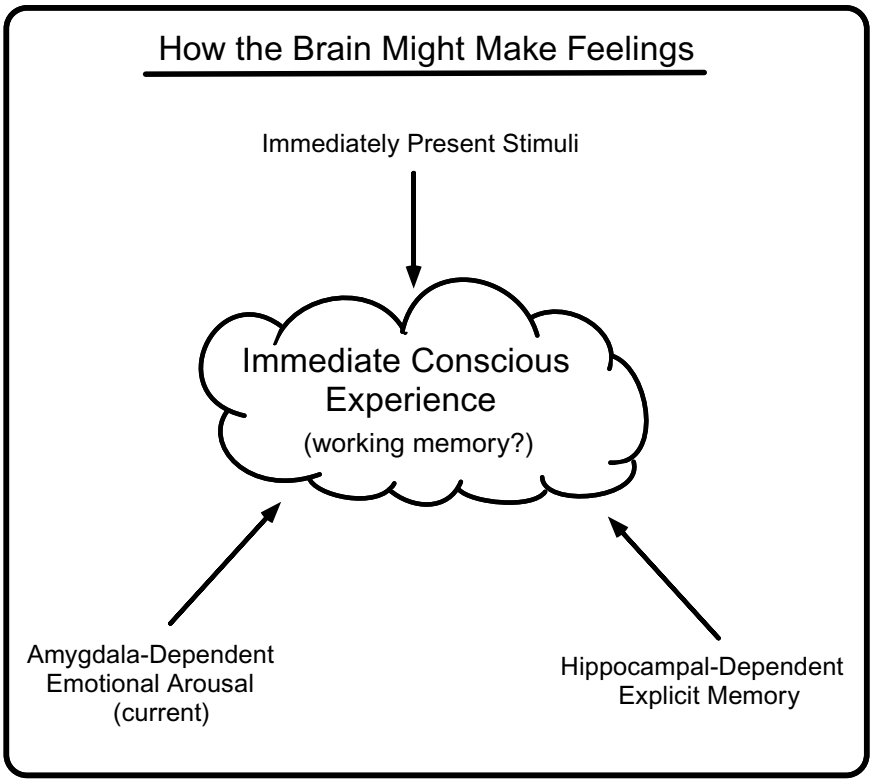

Figure 8 Conscious experiences are often said to reflect the contents of working memory. In this sense, a conscious emotional experience may not be that different from any other kind of conscious experience. The difference would be more in the systems that are providing inputs to working memory rather than in the mechanisms of consciousness itself. In the case of fearful experiences, or fearful feelings, the conscious emotion may be the result of some immediately present stimulus triggering long-term explict memories and amygdala activation. The simultaneous representation in working memory of the outputs of these three, and perhaps other, systems may be the stuff that fearful feelings are made of. Other feelings would come about similarly but would not necessarily involve the amygdala.

By way of projections to cortical areas, the amygdala can influence the operation of perceptual and short-term memory processes, as well as processes in higher-order areas. Although the amygdala does not have extensive connections with the dorsolateral prefrontal cortex, it does communicate with the anterior cingulate and orbital cortex, two other components of the working memory network. But in addition, the amygdala projects to nonspecific systems involved in the regulation of cortical arousal and it controls bodily responses (behavioral, autonomic, endocrine), which then provide feedback that can influence cortical processing indirectly. Thus, working memory receives a greater number of inputs, and receives inputs of a greater variety, in the presence of an emotional stimulus than in the presence of other stimuli. These extra inputs may just be what is required to add affective charge to working memory representations, and thus to turn subjective experiences into emotional experiences.

CONCLUSION

Research on the emotional brain has progressed significantly in recent years, largely as a result of a highly focused approach centered on the study of fear mechanisms, and especially the mechanisms underlying fear conditioning. This work has mapped out pathways involved in fear learning in both experimental animals and humans, and it has begun to shed light on interactions between emotional and cognitive processes in the brain. Although the focus on fear conditioning has its limits, it has proven valuable as a research strategy and provides a foundation upon which to build a broader understanding of mind and brain.

