64

NEURAL CIRCUITRY OF ANXIETY AND STRESS DISORDERS

MICHAEL DAVIS

BRAIN SYSTEMS IN THE GENERATION OF FEAR AND ANXIETY

Role of the Amygdala

Many data now indicate that the amygdala, along with its many efferent connections, is critically involved in emotion. Although the amygdala complex is generally defined by several distinct groups of cells, including the lateral, basal, accessory basal central, medial, and cortical nuclei, new data indicate that it is more useful to think of the amygdala as the *basolateral amygdala* (Bla) and to think of its several target areas as parts of a broader network that subserve more specialized functions (Fig. 64.1). The Bla receives sensory information from the thalamus, cortex (169), and ventral hippocampus (54) and then activates or modulates synaptic transmission in target areas appropriate for the reinforcement signal with which the sensory information has been associated. This involves both positive and negative associations. However, because most of the literature on the amygdala has analyzed the role of the Bla and its adjacent target, the central nucleus of the amygdala (CeA), in aversive conditioning, this work serves as the main focus of this chapter. Brief summaries of the role of Bla outputs to other targets shown in Fig. 64.1 follow. Because the periaqueductal gray (PAG) has received considerable attention in the study of defensive behavior and the hippocampus in the study of contextual fear conditioning, these data are reviewed next. Finally, brain systems and neurotransmitters involved in the inhibition of fear are reviewed, given the clinical significance of this information.

Basolateral Nucleus of the Amygdala to CeA or BNST Pathway as It Relates to Conditioned and Unconditioned Fear

Figure 64.1 shows that the Bla projects directly to the CeA, as well as to a related structure, the lateral division of the bed nucleus of the stria terminalis (BNST), to form part of the *lateral extended amygdala* (6). Figure 64.2 summarizes work done in many different laboratories indicating that the CeA and BNST have direct projections to various anatomic areas that may be expected to be involved in many of the symptoms of fear or anxiety (65). The CeA and BNST have been grouped together because fibers from the Bla that project to the BNST pass through the CeA and cells in the lateral division of the CeA project to the BNST. Thus, many effects previously attributed to the CeA may really depend on the BNST.

Autonomic and Hormonal Measures

Anatomically, the CeA and the BNST are well situated to mediate the various components of the fear response. Both structures send prominent projections to areas such as the lateral hypothalamus, which is involved in activation of the sympathetic autonomic nervous system seen during fear and anxiety (155). Direct projections to the dorsal motor nucleus of the vagus, nucleus of the solitary tract, and ventrolateral medulla may be involved in lateral extended amygdala modulation of heart rate and blood pressure, which are known to be regulated by these brainstem nuclei (222). Projections to the parabrachial nucleus may be involved in respiratory (as well as cardiovascular changes) during fear, because electrical stimulation and lesions of this nucleus are known to alter various measures of respiration. Indirect projections of the CeA to the paraventricular nucleus through the BNST and preoptic area may mediate the prominent neuroendocrine responses to fearful or stressful stimuli.

Attention and Vigilance

Projections from the lateral extended amygdala to the ventral tegmental area may mediate stress-induced increases in dopamine metabolites in the prefrontal cortex (101). Direct projections to the dendritic field of the locus ceruleus or indirect projections through the paragigantocellularis nucleus may mediate the increase in firing rates of cells in the locus ceruleus in the presence of a fearful stimulus. Direct

Michael Davis: Department of Psychiatry, Emory University School of Medicine, Atlanta, Georgia.

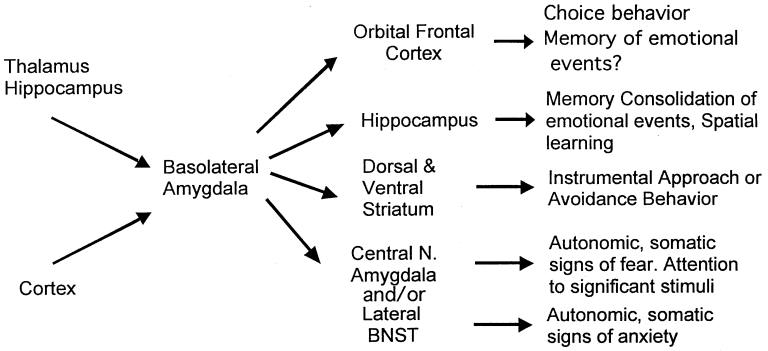

FIGURE 64.1. Schematic diagram of the outputs of the basolateral amygdala to various target areas and how these connections may be involved in fear and anxiety.

projections to the lateral dorsal tegmental nucleus and parabrachial nuclei, which have cholinergic neurons that project to the thalamus, may mediate increases in synaptic transmission in thalamic sensory relay neurons during states of fear. This cholinergic activation, along with increases in thalamic transmission accompanying activation of the locus ceruleus, may thus lead to increased vigilance and superior signal detection in a state of fear or anxiety.

As emphasized by Kapp et al. (141), in addition to its direct connections to the hypothalamus and brainstem, the CeA has the potential for indirect widespread effects on the cortex through its projections to cholinergic neurons that project to the cortex. The rapid development of conditioned bradycardia during pavlovian aversive conditioning, critically dependent on the amygdala, may reflect a general increase in attention.

Motor Behavior

Release of norepinephrine onto motor neurons by lateral extended amygdala activation of the locus ceruleus, or through projections to serotonin containing raphe neurons, could lead to enhanced motor performance during a state of fear, because both norepinephrine and serotonin facilitate excitation of motor neurons. Direct projections to the nucleus reticularis pontis caudalis, as well as indirect projections to this nucleus through the central gray, probably are involved in fear potentiation of the startle reflex. Direct projections to the lateral tegmental field, including parts of the trigeminal and facial motor nuclei, may mediate some of the facial expressions of fear as well as potentiation of the eyeblink reflex. The lateral extended amygdala also projects to regions of the central gray that appear to be a critical part of a general defense system and that have been implicated in conditioned fear in certain behavioral tests including freezing, sonic and ultrasonic vocalization, and stress-induced hypalgesia (20,33,78,103,121,155).

Elicitation of Fear Responses by Electrical or Chemical Stimulation of the Extended Amygdala

Electrical stimulation or abnormal electrical activation of the amygdala (i.e., by temporal lobe seizures) can produce a complex pattern of behavioral and autonomic changes that, taken together, highly resembles a state of fear.

Autonomic and Hormonal Measures

As outlined by Gloor: "The most common affect produced by temporal lobe epileptic discharge is fear. . . . It arises 'out

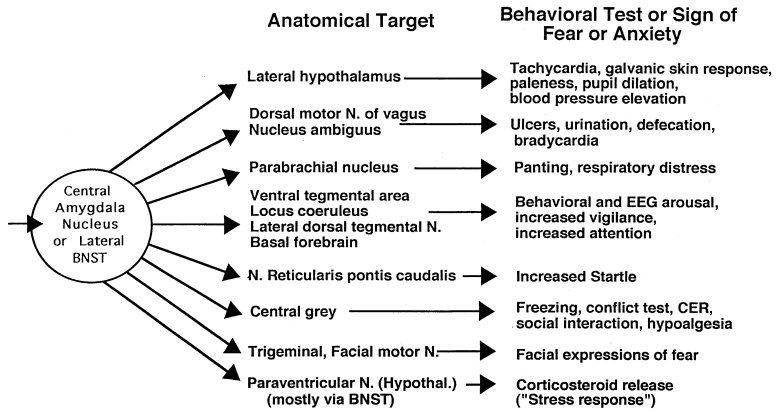

FIGURE 64.2. Schematic diagram of the outputs of the central nucleus of the amygdala and the lateral division of the bed nucleus of the stria terminalis to various target areas and how these connections may be related to specific aspects of fear and anxiety. BNST, bed nucleus of the stria terminalis; CER, conditioned emotional response; EEG, electroencephlographic; N, nucleus.

of the blue.' Ictal fear may range from mild anxiety to intense terror. It is frequently, but not invariably, associated with a rising epigastric sensation, palpitation, mydriasis, and pallor and may be associated with a fearful hallucination, a frightful memory flashback, or both'' (98). In humans, electrical stimulation of the amygdala elicits feelings of fear or anxiety as well as autonomic reactions indicative of fear (57,99). Although other emotional reactions occasionally are produced, the major reaction is one of fear or apprehension.

Electrical stimulation of the CeA or chemical activation by the cholinergic agonist carbachol or the neurotransmitter glutamate produces prominent cardiovascular effects that depend on the species, site of stimulation, and state of the animal. CeA stimulation can also produce gastric ulceration and can increase gastric acid, and these features can be associated with chronic fear or anxiety. It can also alter respiration, a prominent symptom of fear, especially in panic disorder.

Using very small infusion cannulas and very low doses, Sanders and Shekhar found increases in blood pressure and heart rate when the γ-aminobutyric $acid_A$ ($GABA_A$) antagonist bicuculline was infused into the Bla but not the CeA (215). Local infusion of *N*-methyl-D-aspartate (NMDA) or AMPA into the basolateral nucleus also increased blood pressure and heart rate (230). Repeated infusion of initially subthreshold doses of bicuculline into the anterior basolateral nucleus led to a ''priming'' effect in which increases in heart rate and blood pressure were observed after three to five infusions (216). This change in threshold lasted at least 6 weeks and could not be ascribed to mechanical damage or generalized seizure activity based on EEG measurements. Similar changes in excitability were produced by repetitive infusion of very low doses of corticotropin-releasing hormone (CRH) or the related peptide, urocortin (210). Once primed, these animals exhibited behavioral and cardiovascular responses to intravenous sodium lactate, a panic-inducing treatment in certain types of psychiatric patients.

In general, electrical stimulation of the amygdala causes an increase in plasma levels of corticosterone. The effect of electrical stimulation appears to depend on both norepinephrine and serotonin in the paraventricular nucleus. Depletion of these transmitters through local infusions of 6-hydroxydopamine or 5,7-DHT, or local infusion of the norepinephrine or serotonin antagonists prazosin or ketanserin, into the paraventricular nucleus attenuated the effects of electrical stimulation (80).

Attention and Vigilance

Studies in several species indicate that electrical stimulation of the CeA increases attention or processes associated with increased attention. For example, stimulation of sites in the CeA that produce bradycardia (142) also produce low-voltage fast EEG activity (140). In fact, an attention or orienting reflex was the most common response elicited by electrical stimulation of the amygdala (16,241). These and other observations led Kapp et al. to hypothesize that the ''central nucleus and its associated structures function, at least in part, in the acquisition of an increased state of nonspecific attention or arousal manifested in a variety of CRs which function to enhance sensory processing. This mechanism is rapidly acquired, perhaps via an inherent plasticity within the nucleus and associated structures in situations of uncertainty but of potential import; for example, when a neutral stimulus (CS) precedes either a positive or negative reinforcing, unexpected event (US)'' (141). Electrical stimulation of the amygdala can also activate cholinergic cells that are involved in arousal-like effects depending on the state of sleep and perhaps the species.

Motor Behavior

Electrical or chemical stimulation of the CeA produces a reduction of prepotent, ongoing behavior, a critical component in several animal models such as freezing, the operant conflict test, the conditioned emotional response, and the social interaction test. Electrical stimulation of the amygdala also elicits jaw movements and activation of facial motoneurons, which may mimic components of the facial expressions seen during the fear reaction. These motor effects may be indicative of a more general effect of amygdala stimulation, namely, that of modulating brainstem reflexes such as the massenteric, baroreceptor nictitating membrane, eyeblink, and the startle reflex.

Summary of the Effects of Stimulation of the Amygdala

Viewed in this way, the pattern of behaviors seen during fear may result from activation of a single area of the brain (the extended amygdala), which then projects to various target areas that themselves are critical for each of the specific symptoms of fear (the expression of fear), as well as the experience of fear. Moreover, it must be assumed that all these connections are already formed in an adult organism, because electrical stimulation produces these effects in the absence of prior explicit fear conditioning. Thus, much of the complex behavioral pattern seen during a state of ''conditioned fear'' has already been ''hard wired'' during evolution.

