Neurobiology of Fear Responses: The Role of the Amygdala

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Evidence from many different laboratories using a variety of experimental techniques and animal species indicates that the amygdala plays a crucial role in conditioned fear and anxiety, as well as attention. Many amygdaloid projection areas are critically involved in specific signs used to measure fear and anxiety. Electrical stimulation of the amygdala elicits a pattern of behaviors that mimic natural or conditioned fear. Lesions of the amygdala block innate or conditioned fear, as well as various measures of attention, and local infusions of drugs into the amygdala have anxiolytic effects in several behavioral tests. N-*methyl*-D-*aspartate (NMDA) receptors in the amygdala may be important in the acquisition of conditioned fear, whereas non-NMDA receptors are important for the expression of conditioned fear. The peptide corticotropin-releasing hormone appears to be especially important in fear or anxiety and may act within the amygdala to orchestrate parts of the fear reaction.*

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Fear is a hypothetical construct that is used to explain the cluster of behavioral effects that are observed and experienced when an organism faces a life-threatening situation. If suddenly confronted by a stranger holding a gun to your face, you will realize instantly that you are in danger, that you could be beaten or even killed. Your hands will sweat, your heart will pound, and your mouth will feel very dry. You will begin to tremble and feel like you can't catch your breath. You may feel the hair standing out on the back of your neck, and your mind will race, trying to decide whether you should hold still, run, or try to take the gun out of the assailant's hand. Your senses of smell, sight, and hearing will heighten, and your pupils will dilate. Later, if you survive, you will remember this terrible incident over and over again, seeing your assailant's face or the gun in apparently vivid detail. Returning to the place where the incident happened will revive those awful memories, often to the point where you will want to avoid that place forever. Thus, fear is a complex set of behavioral reactions that includes both the *expression* and the *experience* of the emotional event. Sweaty palms, increased heart rate, altered respiration, hair standing on end, and dilated pupils are part of the expression of fear. The feelings of dread of potentially being killed, and of having to decide whether to hold still or run, as well as the feeling of your heart pounding or the hair

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FIGURE 1. General scheme believed to occur during classical conditioning using an aversive conditioned stimulus. During training, the aversive stimulus (such as shock) activates a central fear system that produces a constellation of behaviors generally associated with aversive stimuli (unconditioned responses). After consistent pairings of some neutral stimulus such as a light or tone or puff of air with shock during the training phase, the neutral stimulus is now capable of producing a similar fear state and hence the same set of behaviors (conditioned responses) formerly only produced by the shock.

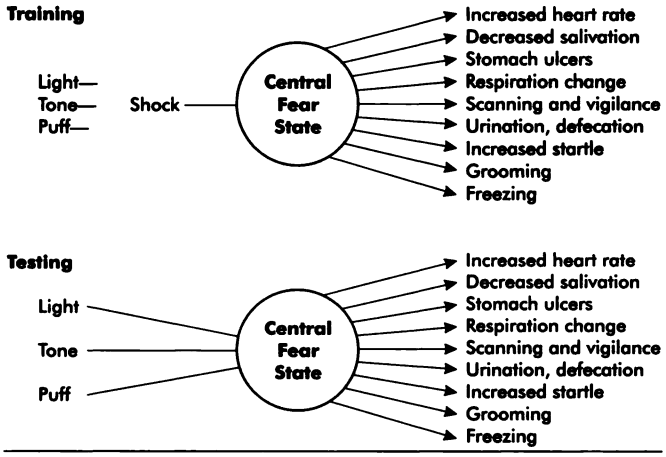


TABLE 1. Correspondence between measures of fear in animals and criteria used to diagnose generalized anxiety in humans

Measures of Fear in Animals	DSM Criteria: Generalized Anxiety
Increased heart rate	Heart pounding
Decreased salivation	Dry mouth
Stomach ulcers	Upset stomach
Respiration change	Increased respiration
Scanning and vigilance	Scanning and vigilance
Increased startle	Jumpiness, easy startle
Urination	Frequent urination
Defecation	Diarrhea
Grooming	Fidgeting
Freezing	Apprehensive expectation

standing upright on the back of your neck, are part of the experience of fear.

Very similar reactions can be seen in animals. If a cat confronts a vicious dog, the cat will assume the familiar "Halloween posture," with its back arched, hair standing on end, and teeth bared. These expressions of fear can be seen easily and measured objectively. We would also presume, based on our own experience, that the cat is experiencing a feeling of fear, of impending death and threat to survival. However, unlike humans, with whom it is possible to discuss the experience of fear and how it feels, such a conversation is not possible with the cat. Hence, we can only infer that the cat is feeling fearful from looking at the situation and the set of behaviors displayed by the cat.

Although the concept is still controversial, it is generally believed that most fears are not innate but instead are learned through experience. For example, monkeys in the wild are terrified by snakes, whereas monkeys bred in captivity are indifferent to snakes. However, once laboratory-raised monkeys see the fear reaction to a snake by another monkey bred in the wild and brought into the laboratory, they rapidly learn the same fear reaction and display it to the snake thereafter.[1] Hence, primates and many other lower animals readily acquire conditioned fear reactions via associations between formerly neutral stimuli and aversive events. Indeed, much of our behavior is determined by the accumulation of a long list of conditioned fears acquired over a lifetime. Very young babies are not afraid of snakes or of strangers holding guns. Such a conditioning mechanism is highly adaptive because it allows us to avoid bad things that have happened to us in the past and not to expose ourselves to things which other people tell us, by their reactions, are potentially dangerous.