At the same time, there is a disturbing rush to embrace the amygdala as the new center of the emotional brain. It seems unlikely that the amygdala is the answer to how all emotions work, and it may not even explain how all aspects of fear work. There is some evidence that the amygdala participates in postitive emotional behaviors, but that role is still poorly understood. If an amygdala theory of emotion is on the horizon, let it get there by data rather than by faith.

Neuroscience meetings these days have numerous papers on the role of the brain in emotion, affect, hedonic tone, and the like. Unless these vague concepts can be operationalized, as was done in the work on fear, they are likely to impede, if not recede, the progress. The future of emotion research can be bright if we keep in mind the way that emotion became respectable again: by focusing on a psychologically well-defined aspect of emotion, by using an experimental approach that simplified the problem in such a way as to make it tractable, by circumventing vague and poorly defined aspects of emotion, and by removing subjective experience as a roadblock to experimentation. This is not to suggest that the hard problems should not be worked on but instead that they should be worked on in a way that advances the field.

LITERATURE CITED

Abel T, Nguyen PV, Barad M, Deuel TAS, Kandel ER, Bourtchuladze R. 1997. Genetic demonstration of a role for PKA in the phase of LTP and in hippocampus-based long-term memory. *Cell* 88:615–26

Adolphs R, Tranel D, Damasio H, Damasio AR. 1995. Fear and the human amygdala. *J. Neurosci.* 15:5879–91

Aggleton JP, ed. 1992. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction.* New York: Wiley-Liss

Aggleton JP, Mishkin M. 1986. The amygdala: sensory gateway to the emotions. In *Emotion: Theory, Research and Experience*, ed. R Plutchik, H Kellerman, 3:281–99. Orlando, FL: Academic

Amaral DG, Price JL, Pitkänen A, Carmichael ST. 1992. Anatomical organization of the primate amygdaloid complex. See Aggleton 1992, pp. 1–66

Armony JL, LeDoux JE. 1999. How danger is encoded: towards a systems, cellular, and computational understanding of cognitive-emotional interactions in fear circuits. See Gazzaniga 1999. In press

Armony JL, Quirk GJ, LeDoux JE. 1998. Differential effects of amygdala lesions on early and late plastic components of auditory cortex spiketrains during fear conditioning. *J. Neurosci.* 18:2592–601

Armony JL, Servan-Schreiber D, Cohen JC, LeDoux JE. 1996. Emotion and cognition interactions in the thalalmo-cortico-amygdala network: theory and model. *Cogn. Neurosci. Soc. Abstr.* 3:76

Armony JL, Servan-Schreiber D, Romanski LM, Cohen JD, LeDoux JE. 1997. Stimulus generalization of fear responses: effects of auditory cortex lesions in a computational model and in rats. *Cereb. Cortex* 7:157–65

Aston-Jones G, Rajkowski J, Kubiak P, Valentino RJ, Shipley MT. 1996. Role of the locus coeruleus in emotional activation. *Prog. Brain. Res.* 107:379–402

Atkins CM, Selcher JC, Petraitis JJ, Trzaskos JM, Sweatt JD. 1998. The MAPK cascade is required for mammalian associative learning. *Nat. Neurosci.* 1:602–9

Baddeley A. 1992. Working memory. *Science.* 255:556–59

Barnes CA. 1995. Involvement of LTP in memory: Are we searching under the streetlight? *Neuron* 15:751–54

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. 1995. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science* 269: 1115–18

Bernard JF, Besson JM. 1990. The spino(trigemino)pontoamygdaloid pathway: electrophysiological evidence for an involvement in pain processes. *J. Neurophysiol.* 63:473–89

Blanchard RJ, Blanchard DC, Fial RA. 1970. Hippocampal lesions in rats and their effect on activity, avoidance, and aggression. *J. Comp. Physiol. Psychol.* 71(1):92–102

Bliss TVP, Collingridge GL. 1993. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361:31–39