For a formerly neutral stimulus to produce the constellation of behavioral effects used to define a state of fear or anxiety, it is only necessary for that stimulus to activate the amygdala, which, in turn, will produce the complex pattern of behavioral changes by virtue of its innate connections to different brain target sites. Viewed in this way, plasticity during fear conditioning probably results from a change in synaptic inputs before or in the Bla (173,192,204), rather than from a change in its efferent target areas. The ability to produce long-term potentiation (LTP) in the Bla (55, 56,58,91,129,226) that can lead to an increase in responsiveness to a physiologic stimulus (203) and the finding

TABLE 64.1. EFFECTS OF LESIONS OF THE AMYGDALA ON CONDITIONED FEAR

Method	Species	Site	Effect of Lesion	Reference
Aspiration (pre)	Human	AC	Decrease galvanic skin response during classic fear conditioning unilateral lesions	153
Aspiration (pre)	Human	AC	Decrease galvanic skin response during classic fear conditioning	26
Electrolytic	Rabbit	Ce	Decrease bradycardia to cue paired with shock	139
Ibotenic acid (pre)	Rabbit	Ce	Decrease bradycardia to cue paired with shock	168
Ibotenic acid (Ce)	Rat	Ce	Decrease blood pressure rise to cue paired with shock	137
Electrolytic (MG)		MG	(Ce, unilateral, MG, contralateral)	
Cooling (pre)	Cat	Ce	Decrease bradycardia, respiratory increases and blood pressure changes to cue paired with shock	259
Electrolytic (pre)	Rat	L	Decrease blood pressure rise during classic conditioning	154,206
NMDA (pre or post)	Rat	C	Decrease secretion of corticosterone and defecation to cue paired with shock; decrease rise in dopamine, serotonin, or norepinephrine metabolites in prefrontal cortex to cue paired with shock	101
Electrolytic (pre)	Rat	Ce	Decrease freezing to cue paired with shock	157
Ibotenic acid (pre)	Rat	Ce and Bla	Decrease freezing to context paired with shock	118
Electrolytic (pre)	Rat	L	Decrease freezing to cue paired with shock	154
Radiofrequency (pre)	Rat	AC	Decrease freezing to cues paired with shock; decrease shock probe avoidance	30
Ibotenic acid (amygdala) M (medial geniculate) (pre)	Rat	Ce, MG	Decrease freezing to cue paired with shock (Ce, unilateral; MG, contralateral), some damage to L and Bla	137
NMDA (pre or post)	Rat	Bla	Decrease acquisition of freezing to odor or context or expression of both when lesions made 1 or 15 days after conditioning	61
NMDA (pre and post)	Rat	Bla	Decrease acquisition or expression of freezing to context or cue paired with shock even when lesions made 1 month after training	166
Lidocaine (pre or pretesting or both)	Rat	Ce and Bla	Decrease expression of freezing to context paired with shock; weaker effect when inactivation given before training	119
Muscimol (pre or post)	Rat	Bla	Decrease freezing when given either before testing or training but not immediately after training	183
NMDA (pre or post)	Rat	Bla	Decrease freezing or high-frequency vocalizations to shock or cues paired with shock	101
Ibotenic acid (pre)	Rat	Ce not Bla	Anticonflict (licking), decrease effects of restraint stress on plus maze	175
Electrolytic (pre)	Rat	Ce not Bla	Anticonflict effect	225,256
Quinolinic acid or 6-OHDA (pre)	Rat	Bla	Decrease reduction in licking during conditioned emotional response test	224
NMDA (pre)	Rat	AC	Decrease avoidance of water spout paired with shock but not with quinine	48
Ibotenic acid (pre)	Rat	Ce, not Bla	Decrease disruption of bar pressing to cue paired with shock; could still avoid shock bar	146
Quinolinic acid (pre)	Rat	Bla not Ce	Decrease avoidance of shocked bar, no reduction of disruption of bar pressing to cue paired with shock	146
NMDA (pre or post)	Rat	Bla	Decrease expression or acquisition of fear-potentiated startle to visual conditioned stimulus	214
NMDA (post)	Rat	Bla	Decrease expression of fear-potentiated startle even when lesions made 1 month after training	159
Ibotenic acid (post)	Rat	Ce	Decrease expression of fear-potentiated startle to visual or auditory conditioned stimulus	52
Ibotenic acid (pre)	Rat	Ce and Bla	Decrease expression of hypoalgesia to context paired with shock (formalin test)	118

AC, amygdala complex; Bla, basolateral complex; central nucleus; MG, medial geniculate; post, posttraining; pre, pretraining.

that local infusion of NMDA antagonists into the amygdala block the acquisition of fear conditioning (65) are consistent with this hypothesis.

Effects of Lesions of the Amygdala on Conditioned and Unconditioned Fear in Rodents and Other Species

Many studies in rodents and other species indicate that lesions of the Bla or CeA block many different measures of conditioned fear, as well as unconditioned fear. Tables 64.1 and 64.2 show selected examples of such studies in animals, which have been extensively reviewed elsewhere (64,65). More recent studies in humans also point to the amygdala in fear and anxiety.

Effects of Lesions of the Amygdala in Humans and Nonhuman Primates

In nonhuman primates (160,184,205) and in humans (9, 117), cells have been found in the amygdala that respond selectively to faces or direction of gaze (42). In humans, removal of the amygdala has been associated with an impairment of memory for faces (4,138,240,257) and deficits in recognition of emotion in people's faces and interpretation of gaze angle (41,50,257). In a very rare case involving bilateral calcification confined to the amygdala (Urbach-Wiethe disease), patient SM046 could not identify the emotion of fear in pictures of human faces and could not draw a fearful face, even though other emotions such as happy, sad, angry, and disgusted were identified and drawn within the normal range. The deficit in recognizing facial expressions of fear

TABLE 64.2. EFFECTS OF LESIONS OF THE AMYGDALA ON UNCONDITIONED FEAR OR STRESS

Method	Species	Site	Effect of Lesion	Reference
Electrolytic	Rat	Ce	Decrease secretion of ACTH to immobilization stress	23,24
Ibotenic acid	Rat	Ce	Decrease rise corticosterone to immobilization stress	242
Radiofrequency	Rat	**	Decrease the compensatory hypersecretion of ACTH that normally occurs following adrenalectomy	7,8
Electrolytic (pretraining but not posttraining)	Rat	Ce	Decrease secretion of corticosterone and prolactin to shock; no effect on epinephrine, norepinephrine	207
Radiofrequency	Rat	Ce	Decrease ulceration produced by restraint	122,123
Radiofrequency	Rat	Ce	Decrease ulceration produced by shock stress	124
Electrolytic	Rat	Ce	Decrease gastric ulcers to water restraint	59
Ibotenic acid	Rat	Ce	No effect on ulcers to water restraint	59
Electrolytic	Rat	Ce	Decrease noise-elicited hypertension	88
Electrolytic	Wild Rat	CO, Ce	Decrease emotionality in measured in terms of flight and defensive behaviors	144,145
Electrolytic	Rat	CO, Me Ce	Increase the number of contacts a rat will make with a sedated cat	30
Electrolytic	Many species	AC	General taming effect	For review, see 100
Electrolytic	Wild Rat	CO, Ce	Decrease emotionality in measured in terms of flight and defensive behaviors	144,145
Electrolytic	Rat	CO, Me Ce	Increase the number of contacts a rat will make with a sedated cat	30
Radiofrequency	Rat	Ce	Decrease jump withdrawal sign in morphine dependent rats after intraperitoned naloxone	51
Radiofrequency	Rat	Ce, L and Bla	Decrease analgesia produced by exposure to cat or shock (tail flick test)	85
Electrolytic	Rat	L or Ce	Decrease loud noise-induced hypoalgesia (tail fick test)	28
Electrolytic	Rat	Ce, not Bla	Decrease analgesic effects of systemic flumazenil (hot plate test)	106
NMDA	Rat	Ce not Bla or Me	Decrease morphine (low dose) induced antinociception (formalin or tail flick tests)	164,165
Lidocaine	Rat	Ce	Decrease morphine induced antinociception (tail flick test)	165

AC, amygdala complex; Bla, basolateral complex; Ce, central nucleus; Me, medial nucleus.

only seemed to occur after bilateral amygdala damage (3). This patient and two others also tended to view even the most threatening faces as trustworthy and approachable (2). A more detailed evaluation of patient SM046 showed that she correctly identified valence (e.g., pleasant versus unpleasant) in faces displaying happy, surprised, afraid, angry, disgusted, or sad emotion, but she was highly abnormal in rating the level of arousal to the afraid, angry, disgusted, and sad faces (1). Another patient (SP) with extensive bilateral amygdala damage also showed a major deficit in her ability to rate levels of fear in human faces, yet was perfectly normal in generating a fearful facial expression in comparison with neurologically normal subjects, based on the ratings of three judges (13).

Patients with unilateral (153) or bilateral (26) lesions of the amygdala also have been reported to have deficits in classic fear conditioning using the galvanic skin response as a measure of fear. In monkeys, removal of the amygdala decreases reactivity to sensory stimuli measured with the galvanic skin response (17,18).

Effects of Local Infusion of Drugs into the Amygdala on Measures of Fear and Anxiety

If the amygdala is critically involved in fear and anxiety, then drugs that reduce fear or anxiety clinically may well act within the amygdala. It is also probable that certain neurotransmitters within the amygdala may be involved in fear and anxiety. In fact, many studies indicate that local infusions of GABA or GABA agonists, benzodiazepines, CRH antagonists, opiate agonists, neuropeptide Y, dopamine antagonists, or glutamate antagonists decrease measures of fear and anxiety in several animal species. Table 64.3 gives selected examples of some of these studies, which have been extensively reviewed (65). Conversely, local infusions of GABA antagonists, CRH or CRH analogues, vasopressin, thyrotropin-releasing hormone, opiate antagonists, cholecystokinin (CCK) or CCK analogues tend to have anxiogenic effects. Table 64.4 shows selected examples of such studies that also have been reviewed (65).

In summary, connections between the Bla and the CeA or BNST are critically involved in various autonomic and motor responses seen during a state of fear or anxiety. However, it is also the case that connections between the basolateral nucleus and other target areas are involved in emotional behavior.

Basolateral Nucleus of the Amygdala to Dorsal Striatum Pathway as It Relates to Avoidance or Escape from Aversive Events

As emphasized by McGaugh, Packard, and others, the amygdala modulates memory in various tasks such as inhibitory avoidance and motor or spatial learning (49,170,171, 185,186). For example, posttraining intracaudate injections of amphetamine enhanced memory in a visible platform water maze task but had no effect in the hidden platform, spatially guided task (185,186). Conversely, posttraining intrahippocampal infusion of amphetamine enhanced memory in the hidden platform water maze task but not in the visible platform task. However, posttraining intraamygdala injections of amphetamine enhanced memory in both water maze tasks (185,186).

Moreover, preretention intrahippocampal lidocaine injections blocked expression of the memory-enhancing effects of posttraining intrahippocampal amphetamine injections in the hidden platform task, and preretention intracaudate lidocaine injections blocked expression of the memory-enhancing effects of posttraining intracaudate amphetamine injections in the visible platform task. However, preretention intraamygdala lidocaine injections did not block the memory-enhancing effect of posttraining intraamygdala amphetamine injections on either task. Finally, in the hidden platform task, posttraining intrahippocampal, but not intracaudate, lidocaine injections blocked the memory-enhancing effects of posttraining intraamygdala the visible platform task, posttraining intracaudate, but not intrahippocampal, lidocaine injections blocked the memory-enhancing effects of posttraining intraamygdala amphetamine. The findings indicate a double dissociation between the roles of the hippocampus and caudate-putamen in memory and suggest that the amygdala exerts a modulatory influence on both the hippocampal and caudate-putamen memory systems.

Perhaps similarly, lesions of the CeA block freezing but not escape to a tone previously paired with shock, whereas lesions of the basal nucleus of the Bla have just the opposite effect (10). However, lesions of the lateral nucleus, which receive sensory information required by both measures, block both freezing and escape. Lesions of the Bla, but not the CeA, also block avoidance of a bar associated with shock (146). It is possible that basolateral outputs to the dorsal or the ventral striatum mediate the escape behavior, given the importance of the striatum in several measures of escape or avoidance learning. However, combined, unilateral lesions of each structure on opposite sides of the brain would be required to evaluate whether this results from serial transmission from the basolateral nucleus to the striatum.

Basolateral Nucleus of the Amygdala to Hippocampus Pathway as It Relates to Avoidance or Escape from Aversive Events

As mentioned earlier, posttraining intrahippocampal as well as intraamygdala injections of amphetamine selectively enhance memory in a hidden platform water maze task (185, 186). Posttraining infusion of norepinephrine into the basolateral nucleus enhanced retention in the hidden platform water maze task, whereas posttraining infusion of propranolol had the opposite effect (113). These results suggest that

TABLE 64.3. EFFECTS OF NEUROTRANSMITTER AGONISTS INFUSED INTO THE AMYGDALA ON FEAR AND ANXIETY

Substance	Species	Site	Effect of Substance Infused	Reference
GABA or chlordiazepoxide	Rat	Ce	Decrease stress-induced gastric ulcers	232
GABA or benzodiazepines	Rat	Bla	Increase punished responding in operant conflict test (anticonflict effect)	105,126,189, 218,239
Benzodiazepines	Rat	Ce	Increase punished responding in operant conflict test (anticonflict effect)	225,234
Midazolam	Rat	Bla	More time on open arms in plus-maze, no effect on shock probe avoidance	188
Diazepam	Rat	Ce or Bla	Decrease freezing to footshock	120,258
Diazepam	Mice	AC	More time in light side in light-dark box test (anxiolytic effect)	60
Muscimol	Rat	Bla	Anxiolytic effect in the social interaction test; no effect in Ce	216
Muscimol	Rat	Bla	Increase punished responding in operant conflict test (anticonflict effect); no effect in Ce	218
a-CRH	Rat	Ce	Block noise-elicited increase in tryptophan hydroxylase in cortex	35
a-CRH	Rat	Ce	Anxiolytic effect (plus maze) in socially defeated rat	116
a-CRH	Rat	Ce	Anxiolytic effect in plus maze during ethanol withdrawal in ethanol-dependent rats; no effect in plus maze in nondependent rats	194
a-CRH	Rat	Ce	Decrease behavioral effects of opiate withdrawal	115
CRH receptor antisense	Rat	Ce	Anxiolytic effect in the plus maze in rats that previously experienced defeat stress	161
a-CRH	Rat	Ce	Decrease duration of freezing to an initial shock treatment or to re-exposure to shock box 24 h later	233
a-CRH	Rat	Ce	No effect on grooming and exploration activity under stress-free conditions	247
Enkephalin analogue	Rat	Ce	Decrease stress-induced gastric ulcers, prevented by 6-OHDA or clozapine	195,196,198
Opiate agonists	Rb	Ce	Block acquisition of conditioned bradycardia	89,90
Morphine	Rat	Ce	Anxiolytic effect in social interaction test	83
Neuropeptide Y	Rat	Bla, not Ce	Anxiolytic effect in social interaction test, blocked by Y-1 antagonist	213
Neuropeptide Y1 agonist	Rat	Ce	Anxiolytic effects in conflict test; NPY-Y2 agonist much less potent	114
Oxytocin	Rat	Ce	Decrease stress-induced bradycardia and immobility responses	209
SCH 23390	Rat	AC	Decrease expression of fear-potentiated startle	151
SCH 23390	Rat	AC	Decrease acquisition and expression of freezing to tone or context; not due to state-dependent learning	107
CNQX	Rat	Bla	Blocks expression of fear-potentiated startle (visual, auditory CS)	149
NBQX	Rat	Bla or Ce	Blocks expression of fear-potentiated startle (visual CS)	243
AP5	Rat	Bla	Block facilitation of eyeblink conditioning by prior stress when given prior to stressor session	227
AP5 or CNQX	Rat	Bla	Anxiolytic effect in social interaction test	212
CNQX	Rat	Ce	Decrease naloxone precipitated withdrawal signs in morphine-dependent rats	235

AC, amygdala complex; Bla, basolateral complex; Ce, central nucleus.