Because conditioned fear occurs across so many different species, it can readily be studied in the laboratory by using a variety of animals. For example, when a light, which initially has no behavioral effect, is paired with an aversive stimulus such as a footshock, the light alone can then elicit a constellation of behaviors that are typically used to define a state of fear in animals. To explain these findings, it is generally assumed[2] that during light–shock pairings (training session) the shock elicits a variety of behaviors that can be used to infer a central state of fear (unconditioned responses; Figure 1). After pairing, the light can now produce the same central fear state, and thus the same set of behaviors, formerly produced by the shock (testing session). Moreover, the behavioral effects that are produced in animals by this formerly neutral stimulus (now called a conditioned stimulus; CS) are similar in many respects to the constellation of behaviors that are used to diagnose generalized anxiety in humans (Table 1).

A variety of animal models have been used to infer a central state of fear or anxiety. In some models, fear is inferred when an animal freezes, thus interrupting some ongoing behavior such as pressing a bar or interacting socially with other animals. In other models, fear is measured by changes in autonomic activity such as heart rate, blood pressure, or respiration, or the production of hormones such as corticosteroids. Fear also can be measured by changes in simple reflexes, such as an elevated startle reflex or a change in facial expression. Thus, fear appears to produce a complex pattern of

behaviors that are often associated with each other.

The purpose of this article is to summarize data supporting the idea that the amygdala, and its many efferent projections, may represent a central fear system involved in both the expression and the acquisition of conditioned and unconditioned fear. The article will review how lesions or electrical stimulation of the amygdala or local infusion of drugs into the amygdala alter several components of fear and/or anxiety. These components include various autonomic and hormonal measures (heart rate, blood pressure, respiration, colonic motility, gastric ulcers, adrenocorticotropin [ACTH] and corticosteroid release). Measures of attention and vigilance, as well as various motor behaviors (freezing, reflex facilitation, elevated plus maze, social interaction, bar pressing or licking in the conflict test, high-frequency vocalization) and hypoalgesia will also be covered. This article will thus update and extend previous reviews on this topic.[3]

Because most of the data have been gathered in rodents, much of the review will focus on rodents, although relevant research in primates will also be included. However, it should be emphasized that it is highly probable that the brain systems that have evolved to produce the autonomic and motor effects indicative of fear, so necessary for survival, have been highly conserved across evolution.

In the interest of space, except where noted, the extensive literature on the role of the amygdala in inhibitory avoidance (see reviews[4,5]) and the emerging literature on the role of the amygdala in conditioned taste aversion[6] and opiate withdrawal[7–10] will not be reviewed. Also, the prominent role of other brain areas, such as the central gray (see reviews[11,12]), will not be reviewed specifically except where noted. Finally, again only in the interest of space, this review will not include data on recording cellular activity in the amygdala.

TABLE 2. Inputs to the amygdala

Source of Inputs	Inputs To: Lateral Nucleus	Basolateral Nucleus	Central Nucleus
Cortex			
Temporal cortex	+		
Perirhinal cortex	+	+	
Entorhinal cortex	+	+	
Hippocampus		+	
Piriform cortex	+	+	
Insular cortex	+	+	+
Medial prefrontal cortex	+	+	+
Peri-amygdaloid cortex	+	+	+
Basal forebrain			
Lateral amygdaloid nucleus	+	+	
Basolateral amygdaloid nucleus	+	+	+
Basomedial amygdaloid nucleus	+	+	+
Ventromedial hypothalamic nucleus	+		+
Lateral hypothalamus			+
Bed nucleus of stria terminalis			+
Thalamus			
Lateral posterior nucleus	+		
Medial geniculate complex	+		
Gustatory thalamic nucleus		+	+
Posterior thalamic nucleus	+	+	+
Midline thalamic nucleus	+	+	+
Brainstem			
Ventral tegmental area	+	+	+
Locus coeruleus	+	+	+
Raphe	+	+	+
Parabrachial nucleus		+	+
Central gray			+
Nucleus of solitary tract			+

ANATOMICAL CONNECTIONS BETWEEN THE CENTRAL NUCLEUS OF THE AMYGDALA AND BRAIN AREAS INVOLVED IN FEAR AND ANXIETY

The amygdala consists of several separate cell groups (nuclei), which receive input from many different brain areas (Table 2). Highly processed sensory information from various cortical areas reaches the amygdala through its lateral and basolateral nuclei.[13,14] In turn, these nuclei project to the central nucleus of the amygdala,[13,15–17] which then projects to hypothalamic and brainstem target areas that directly mediate specific signs of fear and anxiety. A great deal of evidence now indicates that the amygdala and its many efferent projections may represent a central fear system involved in both the expression and the acquisition of conditioned fear.[18–23]

Figure 2 summarizes many reports indicating that the central nucleus of the amygdala has direct projections to various anatomical areas that are likely to be involved in specific symptoms of fear or anxiety.

Autonomic and Hormonal Measures

Direct projections from the central nucleus of the amygdala to the lateral hypothalamus[24,25] appear to be involved in activation of the sympathetic autonomic nervous system seen during fear and anxiety.[26] Direct projections to the dorsal motor nucleus of the vagus, nucleus of the solitary tract, and ventrolateral medulla[25,27–30] may be involved in amygdala modulation of heart rate and blood pressure, which are known to be regulated by these brainstem nuclei. Projections of the central nucleus of the amygdala to the parabrachial nucleus[24,25,31,32] may be involved in respiratory changes

during fear; electrical stimulation or lesions of this nucleus are known to alter various measures of respiration.

Direct projections of the central nucleus of the amygdala to the paraventricular nucleus of the hypothalamus,[33] or indirect projections by way of the bed nucleus of the stria terminalis and preoptic area (which receive input from the amygdala[24,34] and project to the paraventricular nucleus of the hypothalamus),[35] may mediate the prominent neuroendocrine responses to fearful or stressful stimuli.