Bliss TVP, Lomo T. 1973. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J. Physiol.* 232:331–56

Bourtchouladze R, Abel T, Berman N, Gordon R, Lapidus K, Kandel ER. 1998. Different training procedures recruit either one or two criticial periods for contextual memory consolidation, each of which requires protein synthesis and PKA. *Learn. Mem.* 5:365–74

Bourtchouladze R, Frenguelli B, Blendy J, Cioffi D, Schutz G, Silva AJ. 1994. Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell* 79:59–68

Braver TS, Cohen JD, Jonides J, Smith EE, Noll DC. 1997. A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage* 5(1):49–62

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, et al. 1996. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 17:875–87

Brodal A, ed. 1982. *Neurological Anatomy*. New York: Oxford Univ. Press

Buchel C, Morris J, Dolan RJ, Friston KJ. 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* 20:947–57

Burstein R, Potrebic S. 1993. Retrograde labeling of neurons in the spinal cord that project directly to the amygdala or the orbital cortex in the rat. *J. Comp. Neurol.* 335:469

Cahill L, McGaugh JL. 1998. Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.* 21:294–99

Calder AJ, Young AW, Rowland D, Perrett D, Hodges JR, Etcoff NL. 1996. Facial emotion recognition after bilateral amygdala damage: differentially severe impairment of fear. *Cogn. Neuropsychol.* 13:699–745

Campeau S, Davis M. 1995. Involvement of the central nucleus and basolateral complex of the amygdala in fear conditioning measured with fear-potentiated startle in rats trained concurrently with auditory and visual conditioned stimuli. *J. Neurosci.* 15:2301–11

Canteras NS, Swanson LW. 1992. Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHAL anterograde tract-tracing study in the rat. *J. Comp. Neurol.* 324:180–94

Cassell MD, Freedman LL, Shi C. 1999. The intrinsic organization of the central extended amygdala. *Ann. NY Acad. Sci.* 877:217–41

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–49

Cavus I, Teyler T. 1996. Two forms of long-term potentiation in area CA1 activate different signal transduction cascades. *J. Neurophysiol.* 76:3038–47

Chapman PF, Bellavance LL. 1992. NMDA receptor-independent LTP in the amygdala. *Synapse* 11:310–18

Chapman PF, Kairiss EW, Keenan CL, Brown TH. 1990. Long-term synaptic potentiation in the amygdala. *Synapse* 6:271–78

Christianson SA. 1989. Flashbulb memories: special, but not so special. *Mem. Cogn.* 17:435–43

Clugnet MC, LeDoux JE. 1990. Synaptic plasticity in fear conditioning circuits: induction of LTP in the lateral nucleus of the amygdala by stimulation of the medial geniculate body. *J. Neurosci.* 10:2818–24

Damasio A, 1994. *Descarte's Error: Emotion, Reason, and the Human Brain.* New York: Gosset/Putnam

Davidson RJ, Irwin W. 1999. The functional neuroanatomy of emotion and affective style. *Trends Cogn. Sci.* 3:211–21

Davis M. 1992. The Role of the Amygdala in Conditioned Fear. See Aggleton 1992, pp. 255–306

de Olmos J, Alheid G, Beltramino C. 1985. Amygdala. In *The Rat Nervous System*, ed. G Paxinos, pp. 223–334. Orlando, FL: Academic

Dudai Y. 1989. *The Neurobiology of Memory*. New York: Oxford Univ. Press

Eichenbaum H. 1994. The hippocampal system and declarative memory in humans and animals: experimental analysis and historical origins. In *Memory Systems*, ed. DL Schacter, E Tulving, pp. 147–201. Cambridge, MA: MIT Press

Eichenbaum H. 1995. The LTP-memory connection. *Nature* 378:131–32

Ekman P, Davidson R. 1994. *The Nature of Emotion: Fundamental Questions.* New York: Oxford Univ. Press