TABLE 64.4. EFFECTS OF NEUROTRANSMITTER ANTAGONISTS INFUSED INTO THE AMYGDALA ON FEAR AND ANXIETY

Substance	Species	Site	Effect of Substance Infused	Reference
Bicuculline, picrotoxin	Rat	Bla	Anxiogenic effects in the social interaction test; repeated infusion led to sensitization	216
Bicuculline	Rat	Bla	Anxiogenic effects in social interaction, blocked by either NMDA or non-NMDA antagonists into the amygdala	211
Bicuculline (un)	Rat	Bla not Ce	Increases in blood pressure, heart rate, and locomotor activity; bigger effect with repeated infusions	215,216
Bicuculline (un)	Rat	Bla	Increases in blood pressure, heart rate; blocked by infusion of either NMDA or non-NMDA antagonists into the amygdala	211
Bicuculline NMDA, AMPA (un)	Rat	Bla	Increases in blood pressure, heart rate blocked by either NMDA or non-NMDA antagonists infused into Bla or the dorsomedial hypothalamus	229,230
CRH	Rat	Ce	Increase heart rate; effect blocked by a-CRH into Ce	248
CRH, TRH, or CGRP	Rat	Ce	Increase in blood pressure, heart rate, and plasma catecholamines	43
Urocortin or CRH	Rat	Bla	After repeated subthreshold doses get increase in blood pressure to systemic lactate	210
CRH	Rat	Ce, not Bla	Increased grooming and exploration in animals tested under stress-free conditions (i.e., in the home cage)	247,250
CRH	Rat	Ce	Increase defensive burying	249
CRH or Urocortin	Rat	Bla	Anxiogenic effect in plus maze, sensitization with repeated subthreshold doses; now get behavioral and cardiovascular effects to systemic lactate	210
Vasopressin	Rat	Ce	Increased stress-induced bradycardia and immobility responses in rats bred for low rates of avoidance behavior but not the more aggressive rats that show high avoidance rates	209
Vasopressin	Rat	Ce	Bradycardia (low doses) or tachycardia and release of corticosterone (high dose); tachycardia blocked by oxytocin antagonist	208
Vasopressin	Rat	Ce	Immobility, seizures second infusion	251
Vasopressin	Rat	Ce	Immobility in rats bred for low rates of avoidance but not bred for high avoidance rates	209
TRH	Rat	Ce	Increase stress-induced gastric ulcers	196,198
TRH or physostigmine	Rat	Ce	Increase stress-induced gastric ulcers, blocked by muscarinic or benzodiazepine agonists	197
TRH analogue	Rat	Ce	Increase gastric contractility, blocked by vagotomy	182
TRH	Rat	Ce	Produce gastric lesions and stimulated acid secretion	125
TRH analogue	Rat	AC	No effect on gastric secretion, whereas large effect after infusion into dorsal vagal complex or nucleus ambiguus	136
Naloxone	Rat	Ce	Increase stress-induced gastric ulcers	196,198
Naloxone	Rat	AC	Elicit certain signs of withdrawal (depending on site) in morphine-dependent rats (unilateral)	51
Methyl naloxonium	Rat	AC	Place aversion to context where injections given to morphine-dependent rats	231
Methyl naloxonium	Rat	AC	Weak withdrawal signs in morphine-dependent rats	163
Yohimbine	Rat	Ce	Facilitation of the startle reflex	82
CCK analogues	Rat	AC	Anxiogenic effect in plus maze but not clear because significant decrease in overall activity	27
Pentagastrin	Rat	AC	Increase acoustic startle, blocked by CCK B antagonist that also blocked effect of pentagastrin (ICV)	86

AC, amygdala complex; Bla, basolateral complex; Ce, central nucleus; un, unanesthetized.

the amygdala exerts a modulatory influence on hippocampal-dependent memory systems, presumably by direct projections from the basolateral nucleus of the amygdala, perhaps by modulation of LTP in the hippocampus. Lesions (131), NMDA antagonists (132), or local anesthetics (134) infused into the Bla decrease LTP in the dentate gyrus of the hippocampus. Conversely, high-frequency stimulation of the amygdala facilitates induction of LTP in the dentate gyrus (130,133). However, combined, unilateral lesions of each structure on opposite sides of the brain would be required to evaluate whether this results from serial transmission from the basolateral nucleus to the hippocampus.

Basolateral Nucleus of the Amygdala to Frontal Cortex Pathway as It Relates to Emotion

Importance of the Bla in US Representation

After pavlovian conditioning, presentation of a conditioned stimulus (CS) elicits some neural representation of the unconditioned stimulus (US) with which it was paired. For example, the sound of a refrigerator door opening or an electric can opener may bring the family cat into the kitchen in expectation of dinner. Several studies suggest that the Bla, perhaps by connections with cortical areas such as the perirhinal cortex (93), is critical for these US representations based on studies using a procedure called *US devaluation.* In these experiments, a neutral stimulus (e.g., a light) is first paired with food so a conditioned response can be measured. Some animals then have the food paired with something that makes them sick (US devaluation). After such treatment, these animals show a reduction in the conditioned response to the light compared with animals that did not experience US devaluation. This result suggests that, after conditioning, animals have a representation of the value of a reinforcement that is elicited by the cue paired with that US. When that representation is changed, then the behavior elicited by the cue also is changed in the same direction. Lesions of the basolateral, but not the CeA, block US devaluation (112). In a related paradigm, rats are trained to be fearful of a weak shock in the presence of a tone. When this is followed by presentation of a stronger shock, without further tone-shock pairing, more freezing occurs to the tone. Temporary inactivation of the Bla during this *inflation* procedure blocks this effect when testing subsequently occurs with a normal, unlesioned, amygdala (5).

Second-order conditioning also depends on a US representation elicited by a CS. In this procedure, cue 1 is paired with a particular US (e.g., shock or food), and cue 2 is paired with cue 1. After such training, cue 2 elicits a similar behavior as that elicited by cue 1, depending on the US with which cue 1 was paired. Thus, it may elicit approach behavior if cue 1 was formerly paired with food and avoidance if cue 1 was paired with shock. This indicates that cue 1 elicits a representation of the US that then becomes associated with cue 2. Lesions of the Bla, but not the CeA, block second-order conditioning (72,73,112), as do local infusions of NMDA antagonists into the Bla (92).

Importance of the Bla Projection to the Frontal Cortex in Using US Representations to Guide Behavior

Converging evidence now suggests that the connection between the Bla and the prefrontal cortex is critically involved in the way in which a US representation (e.g., very good, pretty good, very bad, pretty bad) guides approach or avoidance behavior. Patients with late- or early-onset lesions of the orbital regions of the prefrontal cortex fail to use important information to guide their actions and decision making (14,25,63). For example, on a gambling task, they choose high, immediate reward associated with long-term loss rather than low, immediate reward associated with positive long-term gains. They also show severe deficits in social behavior and make poor life decisions.

Studies using single-unit recording techniques in rats indicate that cells in both the Bla and the orbitofrontal cortex fire differentially to an odor, depending on whether the odor predicts a positive (e.g., sucrose) or negative (e.g., quinine) US. These differential responses emerge before the development of consistent approach or avoidance behavior elicited by that odor (220). Many cells in the Bla reverse their firing pattern during reversal training (i.e., the cue that used to predict sucrose now predicts quinine and vice versa) (221), although this has not always been observed (217). In contrast, many fewer cells in the orbitofrontal cortex showed selectivity before the behavioral criterion was reached, and many fewer reversed their selectivity during reversal training (221). These investigators suggest that cells in the Bla encode the associative significance of cues, whereas cells in the orbitofrontal cortex are active when that information, relayed from the Bla, is required to guide choice behavior.

Taken together, these data suggest that the connection between the Bla and the frontal cortex may be involved in determining choice behavior based on how an expected US is represented in memory. The necessity for communication between the amygdala and the frontal cortex was shown in monkeys using a ''disconnection approach'' in which the amygdala on one side of the brain and the frontal cortex on the other side were lesioned together (22). Because the reciprocal connections between the two structures are ipsilateral, this procedure completely eliminated activity of the network connections while preserving partial function of each structure. Using this approach in rhesus monkeys, Baxter et al. found a decrease in US devaluation after unilateral neurotoxic lesions of the basolateral nucleus in combination with unilateral aspiration of orbital prefrontal cortex (22). These monkeys continued to approach a food on which they had recently been satiated, whereas control monkeys consistently switched to the other food.

Neuroimaging Studies of the Amygdala in Humans

As reviewed by Whalen (244), neuroimaging studies in normal human subjects have shown activation of the amygdala by presentation of biologically relevant sensory stimuli that probably induce strong negative emotional states. For example, the functional magnetic resonance imaging (fMRI) signal intensity within the amygdala is greater when subjects view graphic photographs of negative material (e.g., mutilated human bodies) compared with when they view neutral pictures (135). Positron emission tomography metabolic activity within the amygdala increased to negative material presented by film clips (199), and the amount of amygdala activity during film clips predicted later recall (47). In addition, fMRI signal intensities in humans during classic fear conditioning increased in response to stimuli that predicted an aversive event (45,150,179).

Amygdala activation also seems to be greater during presentations of fearful faces compared with neutral facial expressions (40,180), happy facial expressions (180,246), or when subjects looked at a fixation point on an otherwise blank screen (246). Whalen et al. used a backward masking technique in which very brief presentations of fearful and happy facial expressions (33 milliseconds) were followed immediately by presentations (167 milliseconds) of neutral faces (245). Most study subjects reported seeing neutral "expressionless" faces, but not any afraid or smiling faces. Nonetheless, the amygdala demonstrated greater fMRI signal intensity to masked fearful faces compared with masked happy faces. In addition, subjects reported that these masked stimuli did not induce any noticeable changes in their state of emotional arousal. As suggested by Whalen (244), "this study offers preliminary support for the notion that the amygdala constantly monitors the environment for such signals. More than functioning primarily for the production of strong emotional states, the amygdala would be poised to modulate the moment-to-moment vigilance level of an organism."

Role of the Periaqueductal (Central) Gray

Outputs from the CeA to the ventral central gray appear to mediate several components of the fear response including freezing, conditioned analgesia, and fear-related vocalizations, but, surprisingly, maybe not cessation of operant behavior (11). More dorsal regions of the PAG play a role in active defensive responses (33), depending on whether the threat is distal or proximal (31,71). Fanselow (79), for example, showed that dorsal, but not ventral, PAG lesions eliminate activity bursts elicited by foot shock, whereas ventral, but not dorsal, PAG lesions diminish freezing responses elicited by cues previously paired with foot shock. Fanselow suggested that these stimuli (i.e., foot shock versus stimuli predicting foot shock) access different points on a "predatory imminence" continuum in which proximal threats activate the dorsal PAG to generate active defensive behaviors. More distal threats activate the ventral PAG and generate passive or preparatory defensive behaviors such as freezing and analgesia. From a similar perspective, Deakin and Graeff et al. proposed that moderately threatening stimuli inhibit the dorsal PAG (66,104), but this inhibition is overcome with more extreme danger, thus allowing active defense or panic behaviors to emerge.

Results from stimulation studies have suggested an anatomic division of function within PAG. In particular, Depaulis and colleagues showed that chemical or electrical stimulation of PAG regions lateral to the aqueduct produces active behaviors such as forward avoidance, defensive aggression, and cardiovascular activation (67,68), whereas stimulation of more ventral regions of the PAG elicits passive responses such as behavioral arrest and decreased cardiovascular output (21,69). Electrical stimulation of the dorsal PAG in humans produces a pattern of cardiovascular effects that resemble those seen during a natural panic attack, and patients often experience fear, anxiety, and the desire to terminate stimulation (162). Exposure of rats to a cat or high-frequency vocalizations of conspecifics that often signal a predator in the environment increases neuronal firing in the dorsal PAG inferred from an increase in the immediate early gene c-*fos* (162).

Based on these and other data, several investigators have suggested that the dorsal PAG may be involved in panic attacks in humans, perhaps resulting from a dysregulation of various transmitters systems within this structure (162). The dorsal PAG has heavy innervation of the panicogenic peptide CCK, which has been shown to excite the majority of cells in this region. CCK antagonists functionally decrease the effects of electrical stimulation of the dorsal PAG, as does elevating serotonin, perhaps relevant to the use of serotonin reuptake inhibitors in the treatment of panic disorder. Whether these effects depend on connections between the amygdala and the PAG or whether they represent examples where the PAG can function autonomously remains to be determined.