Attention and Vigilance

Projections from the amygdala to the ventral tegmental area[36] may mediate stress-induced increases in dopamine metabolites in the prefrontal cortex.[37] Direct amygdaloid projections to the dendritic field of the locus coeruleus,[36,38] or indirect projections via the paragigantocellularis nucleus,[39] may mediate the response of cells in the locus coeruleus to conditioned fear stimuli[40] and may also be involved in other actions of the locus coeruleus linked to fear and anxiety.[41] Direct projections of the amygdala to the lateral dorsal tegmental nucleus[31] and parabrachial nuclei, which have cholinergic neurons that project to the thalamus,[42] may mediate increases in synaptic transmission in thalamic sensory relay neurons[42] during states of fear. This cholinergic activation, along with increases in thalamic transmission accompanying activation of the locus coeruleus,[43] may thus lead to increased vigilance and superior signal detection in a state of fear or anxiety.

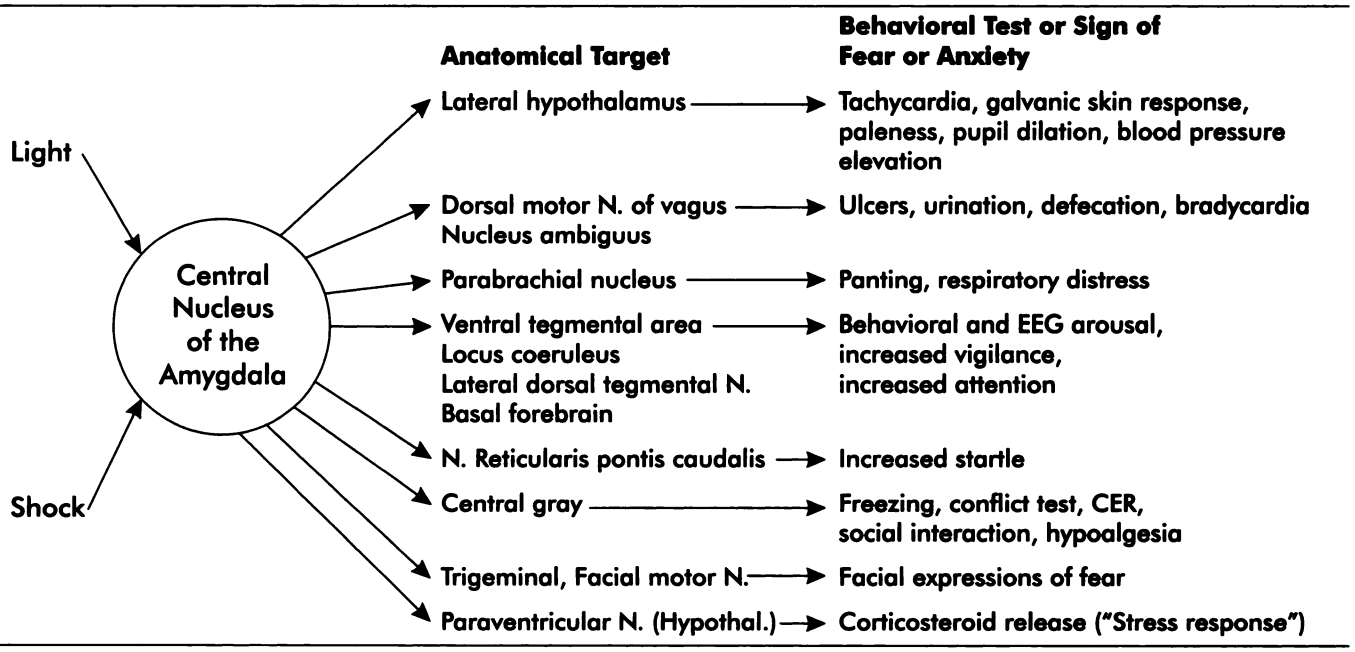
As emphasized by Kapp et al.,[44] in addition to its direct connections to the hypothalamus and brainstem, the central nucleus of the amygdala also has the potential for indirect widespread effects on the cortex via its projections to cholinergic neurons located within the sublenticular substantia innominata, which in turn project to the cortex. In fact, the rapid development of conditioned bradycardia during aversive conditioning, critically dependent on the amygdala, may not simply be a marker of an emotional state of fear, but instead may be a more general process reflecting an increase in attention. In the rabbit, low-voltage fast EEG activity, generally considered a state of cortical readiness for processing sensory information, is acquired during aversive conditioning at the same rate as conditioned bradycardia.[45]

Motor Behavior

Release of norepinephrine onto motor neurons, either via amygdala activation of the locus coeruleus or amygdaloid projections to serotonin-containing raphe neurons,[46] could lead to enhanced motor performance during a state of fear, since both norepinephrine and serotonin facilitate excitation of motor neurons.[47,48]

Direct projections of the central nucleus of the amygdala to the nucleus reticularis pontis caudalis,[49,50] as well as indirect projections to this nucleus via the central gray, probably are involved in fear potentiation

FIGURE 2. **Schematic diagram showing direct connections between the central nucleus of the amygdala and a variety of target areas that may be involved in different animal tests of fear and anxiety. N. = nucleus; Hypothal. = hypothalamus; CER = conditioned emotional response.**



of the startle reflex.[51,52] Direct projections to the lateral tegmental field, including parts of the trigeminal and facial motor nuclei,[53,54] may mediate some of the facial expressions of fear as well as potentiation of the eyeblink reflex.[54,55]

The amygdala also projects to regions of the central gray[56] that appear to be a critical part of a general defense system[57–60] and that have been implicated in conditioned fear in a number of behavioral tests involving freezing,[61] sonic and ultrasonic vocalization,[62] and stress-induced hypoalgesia.[61,63,64]

ELICITATION OF FEAR BY ELECTRICAL OR CHEMICAL STIMULATION OF THE AMYGDALA

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

Autonomic and Hormonal Measures

As outlined by Gloor,[65]

> The most common affect produced by temporal lobe epileptic discharge is fear. . . . It arises "out 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. (p. 513)

In humans, electrical stimulation of the amygdala elicits feelings of fear or anxiety as well as autonomic reactions indicative of fear.[66,67] Although other emotional reactions occasionally are produced, the major reaction is one of fear or apprehension.