Everitt BJ, Robbins TW. 1992. Amygdala-ventral striatal interactions and reward-related processes. See Aggleton 1992, pp. 401–29

Fanselow MS. 1994. Neural organization of the defensive behavior system responsible for fear. *Psychon. Bull. Rev.* 1:429–38

Fanselow MS, LeDoux JE. 1999. Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala. *Neuron* 23:229–32

Frankland PW, Cestari V, Filipkowski RK, McDonald RJ, Silva A. 1998. The dorsal hippocampus is essential for context discrimination, but not for contextual conditioning. *Behav. Neurosci.* 112:863–74

Fuster JM. 1998. Distributed memory for both short and long term. *Neurobiol. Learn. Mem.* 70:268–74

Gaffan D. 1992. Amygdala and the memory of reward. See Aggleton 1992, pp. 471–83

Gallagher M, Holland PC. 1994. The amygdala complex: multiple roles in associative learning and attention. *Proc. Natl. Acad. Sci. USA* 91:11771–76

Gardner H. 1987. *The Mind's New Science: A History of the Cognitive Revolution.* New York: Basic Books

Gazzaniza MS, ed. 1999. *The Cognitive Neurosciences.* Cambridge, MA: MIT Press. In press

Gean P-W, Chang F-C, Hung C-R. 1993. Use-dependent modification of a slow NMDA receptor-mediated synaptic potential in rat amygdalar slices. *J. Neurosci. Res.* 34:635–41

Gentile CG, Jarrell TW, Teich A, McCabe PM, Schneiderman N. 1986. The role of amygdaloid central nucleus in the retention of differential Pavlovian conditioning of bradycardia in rabbits. *Behav. Brain Res.* 20:263–73

Gewirtz JC, Davis M. 1997. Second-order fear conditioning prevented by blocking NMDA receptors in amygdala. *Nature* 388:471–74

Goddard AW, Gorman JM, Charney DS. 1998. Neurobiology of panic disorder. In *Panic Disorder and its Treatment,* ed. JF Rosenblaum, MH Pollack, pp. 57–92. New York: Dekker

Goldman-Rakic PS. 1996. Regional and cellular fractionation of working memory. *Proc. Natl. Acad. Sci. USA* 93:13473–80

Gray JA. 1982. *The Neuropsychology of Anxiety.* New York: Oxford Univ. Press

Helmstetter FJ, Bellgowan PS. 1994. Effects of muscimol applied to the basolateral amygdala on acquisition and expression of contextual fear conditioning in rats. *Behav. Neurosci.* 108:1005–9

Hitchcock J, Davis M. 1986. Lesions of the amygdala but not of the cerebellum or red nucleus block conditioned fear as measured with the potentiated startle paradigm. *Behav. Neurosci.* 100:11–22

Holland PC, Gallagher M. 1999. Amygdala circuitry in attentional and representational processes. *Trends Cogn. Sci.* 3:65–73

Huang YY, Kandel ER. 1998. Postsynaptic induction and PKA-dependent expression of LTP in the lateral amygdala. *Neuron* 21:169–78

Huang YY, Nguyen PV, Abel T, Kandel ER. 1996. Long-lasting forms of synaptic potentiation in the mamalian hippocampus. *Learn. Mem.* 3:74–85

Isaacson RL. 1982. *The Limbic System.* New York: Plenum

Iwata J, LeDoux JE, Meeley MP, Arneric S, Reis DJ. 1986. Intrinsic neurons in the amygdaloid field projected to by the medial geniculate body mediate emotional responses conditioned to acoustic stimuli. *Brain Res.* 383:195–214

Jarrell TW, Gentile CG, Romanski LM, McCabe PM, Schneiderman N. 1987. Involvement of cortical and thalamic auditory regions in retention of differential bradycardia conditioning to acoustic conditioned stimulii in rabbits. *Brain Res.* 412:285–94

Josselyn SA, Carlezon, WA, Shi C, Neve RL, Nestler EJ, Davis M. 1998. Overexpression of CREB in the amygdala of rats facilitates long term memory formation. *Soc. Neurosci. Abs.*

Kaada BR. 1960. Cingulate, posterior orbital, anterior insular and temporal pole cortex. In

Handbook of Physiology: Neurophysiology II, ed. J Field, HJ Magoun, VE Hall, pp. 1345–72. Washington, DC: Am. Physiol. Soc.