Role of the Hippocampus in Contextual Fear Conditioning

Rats given cue-shock pairings learn to be afraid of the cue as well as the place where cue-shock pairings occurred *(context conditioning).* In 1992, two seminal articles reported that the hippocampus was necessary for context but not explicit cue conditioning (148,190). Both studies found that electrolytic lesions of the dorsal hippocampus blocked freezing in the presence of a fearful context but not in the presence of a cue paired with shock in that context. Kim and Fanselow found such effects when lesions were made shortly after training (1 or 7 days) but not 28 days later (148), whereas Phillips and LeDoux used pretraining lesions (190).

Although the role of the hippocampus in contextual fear conditioning had been discovered earlier using a place aversion measure (223), these articles were more influential because they integrated the well-known role of the hippocampus in spatial learning with a simple, yet powerful measure of classic fear conditioning. Contextual freezing was quickly adopted by investigators interested in the role of hippocampal LTP in learning because contextual fear conditioning was rapid and long lasting, like LTP, and it was easy to measure without complex or expensive equipment. The idea was that the hippocampus was required to form a representation of the context and that this representation was then associated with shock, perhaps in the amygdala. The hippocampus was not needed when an explicit cue, such as a tone, was used because this could be relayed directly to the amygdala without having to be processed by the hippocampus.

As attractive as this hypothesis is, there are problems with concluding that the hippocampus is involved in all forms of contextual conditioning (96,97,202). Hippocampal lesions often produce substantial behavioral activation, which may interact with the expression of freezing and lead to a disruption of the freezing response itself, rather than of contextual fear. In fact, hippocampal lesions disrupt not only conditioned freezing responses, but also *unconditioned* freezing responses, such as the response elicited by a rat when confronted by a cat (32,34,147). The finding that hippocampus lesions did not block freezing to an explicit cue makes this competing response interpretation more difficult to accept, but some studies have found that hippocampal lesions disrupt freezing to an explicit cue (167). However, increases in activity cannot account for disruption of contextual freezing by hippocampal lesions in all instances. In an elegantly designed study, Anagnostaras et al. showed that hippocampal lesions disrupted freezing to a context that had been paired with shock shortly before surgery (12). In the same subjects, however, freezing to a second context, that had been paired with shock 28 days preoperatively, was not impaired. Thus, the freezing deficit to the recently conditioned context could not have resulted from an inability to freeze.

Although pretraining electrolytic lesions of the dorsal hippocampus (167) block contextual fear conditioning, neurotoxic lesions fail to do so (97,167,202), as does local infusion of muscimol (128). To explain this difference, Maren et al. suggested that rats with damage to cells in the hippocampus pick out salient explicit cues in the context and use these as elemental cues for fear conditioning (167). However, these investigators suggested that rats with electrolytic lesions do not do this because the lesion disrupts fibers that connect the ventral subiculum to the nucleus accumbens, which decreases exploration and thus sampling of the context to pick out salient explicit cues to associate with shock. In fact, experiments found a blockade of the acquisition but not the expression of contextual fear conditioning measured by freezing using infusion into the nucleus accumbens of a local anesthetic (108). This effect did not occur using tone-shock pairings, even using a weaker trace conditioning procedure that produced relatively low levels of freezing to the tone.

Another possibility is that fibers from the dorsal to the ventral hippocampus are important in these anterograde amnestic effects of electrolytic lesions of the dorsal hippocampus because neurotoxic lesions of either the entire hippocampus (102,202) or just the ventral hippocampus blocked contextual freezing, whereas neurotoxic lesions of the dorsal hippocampus again failed to block contextual conditioning (202). However, in contrast to the hypothesis that contextual fear conditioning involves processes similar to spatial learning, lesions of the ventral hippocampus did not block but instead actually facilitated spatial learning in a water maze task (202). As these investigators concluded, these data directly contradict the ''widely held notion that spatial and contextual forms of learning are essentially different manifestations of the same basic underlying process'' (202). Because these lesions also impaired freezing to a tone, these authors suggested that the ventral lesions disrupted freezing by increasing activity.

Because all these studies have relied on freezing as the measure of conditioned fear, it is important to assess the effects of hippocampal lesions on other behavioral or autonomic responses associated with fear. If hippocampal lesions disrupted multiple measures of contextual fear, it would provide further support for the hippocampal theory of context conditioning. However, posttraining hippocampal lesions were found not to disrupt context-specific potentiated startle, even though context-elicited freezing was disrupted in the same animals (174). This could not be explained by an excitatory effect of hippocampal lesions on startle amplitude itself (96). In contrast, lesions of the CeA completely blocked both freezing and startle.

In another experimental design (95), lesions of the dorsal hippocampus failed to block a phenomenon called *contextual blocking,* whereby prior contextual fear conditioning retards subsequent cue conditioning. However, as in other studies, freezing to the fearful context was blocked by hippocampal lesions. These data, along with several other reports in the literature (96,97,202), severely limit the general impression that the hippocampus is required for contextual fear conditioning. However, it does seem to be involved in certain situations, so further work is needed to predict those occasions in which it is and is not involved.

BRAIN SYSTEMS IN THE INHIBITION OR SUPPRESSION OF FEAR AND ANXIETY

Extinction

The inability to suppress unwanted fear memories or irrational worry is a major problem in many psychiatric disorders, yet very little is known about brain systems involved

in the inhibition of fear. One way to study this important problem is to analyze brain systems involved in *extinction,* defined as a reduction in conditioned fear when the CS is presented many times in the absence of the US. Although such a procedure can decrease the conditioned response, this does not result from an erasure of the original fear memory. Instead, something new is learned that overcomes or competes with the original fear memory. For example, an extinguished conditioned response can return with the passage of time (spontaneous recovery, 187), after a subsequent stressor (reinstatement, 201), or when testing occurs in a different context (renewal, 36). Such results indicate that extinction (but see discussion in ref. 74) may involve a form of active inhibition that is fragile compared with conditioned fear itself.

Conditioned Inhibition

In a conditioned inhibition procedure, cue 1 predicts food or shock, and a compound stimulus (cue 1 plus cue 2) predicts the absence of these USs. There is general agreement that conditioned inhibition, closely related to extinction, does involve active inhibition. In fact, it has been argued that extinction is a special case of conditioned inhibition (38). The *summation test* is the basic method for observing conditioned inhibition (200). In this procedure, the putative conditioned inhibitor (e.g., a light) is presented in compound with an excitatory CS (e.g., a tone). If the combination produces a decrease in the conditioned response below the level observed when the CS is presented alone, then that stimulus is said to act as a conditioned inhibitor. When the conditioned inhibitor is removed, excitation returns to its original level. Various control procedures indicate that a stimulus trained in this way is in fact acting by inhibition.

Because psychotherapy often involves procedures to rid patients of unwanted fear memories, a behavioral analysis of extinction or conditioned inhibition has certain clinical implications, as suggested by Bouton and Swartzentruber (39). As they pointed out, ''performance after extinction is inherently unstable'' (39). Phenomena such as spontaneous recovery and reinstatement may explain why conditioned fears and phobias in humans sometimes seem to return spontaneously without any obvious cause. The renewal effect may explain why fears reduced successfully in the therapist's office reappear when the patient returns home or to work. If a drug is used as an adjunct to therapy, renewal of fear could occur when the fearful stimulus is encountered in the absence of the drug. In fact, animal experiments show that when benzodiazepines are given during extinction, fear of the CS returns when testing occurs in the absence of the drug (37).

Brain Areas in Extinction or Conditioned Inhibition

Sensory Cortex

Assuming that extinction results from active inhibition (see earlier), one could expect that lesions of various brain areas would disrupt either the development or expression of extinction. LeDoux, Romanski, and Xagoraris reported that rats given ablations of visual cortex before light–foot shock pairings failed to show extinction of lick suppression relative to sham controls over days (156). In a similar study employing heart rate conditioning in the rabbit, Teich et al. showed that although bilateral lesions of either auditory or visual cortex did not disrupt acquisition of fear conditioning to a tone CS, auditory cortex lesions, but not visual cortex lesions, blocked extinction of conditioned heart rate responses to the tone (237). Based on known anatomic connections between sensory cortex and thalamic structures, the authors of both experiments concluded that, during extinction, sensory cortices exert a modality specific inhibition of the thalamic structures important for the performance of conditioned responses.

However, my colleague and I found no effect of complete visual cortex lesions on extinction of fear-potentiated startle using a visual CS when the lesions were made either before light-shock pairings or after light-shock pairings and extinction (77). Although there were procedural differences between these reports, the conclusion that sensory cortex is universally involved in extinction of conditioned fear is not supported.

Frontal Cortex

Rats with lesions of the ventral medial prefrontal cortex made before fear conditioning required more days to reach an extinction criterion using an auditory CS and freezing as the measure of fear (178). However, in these same animals, extinction of conditioned fear to contextual cues was not impaired. In an extensive series of experiments, my colleagues and I found normal rates of extinction to both explicit and contextual cues after total removal of the ventral medial prefrontal cortex using both freezing and fear-potentiated startle as measures of conditioned fear (94). Because the lesions in the study by Morgan et al. were performed before fear conditioning (178), the apparent blockade of extinction after ventral medial prefrontal cortex lesions may have resulted from an increase in the strength of original fear conditioning, rather than from interfering with the process of extinction. Although the lesions and shams groups did not differ significantly in their level of freezing before the extinction sessions, freezing to explicit cues often becomes maximal after a very few training trials, so ''ceiling effects'' may well have been operating. Because extinction rate can be a more sensitive index of the strength of original

conditioning than the terminal level of performance before the initiation of extinction (15), the slower rate of extinction in the lesioned animals may have reflected a stronger degree of original learning. Although these authors do not believe their effects can be explained in this way (177), the finding that the lesions had no effect on the rate of extinction of context conditioning, which clearly was not at the ceiling of the freezing scale, is consistent with this interpretation. Similarly, we did not find any effect of pretraining ventral prefrontal cortex lesions on extinction of contextual fear-potentiated startle or freezing (94). In addition, we did not find any effect of ventral medial prefrontal cortex lesions on extinction when lesions were made after fear conditioning but before extinction (94). Morgan and LeDoux also found no effect on the rate of extinction when ventral prefrontal cortex lesions were made after fear conditioning, but before extinction (176). If the frontal cortex is required for the development of extinction or for the inhibition of fear after extinction, one would expect lesions to block the development of extinction, irrespective of whether the lesions were made before or after the initial phase of fear conditioning.

Similarly complex effects on extinction have been reported regarding depletion of dopamine in the prefrontal cortex (181). Preconditioning lesions of dopamine terminals in the medial prefrontal cortex retarded the rate of extinction when a 0.8-mA shock was used but not when a 0.4-mA shock was used. Inspection of the results strongly suggests that the 0.8-mA group was at the ceiling of the measurement scale at the beginning of the extinction session, whereas the 0.4-mA group was not. Conversely, 6-hydroxydopamine lesions of the frontal cortex substantially retarded extinction after 0.8-mA tone-shock pairings, even when the lesions were made after training (181). Thus, it is possible that dopamine levels in the prefrontal cortex are important for extinction when conditioning has produced high, but not more moderate, levels of fear, although further studies using posttraining lesions are required to verify this.

Quirk et al. found that pretraining lesions of the ventral medial prefrontal cortex did not block the development of conditioned freezing or the rate of within session extinction (191). However, the lesioned rats showed much more spontaneous recovery measured 24 hours later. Similar results were found in rats given systemic administration of an NMDA antagonist (193). In contrast, we found no change in the rate or final level of extinction, measured with fear-potentiated startle and freezing, when extinction was assessed over 18 daily sessions using a small number of CS presentations each day (94). There also were no differences in the degree of spontaneous recovery measured 5 days later or in shock-induced reinstatement measured 24 hours after a single foot shock. Hence, the findings of Quirk et al. may depend critically on the use of a relatively small amount extinction training (191,193). Moreover, their lesions were generally more ventral than ours, and this may have contributed to the differences. Clearly, more work needs to be done to examine the limits of the role of the prefrontal cortex in extinction of conditioned fear, given the clinical importance of these data.

Hippocampus

Although a complete review of the hippocampal literature on extinction is beyond the scope of this chapter, this brain area has received a great deal of experimental attention and was once widely believed to be involved in extinction. Theories of extinction confront the problem of designing a mechanism capable of discriminating occasions of reinforcement from nonreinforcement. Douglas suggested that the hippocampus is a nonreinforcement detector providing the organism with the means to ''tune out'' information that is of no motivational consequence (70). It is possible that the hippocampus recognizes that the CS is no longer followed by the US and inhibits relevant sensory or conditioned response production centers.

Various conditioning paradigms have been used to assess the role of the hippocampus in extinction, including the rabbit nictitating membrane response (29,219,228), conditioned heart rate (44), and conditioned suppression (152). Although some of these experiments have found that hippocampal lesions attenuate extinction (219), others have found no effect (228), and still another has shown facilitated extinction (152).

Because extinction is context specific (see earlier), one could expect that lesions of the hippocampus would disrupt this contextual control of extinction. However, direct tests of this hypothesis have not found a disruption of context specific extinction using pretraining lesions. Hence, neither fimbria-fornix lesions (252) nor excitotoxic lesions of the entire hippocampus (87) had any effect on the rate of extinction or on renewal of conditioned fear, although both types of lesions disrupted reinstatement. In contrast, large hippocampal lesions were not found to disrupt reinstatement of appetitively conditioned behavior (84). Overall, therefore, the role of the hippocampus in extinction remains uncertain.