In unanesthetized animals, increases in blood pressure have been found following local infusion of either L-glutamate,[68] the cholinergic muscarinic agonist carbachol,[69] or the $GABA_A$ antagonist bicuculline methiodide.[70] 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 3 to 5 infusions.[71] 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. It is possible, therefore, that long-term stress could lead to similar priming effects, which would then make the amygdala more reactive to subsequent stressors, thereby leading to certain types of psychiatric disorders.

Amygdala stimulation can also produce gastric ulceration,[72] which can be associated with chronic fear or anxiety. Electrical stimulation of the amygdala also alters respiration,[73] a prominent symptom of fear, especially in panic disorder. Electrical stimulation of the amygdala has been shown to increase plasma levels of corticosterone, indicating an excitatory effect of the amygdala on the hypothalamic-pituitary-adrenal axis.[74,75]

Attention and Vigilance

Electrical stimulation of sites in the central nucleus that produce bradycardia[76] also produce low-voltage fast EEG activity in both rabbits[77] and rats,[78] which can be blocked by systemic administration of cholinergic antagonists.[77,78] In the cat, electrical stimulation of the dorsal amygdala, including some sites in the central nucleus, elicited EEG desynchronization; this was not blocked by complete midbrain transection,[79] suggesting that it involved rostral projections from the amygdala to the basal forebrain. In fact, EEG desynchronization produced by amygdala stimulation can be blocked by local infusion of lidocaine into the substantia innominata–ventral pallidum of the basal forebrain ipsilateral, but not contralateral, to the site of stimulation.[78] In addition, electrical stimulation of the central nucleus elicits pupillary dilation and pinna orientation,[80,81] both of which would be associated with an increase in sensory processing; indeed, an attention or orienting reflex was the most common response elicited by electrical stimulation of the amygdala in cats described in references.[80,81] These and other observations have led Kapp et al.[44] 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 [conditioned responses] which function to enhance sensory processing" (p. 241).

Motor Behavior

Electrical or chemical stimulation of the central nucleus of the amygdala produces a cessation of ongoing behavior,[20,69,80–84] 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[20,80,85,86] and activation of facial motoneurons,[87] which probably mediate some 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,[88,89] baroreceptor,[90–92] nictitating membrane,[54] eyeblink,[55] and

startle reflexes.[93,94] The startle reflex is also increased by local infusion of *N*-methyl-D-aspartate (NMDA)[95] as well as the metabotropic glutamate receptor agonist trans-(±)-1-aminocyclopentane-1,3, dicarboxylate (trans-ACPD)[96] into the central nucleus 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 amygdala), which then projects to a variety of target areas that are themselves 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 of 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. In order 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 now 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 to or in the amygdala, rather than from a change in its efferent target areas. The ability to produce long-term potentiation in the amygdala[97–100] and the finding that local infusion of NMDA antagonists into the amygdala blocks the acquisition[101–106] and extinction[107] of fear conditioning are both consistent with this hypothesis.

EFFECTS OF AMYGDALA LESIONS ON CONDITIONED FEAR

The Klüver-Bucy Syndrome

In 1939, following earlier work,[108] Klüver and Bucy[109] described the now classic behavioral syndrome of monkeys with bilateral removal of the temporal lobes, including the amygdala, hippocampus, and surrounding cortical areas. Following such lesions, the monkeys developed "psychic blindness": they would approach animate and inanimate objects without hesitation and examine these objects by mouth rather than by hand, whether the object was a piece of food, feces, a snake, or a light bulb. They also had a strong tendency, almost a compulsion, to attend to and examine every visual stimulus that came into their field of view and showed a marked change in emotional behavior. These monkeys had a striking absence of emotional motor and vocal reactions normally associated with stimuli or situations eliciting fear and anger. As described by Klüver and Bucy,

> The typical reaction of a "wild" monkey when suddenly turned loose in a room consists in getting away from the experimenter as rapidly as possible. It will try to find a secure place near the ceiling or hide in an inaccessible corner where it cannot be seen. If seen, it will either crouch and, without uttering a sound, remain in a state of almost complete immobility or suddenly dash away to an apparently safer place. This behavior is frequently accompanied by other signs of strong emotional excitement. In general, all such reactions are absent in the bilateral temporal monkey. Instead of trying to escape, it will contact and examine one object after another or other parts of the objects, including the experimenter, stranger, or other animals. . . . Expressions of emotions, such as vocal behavior, "chattering," and different facial expressions, are generally lost for several months. In some cases, the loss of fear and anger is complete. (p. 991)

In addition, many monkeys showed striking increases in heterosexual and homosexual behavior never previously observed in this monkey colony.