Kandel ER. 1997. Genes, synapses, and long-term memory. *J. Cell Physiol.* 173:124–25

Kapp BS, Frysinger RC, Gallagher M, Haselton J. 1979. Amygdala central nucleus lesions: effect on heart rate conditioning in the rabbit. *Physiol. Behav.* 23:1109–17

Kapp BS, Whalen PJ, Supple WF, Pascoe JP. 1992. Amygdaloid contributions to conditioned arousal and sensory information processing. See Aggleton 1992, pp. 229–54

Kihlstrom JF. 1987. The cognitive unconscious. *Science* 237:1445–52

Killcross S, Robbins TW, Everitt BJ. 1997. Different types of fear-conditioned behavior mediated by separate nuclei within amygdala. *Nature* 388:377–80

Kim JJ, Fanselow MS. 1992. Modality-specific retrograde amnesia of fear. *Science* 256: 675–77

Kotter R, Meyer N. 1992. The limbic system: a review of its empirical foundation. *Behav. Brain Res.* 52:105–27

Krettek JE, Price JL. 1978. A description of the amygdaloid complex in the rat and cat with observations on intra-amygdaloid axonal connections. *J. Comp. Neurol.* 178:255–80

LaBar KS, Gatenby JC, Gore JC, LeDoux JE, Phelps EA. 1998. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron* 20:937–45

LaBar KS, LeDoux JE, Spencer DD, Phelps EA. 1995. Impaired fear conditioning following unilateral temporal lobectomy in humans. *J. Neurosci.* 15:6846–55

LeDoux JE. 1987. Emotion. In *Handbook of Physiology. 1: The Nervous System*, ed. F Plum, pp. 419–60. Bethesda, MD: Am. Physiol. Soc.

LeDoux JE. 1991. Emotion and the limbic system concept. *Concepts Neurosci.* 2:169–99

LeDoux JE. 1992. Emotion and the Amygdala. See Aggleton 1992, pp. 339–51

LeDoux JE, ed. 1996. *The Emotional Brain.* New York: Simon & Schuster

LeDoux JE, Cicchetti P, Xagoraris A, Romanski L-M. 1990a. The lateral amygdaloid nucleus: Sensory interface of the amygdala in fear conditioning. *J. Neurosci.* 10:1062–69

LeDoux JE, Farb CF, Ruggiero DA. 1990b. Topographic organization of neurons in the acoustic thalamus that project to the amygdala. *J. Neurosci.* 10:1043–54

LeDoux JE, Iwata J, Cicchetti P, Reis DJ. 1988. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *J. Neurosci.* 8:2517–29

LeDoux JE, Ruggiero DA, Forest R, Stornetta R, Reis DJ. 1987. Topographic organization of convergent projections to the thalamus from the inferior colliculus and spinal cord in the rat. *J. Comp. Neurol.* 264:123–46

Lee H, Kim JJ. 1998. Amygdalar NMDA receptors are critical for new fear learning in previously fear-conditioned rats. *J. Neurosci.* 18:8444–54

Lewis M, Haviland J, eds. 1992. *Handbook of Emotions.* New York: Guilford

Li X, Phillips RG, LeDoux JE. 1995. NMDA and non-NMDA receptors contribute to synaptic transmission between the medial geniculate body and the lateral nucleus of the amygdala. *Exp. Brain Res.* 105:87–100

Li XF, Stutzmann GE, LeDoux JL. 1996. Convergent but temporally separated inputs to lateral amygdala neurons from the auditory thalamus and auditory cortex use different postsynaptic receptors: *in vivo* intracellular and extracellular recordings in fear conditioning pathways. *Learn. Mem.* 3:229–42