Neurotransmitters in Extinction

Role of NMDA Receptors in Extinction

Local infusion of NMDA antagonists into the amygdala blocked the development of extinction measured with fear-potentiated startle (76). Intraamygdala infusion of AP5 also blocked extinction using an auditory CS and freezing as a measure of conditioned fear (158). Perhaps similarly, systemic administration of the NMDA antagonist MK-801 fully blocked extinction of conditioned analgesia, a reliable

measure of conditioned fear (62), and this effect could not be explained by state-dependent context extinction. A similar blockade of extinction was reported using a lick-suppression paradigm (19), as well as extinction of the rabbit nictitating membrane preparation (143). Taken together, these data indicate that NMDA antagonists can block the development of extinction measured on subsequent test sessions. This may even occur under conditions in which the antagonist does not block the development of short-term extinction. Thus, systemic injection of the NMDA antagonist CPP before extinction blocked the expression of conditioned freezing by about 40% but did not block the development of extinction. However, the CPP group showed substantial recovery of conditioned freezing measured 24 hours later, a finding suggesting that CPP blocked the long-term development of extinction. (193). Interestingly, these investigators found a similar effect with preconditioning lesions of the ventral prefrontal cortex (191), although the connection between these two sets of data remains to be made.

Role of GABA in Extinction

Several studies have suggested that GABA agonists given before nonreinforced CS presentations interfere with the development of extinction (37,74). However, many of these effects may be attributable to state-dependent learning rather than to a blockade of learning during nonreinforced CS exposure. For example, Bouton, using lick suppression as a measure of fear, showed a blockade of extinction when rats were given chordiazepoxide during nonreinforced CS presentations and were then tested in the absence of the drug (37). However, when chordiazepoxide also was given before testing, extinction was still evident. This finding suggests that the benzodiazepine did not actually block the learning that was occurring during extinction, but, instead, the change in drug state between extinction and testing was the factor that produced renewal (36).

Interestingly, a series of experiments by Harris and Westbrook found similar effects on excitatory conditioning. For example, rats given fear conditioning after injection with benzodiazepines showed an impairment in conditioned freezing measured 24 hours later in the same context compared with rats trained under the drug but tested in a different context (111) or rats given a stressor before testing (109). Thus, the benzodiazepines did not actually prevent original learning, but instead produced a state during conditioning that interfered with retrieval during testing.

Hence, it would seem that GABA agonists do not directly interfere with either excitatory or inhibitory learning, but, instead, act on processes that are important for retrieval of prior learning. However, if extinction is a form of active inhibition, it is possible that GABA may be one of the neurotransmitters necessary for the expression of extinction. In fact, in an elegant set of experiments, Harris and Westbrook provided evidence that extinction is mediated by GABA release (110). Pretraining or pretesting administration of the inverse agonist FG 7142, which decreases GABA transmission, blocked both development and expression of extinction to an auditory CS paired with foot shock, using freezing as a measure. This effect could not be ascribed to state dependency or to a ceiling effect. Pretest administration of FG 7142 reinstated freezing when assessed in the context where extinction took place, but not in a novel context, which itself reinstated freezing, and the two effects were not additive statistically. However, the disruption of extinction by FG 7142 was not complete, a finding leaving open the possibility that other mechanisms and neurotransmitters also may be involved.

Role of Adrenocorticotropic Hormone and Vasopressin in Extinction

Work by DeWied, Van Wiersima, Izquierdo, and Richardson and their co-workers indicated that administration of various peptides such as adrenocorticotropic hormone or vasopressin either before or after extinction training attenuates subsequent extinction performance (for review see ref. 74).

Neural Systems in Conditioned Inhibition

Using fluorodeoxyglucose autoradiography to measure neural activity, Mcintosh and Gonzalez-Lima compared region-specific activity in parallel auditory pathways in two groups presented with a tone-light compound (172). In both groups, the tone was a fear-eliciting CS. The groups differed with respect to the significance of the light, which had been trained as a conditioned inhibitor in one group and as a neutral stimulus in the other. Thus, the experiment allowed for an analysis of whether a conditioned inhibitor modulates activity in sensory areas normally activated by an auditory fear-eliciting CS. Interestingly, in only one area, the ventral medial geniculate nucleus, was there a significant difference in activation between the two groups. This structure showed less activation in the conditioned inhibition group, a finding suggesting that a conditioned inhibitor may act at this locus in the auditory pathway to inhibit conditioned fear normally produced by an auditory CS.

We found normal conditioned inhibition of fear-potentiated startle, using a visual excitatory stimulus and an auditory conditioned inhibitor after lesions of either the medial prefrontal cortex (94) or the nucleus accumbens (75). In addition, local infusion into the nucleus accumbens of either amphetamine or glutamate antagonists did not alter the magnitude of conditioned inhibition, as they alter responding to conditioned reinforcers trained in an operant situation (46,236).

In an appetitive learning situation, Holland et al. reported that lesions of the hippocampus appeared to block

feature negative conditional discrimination (127), a phenomenon closely related to conditioned inhibition.

Several studies suggested that the lateral septum may play an important role in conditioned inhibition. Using pavlovian discriminative fear conditioning, single-unit firing rates in the dorsal lateral septal nucleus increased in the presence of a conditioned inhibitor and decreased in the presence of a conditioned excitor (238,254). This finding was not seen when recordings were made in the medial septal nucleus (253). More recently, Yadin and Thomas reported that stimulation of the same area of dorsolateral septal nucleus inhibited restraint stress-induced ulcers (255). Using c-*fos* mRNA as a measured of neuronal activation, we found a unique increase in c-*fos* in a ventral part of the lateral septum, the so-called septohypothalamic nucleus, when a conditioned inhibitor of fear was presented (53). Curiously, however, lesions of the lateral septal nucleus did not block the expression of conditioned inhibition in preliminary pilot studies, although further work certainly is required to evaluate the role of the lateral septum, perhaps using acute inactivation techniques rather than lesions.

One study suggests that the dorsal central gray may play an important role in conditioned inhibition of fear. Fendt reported that posttest infusions of 5 ng of picrotoxin (a GABA chloride channel blocker) into the dorsal central gray, but not the lateral or ventrolateral central gray, reduced the expression of conditioned inhibition without affecting the expression of conditioned fear (81). Although this result is complicated by the finding that neither 2.5-ng doses nor 10-ng doses affected conditioned inhibition, it raises the intriguing possibility that a conditioned inhibitor of fear releases GABA into the dorsal central gray. Alternatively, because low doses of picrotoxin would be expected to activate the dorsal central gray by removing tonic inhibition, these results could be interpreted as indicating that the dorsal central gray is involved in inhibiting an unknown brain structure mediating conditioned inhibition (81). Given the prominent role of the central gray in the expression of fear (162), more work is needed to investigate the role of the dorsal central gray in conditioned inhibition of fear.

REFERENCES

1. Adolphs R, Russell JA, Tranel D. A role for the human amygdala in recognizing emotion arousal from unpleasant stimuli. *Psychol Sci* 1999;10:167–171.
2. Adolphs R, Trane D, Damasio AR. The human amygdala in social judgment. *Nature* 1998;393:470–474.
3. Adolphs R, Trane D, Damasio H, et al. Fear and the human amygdala. *J Neurosci* 1995;15:5879–5891.
4. Aggleton JP. The functional effects of amygdala lesions in humans: a comparison with findings from monkeys. In: Aggleton JP, ed. *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction.* New York: Wiley–Liss, 1992:485–503.
5. Akbari Y, Mongeau R, Maren S, et al. Reversible inactivation of the basolateral amygdala prevents inflation of fear conditioning in rats. Society for Neuroscience, New Orleans, 1997.
6. Alheid G, deOlmos JS, Beltramino CA. Amygdala and extended amygdala. In: Paxinos G, ed. *The rat nervous system.* New York: Academic Press, 1995:495–578.
7. Allen JP, Allen CF. Role of the amygdaloid complexes in the stress-induced release of ACTH in the rat. *Neuroendocrinology* 1974;15:220–230.
8. Allen JP, Allen CF. Amygdalar participation in tonic ACTH secretion in the rat. *Neuroendocrinology* 1975;19:115–125.
9. Allison T, McCarthy G, Nobre A, et al. Human extrastriate visual cortex and the perception of faces, words, numbers, and colors. *Cereb Cortex* 1994;4:544–554.
10. Amorapanth P, LeDoux JE, Nader K. Different lateral amygdala outputs mediate reactions and actions elicited by a fear-arousing stimulus. *Nat Neurosci* 2000;3:74–79.
11. Amorapanth P, Nader K, LeDoux JE. Lesions of periaqueductal gray dissociate-conditioned freezing from conditioned suppression behavior in rats. *Learn Mem* 1999;6:491–499.
12. Anagnostaras SG, Maren S, Fanselow MS. Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: within-subjects examination. *J Neurosci* 1999;19: 1106–1114.
13. Anderson AK, Phelps EA. Expression without recognition: contributions of the human amygdala to emotional communication. *Psychol Sci* 2000;11:106–111.
14. Anderson SW, Bechara A, Damasio H, et al. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nat Neurosci* 1999;2:1032–1037.
15. Annau Z, Kamin LJ. The conditioned emotional response as a function of US intensity. *J Comp Physiol Psychol* 1961;54: 428–432.
16. Applegate CD, Kapp BS, Underwood MD, et al. Autonomic and somatomotor effects of amygdala central n. stimulation in awake rabbits. *Physiol Behav* 1983;31:353–360.
17. Bagshaw MH, Benzies S. Multiple measures of the orienting reaction and their dissociation after amygdalectomy in monkeys. *Exp Neurol* 1968;20:175–187.
18. Bagshaw MH, Kimble DP, Pribram KH. The GSR of monkeys during orienting and habituation and after ablation of the amygdala, hippocampus and inferotemporal cortex. *Neuropsychologia* 1965;3:111–119.
19. Baker JD, Azorlosa JL. The NMDA antagonist MK-801 blocks the extinction of pavlovian fear conditioning. *Behav Neurosci* 1996;110:618–620.
20. Bandler R, Carrive P. Integrated defence reaction elicted by excitatory amino acid microinjection in the midbrain periaqueductal grey region of the unrestrained cat. *Brain Res* 1988;439: 95–106.
21. Bandler R, Shipley MT. Columnar organization in the midbrain periaqueductal gray: modules for emotional expression? *Trends Neurosci* 1994;17:379–389.
22. Baxter MG, Parker A, Lindner CCC, et al. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. *J Neurosci* 2000;20:4311–4319.
23. Beaulieu S, DiPaolo T, Barden N. Control of ACTH secretion by central nucleus of the amygdala: implication of the serotonergic system and its relevance to the glucocorticoid delayed negative feed-back mechanism. *Neuroendocrinology* 1986;44: 247–254.
24. Beaulieu S, DiPaolo T, Cote J, et al. Participation of the central amygdaloid nucleus in the response of adrenocorticotropin secretion to immobilization stress: opposing roles of the noradrenergic and dopaminergic systems. *Neuroendocrinology* 1987;45: 37–46.
25. Bechara A, Damasio H, Tranel D, et al. Deciding advantageously before knowing the advantageous strategy. *Science* 1997; 275:1293–1294.