Lesions of the temporal lobe also were reported to cause profound changes in the social behavior of monkeys both in the laboratory and in the wild. Following temporal lobe lesions, monkeys rapidly fell in rank within dominance hierarchies established in monkey colonies (see review[110]). Lesioned monkeys now tried to fight with more dominant, larger monkeys, leading to frequent and often severe wounds. In the wild, these inappropriate interactions with other monkeys led to repeated attacks, social isolation, and eventual death.[111,112]

Subsequent studies have shown that all of the emotional components of the Klüver-Bucy syndrome can be reproduced by damage to the amygdala and the surrounding cortical tissue found in the perirhinal and entorhinal cortex.[113–118] The tameness and excessive orality can be reproduced by lesions restricted to only the amygdala.[119] In an extensive series of experiments evaluating both the emotional and the memory effects of lesions of the amygdala versus the hippocampus versus surrounding cortical areas, Zola-Morgan et al.[120] found that lesions of the amygdala disrupted emotional behavior to a set of novel objects, whereas lesions of the hippocampus or surrounding cortical areas did not. Conversely, damage to the hippocampus and the anatomically related perirhinal and parahippocampal cortex impaired memory but not emotional behavior. Moreover, combined damage to the amygdala and hippocampus had no greater effect on memory or emotion than did damage to either structure alone.

Although humans only rarely show the full-blown Klüver-Bucy syndrome following lesions restricted to the amygdala, they consistently show a blunting of emotional reactivity. This finding, along with the frequent change in emotional behaviors seen in Alzheimer's disease and other neurological diseases associated with amygdala pathology, is further evidence for the role of the amygdala in human emotion.[121,122] In fact, recent data using magnetic resonance imaging have shown bilateral activation of the amygdala when subjects view slides with high negative emotional content.[123]

It is not surprising, therefore, that several authors have seen a connection between the social inappropriateness following temporal lobe damage in monkeys and some of the negative or deficit symptoms in schizophrenia, such as inappropriate mood, flat affect, social isolation, poverty of speech, and difficulty in identifying the emotional status of other people.[121,124]

Facial Recognition and Classical Fear Conditioning in Humans

In nonhuman primates[125–127] and humans,[128,129] cells have been found that respond selectively to faces or direction of gaze.[130] In humans, removal of the amygdala has been associated with an impairment of memory for faces[131–134] and deficits in recognition of emotion in people's faces and interpretation of gaze angle.[134] In a very rare case involving bilateral calcification confined to the amygdala (Urbach-Wiethe disease), Patient S. M. 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 happiness, sadness, anger, and disgust were identified and drawn within the normal range. Furthermore, she had no difficulty in identifying the names of familiar faces.[135,136] The deficit in recognizing facial expressions of fear only seemed to occur after bilateral amygdala damage, whereas several patients with unilateral lesions had difficulty in naming familiar faces.[136] On the basis of this double dissociation, Adolphs et al.[136] propose that "the amygdala is required to link visual representation of facial expression, on the one hand, with representations that constitute the concept of fear, on the other" (p. 5879). Two other patients with Urbach-Wiethe disease did not show the normal enhancement in memory for emotional material[137,138] which is known from animal work to be dependent on activation of beta-noradrenergic receptors in the amygdala.[139]

Autonomic and Hormonal Measures

Patients with unilateral[140] or bilateral[141] lesions of the amygdala also have been reported to have deficits in classical fear conditioning in studies using the galvanic skin response as a measure. In monkeys, removal of the amygdala decreases reactivity to sensory stimuli measured with the galvanic skin response.[142,143] In both adult[144–149] and infant mammals,[150] lesions of the central nucleus block conditioned changes in heart rate. In birds, lesions of the archistriatum, believed to be homologous with the mammalian amygdala, block heart rate acceleration in response to a cue paired with a shock.[151] Ibotenic acid lesions of the central nucleus of the amygdala,[152] localized cooling of this nucleus,[153] or lesions of the lateral amygdala nucleus[154,155] also block conditioned changes in blood pressure. Ablation of the central nucleus can reduce the secretion of ACTH,[156] corticosteroids,[157,158] and prolactin.[157] Neurotoxic lesions of the central and basolateral nuclei also block conditioned increases in corticosteroid release.[159] Lesions of the amygdala reduce stress-induced increases in dopamine release in the frontal cortex following mild footshock or exposure to a novel environment[160] or to a cue previously paired with footshock.[159]

Attention and Vigilance

Gallagher, Holland, and co-workers have found results consistent with an attentional role of the central nucleus of the amygdala.[161–163] In these studies, a CS such as a light or a tone is paired with receipt of food. Initially, rats rear when the light goes on or show small startle responses when the tone goes on, both of which habituate with stimulus repetition. When these stimuli are then paired with food, these initial orienting responses return (CS-generated CRs), along with approach behavior to the food cup (unconditioned stimulus [US]–generated responses). Neurotoxic lesions of the central nucleus of the amygdala severely impair CS-generated responses without having any effect on unconditioned orienting responses or US-generated responses. On the basis of these data, the authors concluded that the central nucleus of the amygdala modulates attention to a stimulus that signals a change in reinforcement. Further work seemed to confirm this hypothesis. For example, rats with lesions of the central nucleus fail to benefit from procedures that normally facilitate attention to conditioned stimuli.[162,163]

Differential roles of the central and basolateral nuclei have been found in a phenomenon known as taste-potentiated odor aversion learning. In this test, which requires processing information in two sensory modalities, rats develop aversions to a novel odor paired with illness only when the odor is presented in compound with a distinctive gustatory stimulus. Electrolytic[164] or chemical lesions[165] of the basolateral but not the central nucleus of the amygdala blocked taste-potentiated odor

aversion learning even though they had no effect on taste aversion learning itself. Depletion of dopamine and norepinephrine in the amygdala via local infusion of 6-hydroxydopamine (4 μg/0.5 μl) also blocked odor aversion but not taste aversion.[166] Local infusion of NMDA antagonists into the basolateral nucleus also blocked the acquisition, but not the expression, of taste-potentiated odor aversion but had no effect on taste aversion learning itself.[102] More recently, in a very important study, neurotoxic lesions of the basolateral nucleus, but not the central nucleus, of the amygdala were reported to interfere with second-order conditioning and reinforcer devaluation.[167]

On the basis of these and other data, Hatfield et. al.[167] suggest that the central nucleus of the amygdala regulates attentional processing of cues during associative conditioning, whereas the basolateral nucleus of the amygdala is critically involved in "associative learning processes that give conditioned stimuli access to the motivation value of their associated unconditioned stimuli" (p. 5264).