Livingston KE, Escobar A. 1971. Anatomical bias of the limbic system concept. *Arch. Neurol.* 24:17–21

Lynch G, ed. 1986. *Synapses, Circuits, and the Beginnings of Memory.* Cambridge, MA: MIT Press

MacLean PD. 1949. Psychosomatic disease and the "visceral brain": recent develop-

ments bearing on the Papez theory of emotion. *Psychosom. Med.* 11:338–53

MacLean PD. 1952. Some psychiatric implications of physiological studies on frontotemporal portion of limbic system (visceral brain). *Electroencephalogr. Clin. Neurophysiol.* 4:407–18

MacLean PD. 1970. The triune brain, emotion and scientific bias. See Schmitt 1970, pp. 336–49

Majidishad P, Pelli DG, LeDoux JE. 1996. Disruption of fear conditioning to contextual stimuli but not to a tone by lesions of the accessory basal nucleus of the amygdala. *Soc. Neurosci. Abstr.* 22:1116

Maren S, Aharonov G, Fanselow MS. 1997. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behav. Brain Res.* 88:261–74

Maren S, Aharonov G, Stote DL, Fanselow MS. 1996. N-methyl-**d**-aspartate receptors in the basolateral amygdala are required for both acquisition and expression of the conditional fear in rats. *Behav. Neurosci.* 110:1365–74

Maren S, Fanselow MS. 1995. Synaptic plasticity in the basolateral amygdala induced by hippocampal formation stimulation *in vivo*. *J. Neurosci.* 15:7548–64

Maren S, Poremba A, Gabriel M. 1991. Basolateral amygdaloid multi-unit neuronal correlates of discriminative avoidance learning in rabbits. *Brain. Res.* 549:311–16

Marks I, ed. 1987. *Fears, Phobias, and Rituals: Panic, Anxiety and Their Disorders.* New York: Oxford Univ. Press

Mascagni F, McDonald AJ, Coleman JR. 1993. Corticoamygdaloid and corticocortical projections of the rat temporal cortex: a phaseolus vulgaris leucoagglutinin study. *Neuroscience* 57:697–715

Mayford M, Bach ME, Huang Y-Y, Wang L, Hawkins RD, Kandel ER. 1996. Control of memory formation through regulated expression of a CaMKII transgene. *Science* 274:1678–83

McDonald AJ. 1998. Cortical pathways to the mammalian amygdala. *Prog. Neurobiol.* 55:257–332

McDonald RJ, White NM. 1993. A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. *Behav. Neurosci.* 107:3–22

McGaugh JL, Mesches MH, Cahill L, Parent MB, Coleman-Mesches K, Salinas JA. 1995. Involvement of the amygdala in the regulation of memory storage. In *Plasticity in the Central Nervous System,* ed. JL McGaugh, F Bermudez-Rattoni, RA Prado-Alcala, pp. 18–39. Mahwah, NJ: Erlbaum

McKernan MG, Shinnick-Gallagher P. 1997. Fear conditioning induces a lasting potentiation of synaptic currents in vitro. *Nature* 390:607–11

Miserendino MJD, Sananes CB, Melia KR, Davis M. 1990. Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. *Nature* 345:716–18

Morgan MA, Romanski LM, LeDoux JE. 1993. Extinction of emotional learning: contribution of medial prefrontal cortex. *Neurosci. Lett.* 163:109–13

Morris JS, Ohman A, Dolan RJ. 1998. Conscious and unconscious emotional learning in the human amygdala. *Nature* 393:467–70

Morris JS, Ohman A, Dolan RJ. 1999. A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc. Natl. Acad. Sci. USA* 96:1680–85

Muller J, Corodimas KP, Fridel Z, LeDoux JE. 1997. Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit CS and to contextual stimuli. *Behav. Neurosci.* 111:683–91

Nader K, LeDoux JE. 1997. Is it time in invoke multiple fear learning system? *Trends Cogn. Sci.* 1:241–44