26. Bechara A, Tranel D, Damasio H, et al. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science* 1995;269:1115–1118.
27. Belcheva I, Belcheva S, Petkov VV, et al. Asymmetry in behavioral responses to cholecystokinin microinjected into rat nucleus accumbens and amygdala. *Neuropharmacology* 1994;33: 995–1002.
28. Bellgowan PSF, Helmstetter FJ. Neural systems for the expression of hypoalgesia during nonassociative fear. *Behav Neurosci* 1996;110:727–736.
29. Berger TW, Weikert CL, Basset JL, et al. Lesions of the retrosplinal cortex produce deficits in reversal learning of the rabbit nictitating membrane response: implications for potential interactions between hippocampal and cerebellar brain systems. *Behav Neurosci* 1986;100:802–809.
30. Blanchard DC, Blanchard RJ. Innate and conditioned reactions to threat in rats with amygdaloid lesions. *J Comp Physiol Psychol* 1972;81:281–290.
31. Blanchard DC, Blanchard RJ. Ethoexperimental approaches to the biology of emotion. *Annu Rev Psychol* 1988;39:43–68.
32. Blanchard DC, Blanchard RJ, Lee MC, et al. Movement arrest and the hippocampus. *Physiol Psychol* 1977;5:312–324.
33. Blanchard DC, Williams G, Lee EMC, et al. Taming of wild *Rattus norvegicus* by lesions of the mesencephalic central gray. *Physiol Psychol* 1981;9:157–163.
34. Blanchard RJ, Blanchard DC. The effects of hippocampal lesions on the rat's reaction to a cat. *J Comp Physiol Psychol* 1972; 78:77–82.
35. Boadle-Biber MC, Singh VB, Corley KC, et al. Evidence that corticotropin-releasing factor within the extended amygdala mediates the activation of tryptophan hydroxylase produced by sound stress in the rat. *Brain Res* 1993;628:105–114.
36. Bouton ME, Bolles RC. Contextual control of the extinction of conditioned fear. *Learn Motiv* 1979;10:455–466.
37. Bouton ME, Kenney FA, Rosengard C. State-dependent fear extinction with two benzodiazepine tranquilizers. *Behav Neurosci* 1990;104:44–55.
38. Bouton ME, Nelson JB. Context specificity of target versus feature inhibition in a feature-negative discrimination. *J Exp Psychol Anim Behav Process* 1994;20:51–65.
39. Bouton ME, Swartzentruber D. Sources of relapse after extinction in pavlovian instrumental learning. *Clin Psychol Rev* 1991; 11:123–140.
40. Breiter HC, Etcoff NL, Whalen PJ, et al. Response and habituation of the human amygdala during vissual processing of facial expression. *Neuron* 1996;17:875–887.
41. Broks P, Young AW, Maratos EJ, et al. Face processing impairments after encephalitis: amygdala damage and recognition of fear. *Neuropsychologia* 1998;36:59–70.
42. Brothers L, Ring B. Mesial temporal neurons in the macaque monkey with responses selective for aspects of social stimuli. *Behav Brain Res* 1993;57:53–61.
43. Brown MR, Gray TS. Peptide injections into the amygdala of conscious rats: effects on blood pressure, heart rate and plasma catecholamines. *Regul Pept* 1988;21:95–106.
44. Buchanan SL, Powell DA. Divergencies in pavlovian conditioned heart rate and eyeblink responses produced by hippocampectomy in the rabbit *(Oryctolagus cuniculus). Behav Neural Biol* 1980;30:20–38.
45. Buchel C, Morris J, Dolan RJ, et al. Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* 1998;20:947–957.
46. Burns LH, Everitt BJ, Kelly AE, et al. Glutamate-dopamine interactions in the ventral striatum: role in locomotor activity and responding with conditioned reinforcement. *Psychopharmacology* 1994;115:516–528.
47. Cahill L, Haier RJ, Fallon J, et al. Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci USA* 1996;93:8016–8021.
48. Cahill L, McGaugh JL. Amygdaloid complex lesions differentially affect retention of tasks using appetitive and aversive reinforcement. *Behav Neurosci* 1990;104:532–543.
49. Cahill L, McGaugh JL. Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci* 1998;21:294–299.
50. Calder AJ, Young AW, Rowland D, et al. Facial emotion recognition after bilateral amygdala damage: differentially severe impairment of fear. *Cogn Neuropsychol* 1996;13:699–745.
51. Calvino B, Lagowska J, Ben-Ari Y. Morphine withdrawal syndrome: differential participation of structures located within the amygdaloid complex and striatum of the rat. *Brain Res* 1979; 177:19–34.
52. Campeau S, Davis M. 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* 1995; 15:2301–2311.
53. Campeau S, Falls WA, Cullinan WE, et al. Elicitation and reduction of fear: behavioral and neuroendocrine indices and brain induction of the immediate-early gene *c-fos. Neuroscience* 1997;78:1087–1104.
54. Canteras N, Swanson L. Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: a PHAL anterograde tract-tracing study in the rat. *J Comp Neurol* 1992;324: 180–194.
55. Chapman PF, Bellavance LL. Induction of long-term potentiation in the basolateral amygdala does not depend on NMDA receptor activation. *Synapse* 1992;11:310–318.
56. Chapman PF, Kairiss EW, Keenan CL, et al. Long-term synaptic potentiation in the amygdala. *Synapse* 1990;6:271–278.
57. Chapman WP, Schroeder HR, Guyer G, et al. Physiological evidence concerning the importance of the amygdaloid nuclear region in the integration of circulating function and emotion in man. *Science* 1954;129:949–950.
58. Clugnet MC, LeDoux JE. 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* 1990;10:2818–2824.
59. Coover GD, Murison R, Jellestad FK. Subtotal lesions of the amygdala: the rostral central nucleus in passive avoidance and ulceration. *Physiol Behav* 1992;51:795–803.
60. Costall B, Kelly ME, Naylor RJ, et al. Neuroanatomical sites of action of 5-HT3 receptor agonist and antagonists for alteration of aversive behaviour in the mouse. *Br J Pharmacol* 1989; 96:325–332.
61. Cousens G, Otto T. Both pre- and posttraining excitotoxic lesions of the basolateral amygdala abolish the expression of olfactory and contextual fear conditioning. *Behav Neurosci* 1998;112:1092–1103.
62. Cox J, Westbrook RF. The NMDA receptor antagonist MK-801 blocks acquisition and extinction of conditioned hypoalgesia responses in the rat. *Q J Exp Psychol* 1994;47B:187–210.
63. Damasio AR. *Descartes' error.* New York: Grosset/Putnam, 1994.
64. Davis M. Neurobiology of fear responses: the role of the amygdala. *J Neuropsychiatry Clin Neurosci* 1997;9:382–402.
65. Davis M, Shi C-J. The amygdala. *Curr Biol* 2000;10:R131.
66. Deakin JWF, Graeff FG. 5-HT and mechanisms of defence. *J Psychopharmacol* 1991;5:305–315.
67. Depaulis A, Bandler R, Vergnes M. Characterization of pretentorial periaqueductal gray matter neurons mediating intraspecific defensive behaviors in the rat by microinjections of kainic acid. *Brain Res* 1989;486:121–132.

68. Depaulis A, Keay KA, Bandler R. Longitudinal neuronal organization of defensive reactions in the midbrain periaqueductal gray region of the rat. *Exp Brain Res* 1992;90:307–318.
69. Depaulis A, Keay KA, Bandler R. Quiescence and hyporeactivity evoked by activation of cell bodies in the ventrolateral midbrain periaqueductal gray of the rat. *Exp Brain Res* 1994;99:75–83.
70. Douglas RJ. *Inhibition and learning: pavlovian conditioning in the brain.* London: Academic Press, 1972.
71. Edmunds M. *Defense in animals.* Essex, UK: Longmans, 1974.
72. Everitt BJ, Cador M, Robbins TW. Interactions between the amygdala and ventral striatum in stimulus-reward associations: studies using a second-order schedule of sexual reinforcement. *Neuroscience* 1989;30:63–75.
73. Everitt BJ, Morris KA, O'Brien A, et al. The basolateral amygdala-ventral striatal system and conditioned place preference: further evidence of limbic-striatal interactions underlying reward-related processes. *Neuroscience* 1991;42:1–18.
74. Falls WA, Davis M. Behavioral and physiological analysis of fear inhibition. In: Friedman MJ, Charney DS, Deutch AY, eds. *Neurobiological and clinical consequences of stress: from normal adaptation to PTSD.* Philadelphia: Lippincott–Raven, 1995: 177–202.
75. Falls WA, Josselyn SA, Gewirtz JC, et al. The nucleus accumbens if not critical for condtioned inhibition of fear as measured with fear-potentiated startle. *Soc Neurosci Abstr* 1998;28.
76. Falls WA, Miserendino MJ D, Davis M. Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. *J Neurosci* 1992;12:854–863.
77. Falls WF, Davis M. Visual cortex ablations do not prevent extinction of fear-potentiated startle using a visual conditioned stimulus. *Behav Neural Biol* 1994;60:259–270.
78. Fanselow MS. The midbrain periaqueductal gray as a coordinator of action in response to fear and anxiety. In: Depaulis A, Bandler R, eds. *The midbrain periaqueductal gray matter: functional, anatomical and neurochemical organization.* New York: Plenum, 1991:151–173.
79. Fanselow MS. Neural organization of the defensive behavior system responsible for fear. *Psychonom Bull Rev* 1994;1: 429–438.
80. Feldman S, Weidenfeld J. The excitatory effects of the amygdala on hypothalamo-pituitary-adrenocortical responses are mediated by hypothalamic norepinephrine, serotonin, and CRF-41. *Brain Res Bull* 1998;45:389–393.
81. Fendt M. Different regions of the periaqueductal grey are involved differently in the expression and conditioned inhibition of fear-potentiated startle. *Eur J Neurosci* 1998;10:3876–3884.
82. Fendt M, Koch M, Schnitzler HU. Amygdaloid noradrenaline is involved in the sensitization of the acoustic startle response in rats. *Pharmacol Biochem Behav* 1994;48:307–314.
83. File SE, Rodgers RJ. Partial anxiolytic actions of morphine sulphate following microinjection into the central nucleus of the amygdala in rats. *Pharmacol Biochem Behav* 1979;11:313–318.
84. Fox GD, Holland PC. Neurotoxic hippocampal lesions fail to impair reinstatement of an appetitively conditioned response. *Behav Neurosci* 1998;112:255–260.
85. Fox RJ, Sorenson CA. Bilateral lesions of the amygdala attenuate analgesia induced by diverse environmental challenges. *Brain Res* 1994;648:215–221.
86. Frankland PW, Josselyn SA, Bradwejn J, et al. Activation of amygdala cholecystokinin B receptors potentiates the acoustic startle response in the rat. *J Neurosci* 1997;17:1838–1847.
87. Frohardt R, Guarraci FA, Bouton ME. The effects of neurotoxic hippocampal lesions on two effects of context following fear extinction. *Behav Neurosci* 2000;114:227–240.
88. Galeno TM, VanHoesen GW, Brody MJ. Central amygdaloid nucleus lesion attenuates exaggerated hemodynamic responses to noise stress in the spontaneously hypertensive rat. *Brain Res* 1984;291:249–259.
89. Gallagher M, Kapp BS, McNall CL, et al. Opiate effects in the amygdala central nucleus on heart rate conditioning in rabbits. *Pharmacol Biochem Behav* 1981;14:497–505.
90. Gallagher M, Kapp BS, Pascoe JP. Enkephalin analogue effects in the amygdala central nucleus on conditioned heart rate. *Pharmacol Biochem Behav* 1982;17:217–222.
91. Gean PW, Chang FC, Huang CC, et al. Long-term enhancement of EPSP and NMDA receptor-mediated synaptic transmission in the amygdala. *Brain Res Bull* 1993;31:7–11.
92. Gewirtz J, Davis M. Second order fear conditioning prevented by blocking NMDA receptors in the amygdala. *Nature* 1997; 388:471–474.
93. Gewirtz JC, Davis M. Application of pavlovian higher-order conditioning to the analysis of the neural substrates of learning and memory. *Neuropharmacology* 1998;37:453–460.
94. Gewirtz JC, Falls WA, Davis M. Normal conditioned inhibition and extinction of freezing and fear potentiated startle following electrolytic lesions of medial prefrontal cortex. *Behav Neurosci* 1997;111:712–726.
95. Gewirtz JC, McNish KA, Davis M. Disruption of contextual freezing, but not contextual "blocking" of fear-potentiated startle after lesions of the dorsal hippocampus. *Behav Neurosci* 2000; 114:64–76.
96. Gewirtz JC, McNish KA, Davis M. Is the hippocampus necessary for contextual fear conditioning? *Behav Brain Res* 2000; 110:83–95.
97. Gisquet-Verrier P, Dutrieux G, Richer P, et al. Effects of lesions to the hippocampus on contextual fear: evidence for a disruption of freezing and avoidance behavior but not context conditioning. *Behav Neurosci* 1999;113:507–522.
98. Gloor P. Role of the amygdala in temporal lobe epilepsy. In: Aggleton JP, ed. *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction.* New York: Wiley–Liss, 1992: 505–538.
99. Gloor P, Olivier A, Quesney LF. The role of the amygdala in the expression of psychic phenomena in temporal lobe seizures. In: Ben-Ari Y, ed. *The amygdaloid complex.* New York: Elsevier/ North Holland, 1981:489–507.
100. Goddard GV. Functions of the amygdala. *Psychol Bull* 1964; 62:89–109.
101. Goldstein LE, Rasmusson AM, Bunney BS, et al. Role of the amygdala in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress in the rat. *J Neurosci* 1996;16:4787–4798.
102. Good M, Honey RC. Dissociable effects of selective lesions to hippocampal subsytems on exploratory behavior, contextual learning and spatial learning. *Behav Neurosci* 1997;111: 487–493.
103. Graeff FG. Animal models of aversion. In: Simon P, Soubrie P, Wildlocher D, eds. *Selected models of anxiety, depression and psychosis.* vol 1. Basel: Karger, 1988:115–141.
104. Graeff FG, Silveira MCL, Nogueira RL, et al. Role of the amygdala and periaqueductal gray in anxiety and panic. *Behav Brain Res* 1993;58:123–131.
105. Green S, Vale AL. Role of amygdaloid nuclei in the anxiolytic effects of benzodiazepines in rats. *Behav Pharmacol* 1992;3: 261–264.
106. Grijalva CV, Levin ED, Morgan M, et al. Contrasting effects of centromedial and basolateral amygdaloid lesions on stress-related responses in the rat. *Physiol Behav* 1990;48:495–500.
107. Guarraci FA, Frohardt RJ, Kapp BS. Amygdaloid D1 dopamine receptor involvement in pavlovian fear conditioning. *Brain Res* 1999;827:28–40.
108. Haralambous T, Westbrook RF. An infusion of bupivacaine