Somewhat similar conclusions have been reached by Halgren,[168] based on recording of stimulus-evoked electrical activity in the amygdala in epileptic patients. In these studies, subjects are presented with a series of visual or auditory stimuli and are instructed to ignore some of them and attend to others. Averaged evoked responses show a prominent negative-positive component occurring roughly 200–300 ms after stimulus onset (N200/P300). These components, especially N200, are prominent within the amygdala and are much larger when elicited by a stimulus to which the subject is asked to attend. Halgren summarizes the cognitive conditions that evoke the N200/P300 as being stimuli that are novel or that are signals for behavioral tasks and hence require to be attended to and processed. Moreover, these components, along with other autonomic measures of the orienting reflex, seem to form an overall reaction of humans to stimuli that demand their evaluation.

Motor Behavior

Lesions of the amygdala eliminate or attenuate conditioned freezing normally seen in response to a stimulus formerly paired with shock,[26,147–149,159,169–179] a novel environment,[180] or a dominant male rat,[181,182] or presented during a continuous passive avoidance test.[183] Inactivation of the amygdala by direct infusion of lidocaine[171] or muscimol[184] prior to testing reduced conditioned freezing. However, the same doses infused prior to training did not fully block acquisition of contextual fear conditioning.[171,184]

Lesions of the amygdala counteract the normal reduction of bar pressing or licking in the operant conflict test[185–187] and the conditioned emotional response paradigm.[188,189] In birds, lesions of the archistriatum also block the development of a conditioned emotional response.[190]

Lesions of the central nucleus or of the lateral and basolateral nuclei of the amygdala block high-frequency vocalizations,[159] as well as reflex facilitation such as fear-potentiated startle[150,172,191–195] or tone-enhanced excitability of the nictitating membrane response.[196] Lesions of the amygdala also produce a dramatic decrease in shock-probe avoidance[197] but do not affect more active kinds of anxiogenic behaviors such as open arm time in the plus maze or burying a noxious shock probe, which are affected by lesions of the septum[197] as well as anxiolytic drugs. Furthermore, the magnitude of the anxiolytic effects after combined lesions of both structures was comparable to their magnitude after individual lesions, suggesting that the septum and amygdala independently control different fear-related behaviors.

Hypoalgesia

Lesions of the central nucleus of the amygdala block conditioned analgesia produced by reexposure to cues associated with noxious stimulation.[170,198,199] This effect does not seem to be due to a blockade of learning because the lesions can be made after training and still block the expression of conditioned analgesia.[200] NMDA lesions of the central, but not the basolateral or medial, nucleus of the amygdala blocked antinociception produced by a low dose of morphine in the formalin[201] or heat-evoked tail-flick test.[202] Direct infusion of lidocaine into the central nucleus had the same effect in the tail-flick test.[202]

These findings, along with a large literature implicating the amygdala in many other measures of fear, such as active and passive avoidance[5,23,82,139,203,204] and evaluation and memory of emotionally significant sensory stimuli,[139,205–217] provide strong evidence for a crucial role of the amygdala in fear.

EFFECTS OF AMYGDALA LESIONS ON UNCONDITIONED FEAR

Autonomic and Hormonal Measures

Lesions of the amygdaloid complex inhibit adrenocortical responses following olfactory or sciatic nerve stimulation[218] or exposure to visual or auditory stimuli.[219] In the study of exposure to stimuli,[219] lesions of the medial or central nuclei blocked these effects on the hypothalamic-pituitary axis, whereas lesions of the basal nucleus did not. Lesions of the amygdaloid complex also attenuate the compensatory hypersecretion of ACTH that normally occurs following adrenalectomy.[220] Le-

sions of the central nucleus have been found to significantly attenuate ulceration produced by restraint[221,222] or shock stress[223] or elevated levels of plasma corticosterone produced by restraint stress.[156,224] Lesions of the medially projecting component of the ventroamygdalofugal pathway, which carries the fibers connecting the central nucleus of the amygdala to the hypothalamus, attenuate the increase in ACTH secretion following adrenalectomy, whereas lesions of the stria terminalis do not.[220] Finally, lesions of the amygdala have been reported to block the capability of high levels of noise, which may be an unconditioned fear stimulus,[225] to produce hypertension[226] or activation of tryptophan hydroxylase.[227]

Motor Behavior

Lesions of the amygdala are known to block several measures of innate fear in different species.[169,204] Lesions of the cortical amygdaloid nucleus and perhaps the central nucleus markedly reduce emotionality in wild rats, measured in terms of flight and defensive behaviors.[228,229] Large amygdala lesions, or those which have damaged the cortical, medial, and in several cases the central nucleus, dramatically increase the number of contacts a rat will make with a sedated cat.[169] In fact, some of these lesioned animals crawl all over the cat and even nibble its ear, a behavior never shown by the nonlesioned animals. Following lesions of the archistriatum, birds become docile and show little tendency to escape from humans,[230,231] consistent with a general taming effect of amygdala lesions reported in many species.[232]