Nauta WJH. 1979. Expanding borders of the limbic system concept. In *Functional Neurosurgery,* ed. T Rasmussen, R Marino, pp. 7–23. New York: Raven

Nauta WJH, Karten HJ. 1970. A general profile of the vertebrate brain, with sidelights on the ancestry of cerebral cortex. See Schmitt 1970, pp. 7–26

Neisser U. 1967. *Cognitive Psychology.* Englewood Cliffs, NJ: Prentice Hall

Nicoll RA, Malenka RC. 1995. Contrasting properties of two forms of long-term potentiation in the hippocampus. *Nature* 377:115–18

Öhman A. 1992. Fear and anxiety as emotional phenomena: clinical, phenomenological, evolutionary perspectives, and information-processing mechanisms. See Lewis & Haviland, pp. 511–36

Ono T, Nishijo H. 1992. Neurophysiological basis of the Kluver-Bucy syndrome: responses of monkey amygdaloid neurons to biologically significant objects. See Aggleton 1992, pp. 167–90

Packard MG, Cahill L, McGaugh JL. 1994. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proc. Natl. Acad. Sci. USA* 91:8477–81

Panksepp J. 1998. *Affective Neuroscience: The Foundations of Human and Animal Emotions.* New York: Oxford Univ. Press

Paré D, Smith Y, Paré JF. 1995. Intra-amygdaloid projections of the basolateral and basomedial nuclei in the cat: *Phaseolus vulgaris*–leucoagglutinin anterograde tracing at the light and electron microscopic level. *Neuroscience* 69:567–83

Pascoe JP, Kapp BS. 1985. Electrophysiological characteristics of amygdaloid central nucleus neurons during Pavlovian fear conditioning in the rabbit. *Behav. Brain. Res.* 16:117–33

Pavlov IP. 1927. *Conditioned Reflexes.* New York: Dover

Phelps EA, Anderson AK. 1997. Emotional memory: What does the amygdala do? *Curr. Biol.* 7:311–14

Phillips RG, LeDoux JE. 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav. Neurosci.* 106:274–85

Pitkänen A, Savander V, LeDoux JL. 1997. Organization of intra-amygdaloid circuitries: an emerging framework for understanding functions of the amygdala. *Trends Neurosci.* 20:517–23

Pitman RK, Orr SP. 1999. Post-traumatic stress disorder: emotion, conditioning, and memory. See Gazzaniga 1999. In press

Pribram KH, Melges FT. 1969. Psychophysiological basis of emotion. In *Handbook of Clinical Neurology,* ed. PJ Vinken, GW Bruyn, pp. 316–42. Amsterdam: North-Holland Publ.

Pribram KH, Reitz S, McNeil M, Spevack AA. 1979. The effect of amygdalectomy on orienting and classical conditioning in monkeys. *Pavlov. J. Biol. Sci.* 14:203–17

Quirk GJ, Armony JL, LeDoux JE. 1997. Fear conditioning enhances different temporal components of toned-evoked spike trains in auditory cortex and lateral amygdala. *Neuron* 19:613–24

Quirk GJ, Repa JC, LeDoux JE. 1995. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. *Neuron* 15:1029–39

Rogan M, Staubli U, LeDoux J. 1997. Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* 390:604–7

Rogan MT, LeDoux JE. 1995. LTP is accompanied by commensurate enhancement of auditory—evoked responses in a fear conditioning circuit. *Neuron* 15:127–36

Rolls ET. 1992. Neurophysiology and functions of the primate amygdala. See Aggleton 1992, pp. 143–65

Rolls ET. 1999. *The Brain and Emotion.* New York: Oxford Univ. Press

Romanski LM, LeDoux JE. 1992. Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala projections as auditory conditioned stimulus pathways. *J. Neurosci.* 12:4501–9