into the nucleus accumbens disrupts the acquisition but not the expression of contextual fear conditioning. *Behav Neurosci* 1999; 113:925–940.
109. Harris JA, Westbrook RF. Benzodiazepine-induced amnesia in rats: reinstatement of conditioned performance by noxious stimulation on test. *Behav Neurosci* 1998;112:183–192.
110. Harris JA, Westbrook RF. Evidence that GABA transmission mediates context-specific extinction of learned fear. *Psychopharmacology* 1998;140:105–115.
111. Harris JA, Westbrook RF. The benzodiazepine midazolam does not impair pavlovian fear conditioning but regulates when and where fear is expressed. *J Exp Psychol Anim Behav Process* 1999; 25:236–246.
112. Hatfield T, Han J-S, Conley M, et al. Neurotoxic lesions of basolateral, but not central, amygdala interfere with pavlovian second-order conditioning and reinforcer devaluation effects. *J Neurosci* 1996;16:5256–5265.
113. Hatfield T, McGaugh JL. Norepinephrine infused into the basolateral amygdala posttraining enhances retention in the spatial water maze task. *Neurobiol Learn Mem* 1999;71:232–239.
114. Heilig M, McLeod S, Brot M, et al. Anxiolytic-like action of neuropeptide Y: mediation by Y1 receptors in amygdala, and dissociation from food intake effects. *Neuropsychopharmacology* 1993;8:357–363.
115. Heinrichs SC, Menzaghi F, Schulteis G, et al. Suppression of corticotropoin-releasing factor in the amygdala attenuates aversive consequences of morphine withdrawal. *Behav Pharmacol* 1995;6:74–80.
116. Heinrichs SC, Pich EM, Miczek KA, et al. Corticotropin-releasing factor antagonist reduces emotionality in socially defeated rats via direct neurotropic action. *Brain Res* 1992;581:190–197.
117. Heit G, Smith ME, Halgren E. Neural encoding of individual words and faces by the human hippocampus and amygdala. *Nature* 1988;333:773–775.
118. Helmstetter FJ. The amygdala is essential for the expression of conditioned hypoalgesia. *Behav Neurosci* 1992;106:518–528.
119. Helmstetter FJ. Contribution of the amygdala to learning and performance of conditional fear. *Physiol Behav* 1992;51: 1271–1276.
120. Helmstetter FJ. Stress-induced hypoalgesia and defensive freezing are attenuated by application of diazepam to the amygdala. *Pharmacol Biochem Behav* 1993;44:433–438.
121. Helmstetter FJ, Tershner SA, Poore LH, et al. Antinociception following opioid stimulation of the basolateral amygdala is expressed through the periaqueductal gray and rostral ventromedial medulla. *Brain Res* 1998;779:104–118.
122. Henke PG. The amygdala and restraint ulcers in rats. *J Comp Physiol Psychol* 1980;94:313–323.
123. Henke PG. Facilitation and inhibition of gastric pathology after lesions in the amygdala in rats. *Physiol Behav* 1980;25:575–579.
124. Henke PG. Attenuation of shock-induced ulcers after lesions in the medial amygdala. *Physiol Behav* 1981;27:143–146.
125. Hernandez DE, Salaiz AB, Morin P, et al. Administration of thyrotropin-releasing hormone into the central nucleus of the amygdala induces gastric lesions in rats. *Brain Res Bull* 1990; 24:697–699.
126. Hodges H, Green S, Glenn B. Evidence that the amygdala is involved in benzodiazepine and serotonergic effects on punished responding but not on discrimination. *Psychopharmacology* 1987;92:491–504.
127. Holland PC, Lamoureux JA, Han J-S, et al. Hippocampal lesions interfere with pavlovian negative ossasion setting. *Hippocampus* 1999;9:143–157.
128. Holt W, Maren S. Muscimol inactivation of the dorsal hippocampus impairs contextual retrieval of fear memory. *J Neurosci* 1999;19:9054–9062.
129. Huang YY, Kandel ER. Postsynaptic induction and PKA-dependent expression of LTP in the lateral amygdala. *Neuron* 1998;21:169–178.
130. Ikegaya Y, Abe K, Saito H, et al. Medial amygdala enhances synaptic transmission and synaptic plasticity in the dentate gyrus of rats *in vivo. J Neurophysiology* 1995;74:2201–2203.
131. Ikegaya Y, Saito H, Abe K. Attenuated hippocampal long-term potentiation in basolateral amygdala-lesioned rats. *Brain Res* 1994;1994:157–164.
132. Ikegaya Y, Saito H, Abe K. Amygdala *N*-methyl-D-aspartate receptors participate in the induction of long-term potentiation in the dentate gyrus *in vivo. Neurosci Lett* 1995;192:193–196.
133. Ikegaya Y, Saito H, Abe K. High-frequency stimulation of the basolateral amygdala facilitates the induction of long-term potentiation in the dentate gyrus *in vivo. Neurosci Res* 1995;22: 203–207.
134. Ikegaya Y, Saito H, Abe K. Requirement of basolateral amygdala neuron activity for the induction of long-term potentiation in the dentate gyrus *in vivo. Brain Res* 1995;671:351–354.
135. Irwin W, Davidson RJ, Lowe MJ, et al. Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *Neuroreport* 1996;7:1765–1769.
136. Ishikawa T, Yang H, Tache Y. Medullary sites of action of the TRH analogue, RX 77368, for stimulation of gastric acid secretion in the rat. *Gastroenterology* 1988;95:1470–1476.
137. Iwata J, LeDoux JE, Meeley MP, et al. Intrinsic neurons in the amygdala field projected to by the medial geniculate body mediate emotional responses conditioned to acoustic stimuli. *Brain Res* 1986;383:195–214.
138. Jacobson R. Disorders of facial recognition, social behaviour and affect after combined bilateral amygdalotomy and subcaudate tractotomy: a clinical and experimental study. *Psychol Med* 1986;16:439–450.
139. Kapp BS, Frysinger RC, Gallagher M, et al. Amygdala central nucleus lesions: effect on heart rate conditioning in the rabbit. *Physiol Behav* 1979;23:1109–1117.
140. Kapp BS, Supple WF, Whalen PJ. Effects of electrical stimulation of the amygdaloid central nucleus on neocortical arousal in the rabbit. *Behav Neurosci* 1994;108:81–93.
141. Kapp BS, Whalen PJ, Supple WF, et al. Amygdaloid contributions to conditioned arousal and sensory information processing. In: Aggleton JP, ed. *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction.* New York: Wiley–Liss, 1992:229–254.
142. Kapp BS, Wilson A, Pascoe JP, et al. A neuroanatomical systems analysis of conditioned bradycardia in the rabbit. In: Gabriel M, Moore J, eds. *Neurocomputation and learning: foundations of adaptive networks.* New York: Bradford Books, 1990:55–90.
143. Kehoe EJ, Macrae M, Hutchinson CL. MK-801 protects conditioned response from extinction in the rabbit nictitating membrane preparation. *Psychobiology* 1996;24:127–135.
144. Kemble ED, Blanchard DC, Blanchard RJ. Effects of regional amygdaloid lesions on flight and defensive behaviors of wild black rats *(Rattus rattus). Physiol Behav* 1990;48:1–5.
145. Kemble ED, Blanchard DC, Blanchard RJ, et al. Taming in wild rats following medial amygdaloid lesions. *Physiol Behav* 1984;32:131–134.
146. Killcross S, Robbins TW, Everitt BJ. Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. *Nature* 1997;388:377–380.
147. Kim C, Kim CC, Kim JK, et al. Fear response and aggressive behavior in hippocampectomized house rats. *Brain Res* 1971; 29:237–251.
148. Kim JJ, Fanselow MS. Modality-specific retrograde amnesia of fear. *Science* 1992;256:675–677.
149. Kim M, Campeau S, Falls WA, et al. Infusion of the non-

NMDA receptor antagonist CNQX into the amygdala blocks the expression of fear-potentiated startle. *Behav Neural Biol* 1993;59:5–8.
150. LaBar KS, Gatenby JC, Gore JC, et al. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron* 1998;20:937–945.
151. Lamont EW, Kokkinidis L. Infusion of the dopamine D1 receptor antagonist SCH 23390 into the amygdala blocks fear expression in a potentiated startle paradigm. *Brain Res* 1998;795: 128–136.
152. Leaton RN, Borszcz GS. Hippocampal lesions and temporally chained conditioned stimuli in a conditioned suppression paradigm. *Psychobiology* 1990;18:81–88.
153. LeBar KS, LeDoux JE, Spencer DD, et al. Impaired fear conditioning following unilateral temporal lobectomy in humans. *J Neurosci* 1995;15:6846–6855.
154. LeDoux JE, Cicchetti P, Xagoraris A, et al. The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. *J Neurosci* 1990;10:1062–1069.
155. LeDoux JE, Iwata J, Cicchetti P, et al. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *J Neurosci* 1988;8: 2517–2529.
156. LeDoux JE, Romanski L, Xagoraris A. Indelibility of subcortical memories. *J Cogn Neurosci* 1989;1:238–243.
157. LeDoux JE, Sakaguchi A, Reis DJ. Interuption of projections from the medial geniculate mediate emotional responses conditioned to acoustic stimuli. *J Neurosci* 1986;17:615–627.
158. Lee H, Kim J. Amygdalar NMDA receptors are critical for new fear learning in previously fear-conditioned rats. *J Neurosci* 1998;18:8444–8454.
159. Lee Y, Walker D, Davis M.Lack of a temporal gradient of retrograde amnesia following NMDA-induced lesions of the basolateral amygdala assessed with the fear-potentiated paradigm. *Behav Neurosci.* 1996;110:836–839.
160. Leonard CM, Rolls ET, Wilson FAW, et al. Neurons in the amygdala of the monkey with responses selective for faces. *Behav Brain Res* 1985;15:159–176.
161. Liebsch G, Landgraf R, Gerstberger R, et al. Chronic infusion of a CRH1 receptor antisense oligodeoxynucleotide into the central nucleus of the amygdala reduced anxiety-related behavior in socially defeated rats. *Regul Pept* 1995;59:229–239.
162. Lovick TA. Panic disorder: a malfunction of multiple transmitter control systems with the midbrain periaqueductal gray matter. *Neuroscientist* 2000;6:48–59.
163. Maldonado R, Stinus L, Gold LH, et al. Role of different brain structures in the expression of the physical morphine withdrawal syndrome. *J Pharmacol Exp Ther* 1992;261:669–677.
164. Manning BH, Mayer DJ. The central nucleus of the amygdala contributes to the production of morphine antinociception in the formalin test. *Pain* 1995;63:141–152.
165. Manning BH, Mayer DJ. The central nucleus of the amygdala contributes to the production of morphine antinociception in the rat tail-flick test. *J Neurosci* 1995;15:8199–8213.
166. Maren S, Aharonov G, Fanselow MS. Retrograde abolition of conditioned fear after excitotoxic lesions in the basolateral amygdala of rats: absence of a temporal gradient. *Behav Neurosci* 1996;110:718–726.
167. Maren S, Aharonov G, Fanselow MS. Neurotoxic lesions of the dorsal hippocampus and pavlovian fear conditioning. *Behav Brain Res* 1997;88:261–274.
168. McCabe PM, Gentile CG, Markgraf CG, et al. Ibotenic acid lesions in the amygdaloid central nucleus but not in the lateral subthalamic area prevent the acquisition of differential pavlovian conditioning of bradycardia in rabbits. *Brain Res* 1992; 580:155–163.
169. McDonald AJ. Cortical pathways to the mammalian amygdala. *Prog Neurobiol* 1998;55:257–332.
170. McGaugh JL, Introini-Collison IB, Cahill L, et al. Neuromodulatory systems and memory storage: role of the amygdala. *Behav Brain Res* 1993;58:81–90.
171. McGaugh JL, Introini-Collison IB, Cahill L, et al. Involvement of the amygdala in neuromodulatory influences on memory storage. In: Aggleton JP, ed. *The amygdala: neurobiological aspects of emotion, memory and mental dysfunction.* New York: Wiley–Liss, 1992:431–451.
172. McIntosh AR, Gonzalez-Lima F. Functional network interactions between parallel auditory pathways during pavlovian conditioned inhibition. *Brain Res* 1995;683:228–241.
173. McKernan MG, Shinnick-Gallagher P. Fear conditioning induces a lasting potentiation of synaptic currents *in vitro. Nature* 1997;390:607–611.
174. McNish KA, Gewirtz JC, Davis M. Evidence of contextual fear conditioning following lesions of the hippocampus: a disruption of freezing but not fear-potentiated startle. *J Neurosci* 1997;17: 9353–9360.
175. Moller C, Wujkybdm K, Sommer W, et al. Decreased experimental anxiety and voluntary ethanol consumption in rats following central but not basolateral amygdala lesions. *Brain Res* 1997;760:94–101.
176. Morgan MA, LeDoux JE. Medial prefrontal cortex (mPFC) and the extinction of fear: Differential effecs of pre- or post-training lesions. *Soc Neurosci Abstr* 1996;22:1116.
177. Morgan MA, LeDoux JE. Contribution of ventrolateral prefrontal cortex to the acquistion and extinction of conditioned fear in rats. *Neurobiol Learn Mem* 1999;72:244–251.
178. Morgan MA, Romanski LM, LeDoux JE. Extinction of emotional learning: contribution of medial prefrontal cortex. *Neurosci Lett* 1993;163:109–113.
179. Morris JS, Friston KJ, Buchel C, et al. A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* 1998;121:47–57.
180. Morris JS, Frith CD, Perrett DI, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* 1996;383:812–815.
181. Morrow BA, Elsworth JD, Rasmusson AM, et al. The role of mesoprefrontal dopamine neurons in the acquisition and expression of conditioned fear in the rat. *Neuroscience* 1999;92: 553–564.
182. Morrow NS, Hodgson DM, Garrick T. Microinjection of thyrotropin-releasing hormone analogue into the central nucleus of the amygdala stimulates gastric contractility in rats. *Brain Res* 1996;735:141–148.
183. Muller J, Corodimas KP, Fridel Z, et al. Functional inactivation of the lateral and basal nuclei of the amygdala by muscimol infusion prevents fear conditioning to an explicit conditioned stimulus and to contextual stimuli. *Behav Neurosci* 1997;111: 683–691.
184. Nakamura K, Mikami A, Kubota K. Activity of single neurons in the monkey amygdala during performance of a visual discrimination task. *J Neurophysiol* 1992;67:1447–1463.
185. Packard MG, Cahill L, McGaugh JL. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proc Natl Acad Sci USA* 1994;91:8477–8481.
186. Packard MG, Teather LA. Amygdala modulation of multiple memory systems: hippocampus and caudate-putamen. *Neurobiol Learn Mem* 1998;69:163–203.
187. Pavlov IP. *Conditioned reflexes.* Oxford: Oxford University Press, 1927.
188. Pesold C, Treit D. The central and basolateral amygdala differentially mediate the anxiolytic effects of benzodiazepines. *Brain Res* 1995;671:213–221.