Lesions of the central nucleus of the amygdala block the increase in acoustic startle amplitude often observed after a series of footshocks.[233] The increase may represent an unconditioned effect of shock on the startle reflex,[234] although it might also represent a very rapid conditioned increase in startle due to contextual conditioning.[235]

Hypoalgesia

Lesions of the central nucleus block unconditioned analgesia to cat exposure,[198] loud noise,[236] or footshock,[198] but see Watkins et al.[199] Lesions of the central nucleus, but not the basolateral amygdala, tend to blunt analgesic effects of systemic administration of flumazenil as measured with the tail-flick test.[237]

Other data indicate that the amygdala appears to be involved in some types of aversive conditioning, but the extent of its involvement may depend on the exact unconditioned aversive stimulus that is used. For example, electrolytic lesions of the basolateral nucleus[238] or fiber-sparing chemical lesions of most of the amygdaloid complex[239] attenuate thirsty rats' avoidance of an electrified water spout through which they previously were accustomed to receive water. Importantly, however, these same lesioned animals did not differ from controls in the rate at which they found the water spout over successive test days or their avoidance of the water spout when quinine was added to the water.[239] This result led Cahill and McGaugh[239] to suggest that "the degree of arousal produced by the unconditioned stimulus, and not the aversive nature per se, determined the level of amygdala involvement" (p. 541). Perhaps this formulation may explain some of the apparently contradictory results concerning the effects of amygdala lesions on conditioned taste aversion (see reviews[6,240,241]).

EFFECTS OF LOCAL INFUSION OF DRUGS INTO THE AMYGDALA ON MEASURES OF FEAR AND ANXIETY

Clinically, fear is considered to be more stimulus-specific than anxiety, despite very similar symptoms. Figure 2 (p. 385) suggests that spontaneous activation of the central nucleus of the amygdala would produce a state resembling fear in the absence of any obvious eliciting stimulus. In fact, as mentioned earlier, fear and anxiety often precede temporal lobe epileptic seizures,[65,67] which are usually associated with abnormal electrical activity of the amygdala.[242]

An important implication of this distinction is that treatments that block conditioned fear might not necessarily block anxiety. For example, if a drug decreased transmission along a sensory pathway required for a conditioned stimulus to activate the amygdala, then that drug might be especially effective in blocking conditioned fear. However, if anxiety resulted from activation of the amygdala *not* involving that sensory pathway, then that drug might not be especially effective in reducing anxiety. On the other hand, drugs that act specifically in the amygdala should affect both conditioned fear and anxiety. Moreover, drugs that act at various target areas might be expected to provide selective actions affecting some, but not all, of the somatic symptoms associated with anxiety.

It is also probable that certain neurotransmitters within the amygdala especially may be involved in fear and anxiety. For example, the amygdala has a high density of corticotropin-releasing hormone (CRH) receptors[243] and CRH nerve endings,[244] and several recent papers indicate that stress, as well as conditioned fear, can induce a release of CRH in the amygdala that results in various anxiogenic effects. For example, 20 minutes

of restraint stress led to an increase of extracellular CRH-like immunoreactivity levels in the amygdala as measured by microdialysis.[245] In ethanol-dependent rats there was an increase in CRH-like immunoreactivity in microdialysis samples 6 to 8 hours after ethanol removal. The CRH release reached a peak 10 to 12 hours after ethanol removal, at the same time that anxiogenic-like behaviors were observed in the elevated plus maze. CRH-like immunoreactivity also was reported to have decreased by 58% in the amygdala 48 hours after withdrawal from chronic cocaine use, suggesting increased release and degradation of CRH following drug withdrawal.[246]

Individual differences in general levels of fear or anxiety may be related to differences in the amount of CRH found in the amygdala. For example, Fawn-hooded rats, a strain derived from Wistar, Long-Evans, and brown rats, show more freezing in response to stress, have an increased preference for alcohol, develop adult-onset hypertension, and have elevated levels of urinary catecholamines. Compared with Wistar rats, this strain also has higher levels of CRH mRNA in the central nucleus of the amygdala.[247] In addition, rats that experienced prenatal stress, which apparently developed high levels of anxiety, had higher CRH levels in amygdala tissue compared with nonstressed controls, and the higher CRH levels were associated with a higher depolarization (KCl)–induced CRH release from amygdala minces.[248]

If the amygdala is critically involved in fear and anxiety, then drugs that reduce fear or anxiety clinically may well act within the amygdala. A variety of measures suggest that the anxiolytic effects of both opiates and benzodiazepines may result from binding to receptors in the amygdala.

Autonomic and Hormonal Measures

CRH (30 ng) infused into the central nucleus of the amygdala increased heart rate compared with heart rates in vehicle-infused animals.[249] Pretreatment with alpha-helical CRH [9-41], a CRH antagonist, dose-dependently reduced the CRH-induced tachycardia at doses that had no effects on heart rate by themselves. On the other hand, there were no effects of local infusion of CRH or alpha-helical CRH [9-41] on plasma levels of epinephrine, norepinephrine, or corticosterone. Boadle-Biber et al.[250] found that CRH infused into the central nucleus increased tryptophan hydroxylase activity measured in the cortex and that this effect of CRH could be blocked by prior administration of alpha-helical CRH [9-41] into the central nucleus. Moreover, like amygdala lesions,[227] infusion of alpha-helical CRH [9-41] into the amygdala blocked the increase in tryptophan hydroxylase in response to loud noise.[250]