Romanski LM, LeDoux JE. 1993. Information cascade from primary auditory cortex to the amygdala: corticocortical and cortico-

amygdaloid projections of temporal cortex in the rat. *Cereb. Cortex.* 3:515–32

Romanski LM, LeDoux JE, Clugnet MC, Bordi F. 1993. Somatosensory and auditory convergence in the lateral nucleus of the amygdala. *Behav. Neurosci.* 107:444–50

Schafe GE, Nadel NV, Sullivan GM, Harris A, LeDoux JE. 1999. Memory consolidation for contextual and auditory fear conditioning is dependent on protein synthesis, PKA, and MAP kinase. *Learn. Mem.* 6:97–110

Schmitt FO, ed. 1970. *Neurosciences: Second Study Program.* New York: Rockefeller Univ. Press

Scott SK, Young AW, Calder AJ, Hellawell DJ, Aggleton JP, Johnson M. 1997. Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature* 385:254–57

Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Psychol.* 20:11–21

Seligman MEP. 1971. Phobias and preparedness. *Behav. Ther.* 2:307–20

Shi C, Davis M. 1998. Pain pathways involved in fear conditioning measured with fear potentiated startle: lesion studies. *J. Neurosci.* 19:420–30

Siegel A, Edinger H. 1981. Neural control of aggression and rage behavior. In *Handbook of the Hypothalamus.* Vol. 3. *Behavioral Studies of the Hyphothalamus,* ed. PJ Morgane, J Panksepp, pp. 203–40. New York: Dekker

Siegel A, Roeling TA, Gregg TR, Kruk MR. 1999. Neuropharmacology of brain-stimulation-evoked aggression. *Neurosci. Biobehav. Rev.* 23:359–89

Squire LR, Knowlton B, Musen G. 1993. The structure and organization of memory. *Annu. Rev. Psychol.* 44:453–95

Stevens CF. 1998. A million dollar question: Does LTP = memory? *Neuron* 20:1–2

Swanson LW. 1983. The hippocampus and the concept of the limbic system. In *Neurobiology of the Hippocampus,* ed. W Seifert, pp. 3–19. London: Academic

Turner BH, Mishkin M, Knapp M. 1980. Organization of the amygdalopetal projections from modality-specific cortical association areas in the monkey. *J. Comp. Neurol.* 191:515–43

Turner BH, Zimmer J. 1984. The architecture and some interconnections of the rat amygdala and lateral periallocortex. *J. Comp. Neurol.* 227:540–57

Uwano T, Nishijo H, Ono T, Tamura R. 1995. Neuronal responsiveness to various sensory stimuli, and associative learning in the rat amygdala. *Neuroscience* 68:339–61

van de Kar LD, Piechowski RA, Rittenhouse PA, Gray TS. 1991. Amygdaloid lesions: differential effect on conditioned stress and immobilization-induced increases in corticosterone and renin secretion. *Neuroendocrinology* 54:89–95

Vazdarjanova A, McGaugh JL. 1998. Basolateral amygdala is not critical for cognitive memory of contextual fear conditioning. *Proc. Nat. Acad. Sci. USA* 95:15003–7

Weinberger NM. 1995. Retuning the brain by fear conditioning. In *The Cognitive Neurosciences,* ed. MS Gazzaniga, pp. 1071–90. Cambridge, MA: MIT Press

Weinberger NM. 1998. Physiological memory in primary auditory cortex: characteristics and mechanisms. *Neurobiol. Learn. Mem.* 70:226–51

Weisskopf MG, Bauer E, LeDoux JE. 1999. L-type voltage gated calcium channels mediate NMDA-independent associative long-term potentiation at thalamic input synapses to the amygdala. *J. Neurosci.* 10512–19

Weisskopf MG, LeDoux JE. 1999. Distinct populations of NMDA receptors at subcortical and cortical inputs to principal cells of the lateral amygdala. *J. Neurophysiol.* 81:930–34

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA. 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J. Neurosci.* 18:411–18

Wilensky AE, Schafe GE, LeDoux JE. 1999. Functional inactivation of the amygdala before but not after auditory fear conditioning prevents memory formation. *J. Neurosci.* 19 RC48 1–5