189. Petersen EN, Braestrup C, Scheel-Kruger J. Evidence that the anticonflict effect of midazolam in amygdala is mediated by the specific benzodiazepine receptor. *Neurosci Lett* 1985;53: 285–288.
190. Phillips RG, LeDoux JE. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav Neurosci* 1992;106:274–285.
191. Quirk GJ, Kohanski GJ, Ayala O. Lesions of medial prefrontal cortex retard extinction of fear conditioning between sessions, but not within a session. *Soc Neurosci Abstr* 1998;28:1683.
192. Quirk GJ, Repa JC, LeDoux JE. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. *Neuron* 1995;15: 1029–1039.
193. Quirk GJ, Rosaly E, Romero RV, et al. NMDA receptors are required for long-term but not short-term memory of extinction learning. *Soc Neurosci Abstr* 1999;25:1620.
194. Rassnick S, Heinrichs SC, Britton KT, et al. Microinjection of a corticotroin-releasing factor antagonist into the central nucleus of the amygdala reverses anxiogenic-like effects of ethanol withdrawal. *Brain Res* 1993;605:25–32.
195. Ray A, Henke PG. Enkephalin-dopamine interactions in the central amygdalar nucleus during gastric stress ulcer formation in rats. *Behav Brain Res* 1990;36:179–183.
196. Ray A, Henke PG. TRH-enkephalin interactions in the amygdaloid complex during gastric stress ulcer formation in rats. *Regul Pept* 1991;35:11–17.
197. Ray A, Henke PG, Sullivan RM. Effects of intra-amygdalar thyrotropin releasing hormone (TRH) and its antagonism by atropine and benzodiazepines during stress ulcer formation in rats. *Pharmacol Biochem Behav* 1990;36:597–601.
198. Ray A, Sullivan RM, Henke PG. Interactions of thyrotropin-releasing hormone (TRH) with neurotensin and dopamine in the central nucleus of the amygdala during stress ulcer formation in rats. *Neurosci Lett* 1988;91:95–100.
199. Reiman EM, Lane RD, Ahern GL, et al. Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry* 1997;54:918–925.
200. Rescorla RA. Pavlovian conditioned inhibition. *Psychol Bull* 1969;72:77–94.
201. Rescorla RA, Heth CD. Reinstatement of fear to an extinguished conditioned stimulus. *J Exp Psychol Anim Behav Process* 1975;1:88–96.
202. Richmond MA, Pouzet B, Veenman L, et al. Dissociating context and space within the hippocampus: effects of complete, dorsal, and ventral excitotixic hippocampal lesions on conditioned freezing and spatial learning. *Behav Neurosci* 1999;113: 1189–1203.
203. Rogan MT, LeDoux JE. LTP is accompanied by commensurate enhancement of auditory-evoked responses in a fear conditioning circuit. *Neuron* 1995;15:127–136.
204. Rogan MT, Staubli UV, LeDoux JE. Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* 1997;390:604–607.
205. Rolls ET. Neurons in the cortex of the temporal lobe and in the amygdala of the monkey with responses selective for faces. *Hum Neurobiol* 1984;3:209–222.
206. Romanski LM, Clugnet MC, Bordi F, et al. Somatosensory and auditory convergence in the lateral nucleus of the amygdala. *Behav Neurosci* 1993;107:444–450.
207. Roozendaal B, Koolhaas JM, Bohus B. Central amygdaloid involvement in neuroendocrine correlates of conditioned stress responses. *J Neuroendocrinol* 1992;4:483–489.
208. Roozendaal B, Schoorlemmer GH, Koolhaas JM, et al. Cardiac, neuroendocrine, and behavioral effects of central amygdaloid vasopressinergic and oxytocinergic mechanisms under stress-free conditions in rats. *Brain Res Bull* 1993;32:573–579.
209. Roozendaal B, Wiersma A, Driscoll P, et al. Vasopressinergic modulation of stress responses in the central amygdala of the Roman high-avoidance and low-avoidance rat. *Brain Res* 1992; 596:35–40.
210. Sajdyk TJ, Schober DA, Gehlert DR, et al. Role of corticotropin-releasing factor and urocortin within the basolateral amygdala of rats in anxiety and panic responses. *Behav Brain Res* 1999;100:207–215.
211. Sajdyk TJ, Shekhar A. Excitatory amino acid receptor antagonists block the cardiovascular and anxiety responses elicited by γ-aminobutyric acid: a receptor blockade in the basolateral amygdala of rats. *J Pharmacol Exp Ther* 1997;283:969–977.
212. Sajdyk TJ, Shekhar A. Excitatory amino acid receptors in the bsolateral amygdala regulate anxiety responses in the social interaction test. *Brain Res* 1997;764:262–264.
213. Sajdyk TJ, Vandergriff MG, Gehlert DR. Amygdalar neuropeptide Y Y-1 receptors mediate the anxiolytic-like actions of neuropeptide Y in the social interaction test. *Eur J Pharmacol* 1999; 368:143–147.
214. Sananes CB, Davis M. *N*-methyl-D-aspartate lesions of the lateral and basolateral nuclei of the amygdala block fear-potentiated startle and shock sensitization of startle. *Behav Neurosci* 1992;106:72–80.
215. Sanders SK, Shekhar A. Blockade of $GABA_A$ receptors in the region of the anterior basolateral amygdala of rats elicits increases in heart rate and blood pressure. *Brain Res* 1991;576: 101–110.
216. Sanders SK, Shekhar A. Regulation of anxiety by $GABA_A$ receptors in the rat amygdala. *Pharmacol Biochem Behav* 1995;52: 701–706.
217. Sanghera MK, Rolls ET, Roper-Hall A. Visual responses of neurons in the dorsolateral amygdala of the alert monkey. *Exp Neurol* 1979;63:610–626.
218. Scheel-Kruger J, Petersen EN. Anticonflict effect of the benzodiazepines mediated by a GABAergic mechanism in the amygdala. *Eur J Pharmacol* 1982;82:115–116.
219. Schmaltz LW, Theiosus J. Acquisition and extinction of a classically conditioned response in hippocampectomized rabbits *(Oryctolagus cuniculus). J Comp Physiol Psychol* 1972;79:328–333.
220. Schoenbaum G, Chiba AA, Gallagher M. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. *Nat Neurosci* 1998;1:155–159.
221. Schoenbaum G, Chiba AA, Gallagher M. Neural encoding in orbitofrontal cortex and basolateral amygdala during olfactory discrimination learning. *J Neurosci* 1999;19:1876–1884.
222. Schwaber JS, Kapp BS, Higgins GA, et al. Amygdaloid basal forebrain direct connections with the nucleus of the solitary tract and the dorsal motor nucleus. *J Neurosci* 1982;2:1424–1438.
223. Selden NR, Everitt BJ, Jarrard LE, et al. Complementary roles for the amygdala and hippocampus in aversive conditioning to explicit and contextual cues. *Neuroscience* 1991;42:335–350.
224. Selden NRW, Everitt BJ, Jarrard LE, et al. Complementary roles for the amygdala and hippocampus in aversive conditioning to explicit and contextual cues. *Neuroscience* 1991;42:335–350.
225. Shibata K, Kataoka Y, Yamashita K, et al. An important role of the central amygdaloid nucleus and mammillary body in the mediation of conflict behavior in rats. *Brain Res* 1986;372: 159–162.
226. Shindou T, Watanabe S, Yamamoto K, et al. NMDA receptor-dependent formation of long-term potentiation in the rat medial amygdala neuron in an in vitro slice prepartation. *Brain Res Bull* 1993;31:667–672.
227. Shors TJ, Mathew PR. NMDA receptor antagonism in the lateral/basolateral but not central nucleus of the amygdala prevents

the induction of facilitated learning in response to stress. *Learn Mem* 1998;5:220–230.
228. Solomon PR. Role of hippocampus in blocking and conditioned inhibition of the rabbit's nictitating membrane response. *J Comp Physiol Psychiatry* 1977;91:407–417.
229. Soltis RP, Cook JC, Gregg AE, et al. EAA receptors in the dorsomedial hypothalamic area mediate the cardiovascular response to activation of the amygdala. *Am J Physiol* 1998;275: R624–R631.
230. Soltis RP, Cook JC, Gregg AE, et al. Interaction of GABA and excitatory amino acids in the basolateral amygdala: role in cardiovascular regulation. *J Neurosci* 1997;17:9367–9374.
231. Stinus L, LeMoal M, Koob GF. Nucleus accumbens and amygdala are possible substrates for the aversive stimulus effects of opiate withdrawal. *Neuroscience* 1990;37:767–773.
232. Sullivan RM, Henke PG, Ray A, et al. The GABA/benzodiazepine receptor complex in the central amygdalar nucleus and stress ulcers in rats. *Behav Neural Biol* 1989;51:262–269.
233. Swiergiel AH, Takahashi LK, Kalin NH. Attenuation of stress-induced behavior by antagonism of corticotropin-releasing factor in the central amygdala of the rat. *Brain Res* 1993;623: 229–234.
234. Takao K, Nagatani T, Kasahara K-I, et al. Role of the central serotonergic system in the anticonflict effect of *d*-AP159. *Pharmacol Biochem Behav* 1992;43:503–508.
235. Taylor JR, Punch LJ, Elsworth JD. A comparison of the effects of clonidine and CNQX infusion into the locus coeruleus and the amygdala on naloxone-precipitated opiate withdrawal in the rat. *Psychopharmacology* 1998;138:133–142.
236. Taylor JR, Robbins TW. Enhanced behavioral control by conditioned reinforcers following microinjections of D-amphetamine into the nucleus accumbens. *Psychopharmacology* 1984;84: 405–412.
237. Teich AH, McCabe PM, Gentile CG, et al. Role of auditory cortex in the acquisition of differential heart rate conditioning. *Physiol Behav* 1988;44:405–412.
238. Thomas E, Yadin E, Strickland CE. Septal unit activity during classical conditioning: a regional comparison. *Brain Res* 1991; 547:303–308.
239. Thomas SR, Lewis ME, Iversen SD. Correlation of [3H]diazepam binding density with anxiolytic locus in the amygdaloid complex of the rat. *Brain Res* 1985;342:85–90.
240. Tranel D, Hyman BT. Neuropsychological correlates of bilateral amygdala damage. *Arch Neurol* 1990;47:349–355.
241. Ursin H, Kaada BR. Functional localization within the amygdaloid complex in the cat. *Electroencephalogr Clin Neurophysiol* 1960;12:109–122.
242. Van de Kar LD, Piechowski RA, Rittenhouse PA, et al. Amygdaloid lesions: differential effect on conditioned stress and immobilization-induced increases in cortiocosterone and renin secretion. *Neuroendocrinology* 1991;15:89–95.
243. Walker DL, Davis M. Double dissociation between the involvement of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in light-enhanced versus fear-potentiated startle. *J Neurosci* 1997;17:9375–9383.
244. Whalen PJ. Fear, vigilance, and ambiguity: initial neuroimaging studies of the human amygdala. *Curr Dir Psychol Sci* 1999;7: 177–188.
245. Whalen PJ, Rauch SL, Etcoff NL, et al. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci* 1998;18:411–418.
246. Whalen PJ, Shin LM, McInerney SC, et al. Greater fMRI activation to fearful vs. angry facial expression in the amygdaloid region. *Neurosci Abstr* 1998;24:692.
247. Wiersma A, Baauw AD, Bohus B, et al. Behavioural activation produced by CRH but not α-helical CRH (CRH-receptor antagonist) when microinfused into the central nucleus of the amygdala under stress-free conditions. *Psychoneuroendocrinology* 1995;20:423–432.
248. Wiersma A, Bohus B, Koolhaas JM. Corticotropin-releasing hormone microinfusion in the central amygdala diminishes a cardiac parasympathetic outflow under stress-free conditions. *Brain Res* 1993;625:219–227.
249. Wiersma A, Bohus B, Koolhaas JM. Corticotropin-releasing hormone microinfusion in the central amygdala enhances active behaviour responses in the conditioned burying paradigm. *Stress* 1997;1:113–122.
250. Wiersma A, Tuinstra T, Koolhaas JM. Corticotropin-releasing hormone microinfusion into the basolateral nucleus of the amygdala does not induce any changes in cardiovascular, neuroendocrine or behavioural output in a stress-free condition. *Brain Res* 1993;625:219–227.
251. Willcox BJ, Poulin P, Veale WL, et al. Vasopressin-induced motor effects: localization of a sensitive site in the amygdala. *Brain Res* 1992;596:58–64.
252. Wilson A, Brooks D, Bouton ME. The role of the rat hippocampal system in several effects of context extincition. *Behav Neurosci* 1995;109:828–836.
253. Yadin E. Unit activity in the medial septum during differential appetitive conditioning. *Behav Brain Res* 1989;33:45–50.
254. Yadin E, Thomas E. Septal correlates of conditioned inhibition. *J Comp Physiol Psychol* 1981;95:331–340.
255. Yadin E, Thomas E. Stimulation of the lateral septum attenuates immobilization-induced stress ulcers. *Physiol Behav* 1996;59: 883–886.
256. Yamashita K, Kataoka Y, Shibata K, et al. Neuroanatomical substrates regulating rat conflict behavior evidenced by brain lesioning. *Neurosci Lett* 1989;104:195–200.
257. Young AW, Aggleton JP, Hellawell DJ, et al. Face processing impairments after amygdalotomy. *Brain* 1995;118:15–24.
258. Young BJ, Helmstetter FJ, Rabchenuk SA, et al. Effects of systemic and intra-amygdaloid diazepam on long-term habituation of acoustic startle in rats. *Pharmacol Biochem Behav* 1991;39: 903–909.
259. Zhang JX, Harper RM, Ni H. Cryogenic blockade of the central nucleus of the amygdala attenuates aversively conditioned blood pressure and respiratory responses. *Brain Res* 1986;386: 136–145.