Motor Behaviors

Benzodiazepines, GABA Agonists and Antagonists: Many studies have shown that local infusion of benzodiazepines into the amygdala has anxiolytic effects in the operant conflict test,[251–258] freezing,[259,260] the light-dark box measure in mice,[261] shock probe avoidance,[262] and the elevated plus maze,[263,264] and that it antagonizes the discriminative stimulus properties of pentylenetetrazol.[265] Infusion of diazepam into the amygdala also accelerated the rate of between-session habituation of the startle response.[260] This finding is consistent with the idea that loud startle stimuli produce contextual fear conditioning that competes with the expression of long-term habituation.[266] A reduction of contextual fear conditioning via diazepam infusion into the amygdala should thus increase long-term habituation, as it does after systemic administration.[260]

The anticonflict effect[251,254,257] or the decrease in shock probe avoidance[262] can be reversed by systemic administration of the benzodiazepine antagonist flumazenil or coadministration into the amygdala of the γ-aminobutyric acid (GABA) antagonist bicuculline,[255] and these effects can be mimicked by local infusion into the amygdala of GABA[251] or the GABA agonist muscimol.[255] In general, anxiolytic effects of benzodiazepines occur after local infusion into the lateral and basolateral nuclei[253–255,258,263] (the nuclei of the amygdala that have high densities of benzodiazepine receptors) and not after local infusion into the central nucleus,[253,255,263] although effects have been reported after infusion into the central nucleus.[187,256,267] More recently, consistent with earlier work,[263] Pesold and Treit[264] reported that local infusion of midazolam into the basolateral nucleus had an anxiolytic effect in the plus maze but did not impair shock-probe avoidance, whereas infusion into the central nucleus impaired shock-probe avoidance but did not affect plus maze performance. Both of the site-specific effects of midazolam could be blocked by systemic administration of flumazenil.

Sanders and Shekhar[71] found that infusion of the $GABA_A$ antagonists bicuculline or picrotoxin into the anterior basolateral nucleus had anxiogenic effects in the social interaction test. These same doses had no effect when infused into the central nucleus. Conversely, infusion of the $GABA_A$ agonist muscimol into the central nucleus had an anxiolytic effect, whereas it had no effect when infused into the basolateral nucleus. These data suggest a tonic, and perhaps maximal, level of GABA inhibition in the basolateral, but not the cen-

tral, nucleus of the amygdala. 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 3 to 5 infusions.[71] The increases were accompanied by anxiogenic effects in the conflict and social interaction tests.

Taken together, these results suggest that drug actions in the amygdala may be sufficient to explain both fear-reducing and anxiety-reducing effects of various drugs given systemically. In fact, local infusion into the amygdala of the benzodiazepine antagonist flumazenil significantly attenuated the anticonflict effect of the benzodiazepine agonist chlordiazepoxide given systemically.[251] Similarly, Sanders and Shekhar[268] found that local infusion of the benzodiazepine antagonist flumazenil or the GABA antagonist bicuculline into the anterior part of the basolateral nucleus, at doses that had no anxiogenic effects by themselves, blocked the anxiolytic effect of systemically administered chlordiazepoxide on the social interaction test. These are very powerful experimental designs and strongly implicate the amygdala in mediating the anxiolytic effects of benzodiazepines.

Nonetheless, it should be emphasized that benzodiazepines can still have anxiolytic effects in animals with lesions of the amygdala.[185,269–271] Although these important results could be interpreted to indicate that the amygdala is not necessary for mediating anxiolytic effects of benzodiazepines, such a conclusion is difficult to reconcile with the many studies outlined above. Hence, it may be that other brain structures take over for the amygdala after it is lesioned (see Kim and Davis[194]) and that benzodiazepine binding in these other structures accounts for the anxiolytic effects after amygdala lesions.

Corticotropin-Releasing Hormone: Several studies now suggest an important role for CRH in the amygdala in mediating various anxiogenic effects in the plus maze as well as other tests. Local infusion of alpha-helical CRH [9-41] (250 ng) in the central nucleus attenuated the anxiogenic effect of social defeat[272] or ethanol withdrawal in ethanol-dependent rats[273] in the plus maze. Higher doses were not effective, perhaps due to partial agonist effects of this compound. Doses effective in the plus maze had no effect on plasma ACTH or corticosterone release, although these values returned to baseline earlier than in controls after antagonist infusion. The antagonist had no effect on overall activity or percentage of time in open arms of the maze in rats not dependent on ethanol. Liebsch et al.[274] found that local infusion into the central nucleus of the CRH receptor mRNA antisense oligodeoxynucleotide had an anxiolytic effect in the plus maze in rats that had previously experienced defeat stress. Infusion of the scrambled sequence oligodeoxynucleotide had no effect.

Using freezing as a measure, Swiergiel et al.[275] found that local infusion of low doses (50 and 100 ng) of alpha-helical CRH [9-41] into the central nucleus reduced the duration of freezing to an initial shock treatment. A higher dose (200 ng) was not effective. Infusion of the antagonist into the central nucleus immediately prior to reexposure to the shock box 24 hours later also attenuated freezing duration, indicating that the reduction in freezing by alpha-helical CRH [9-41] was not due to an alteration in sensitivity to the footshock.

In all of the above examples, infusion of the CRH antagonists produced behavioral effects in animals that had undergone prior stress, a condition that may be necessary to detect effects following local infusion into the amygdala. For example, although CRH infused into the central nucleus could produce increased grooming and exploration in animals tested under stress-free conditions (that is, in the home cage of the rat), local infusion of alpha-helical CRH [9-41] (0.1 and 1.0 μg/cannula) had no effect on activity under these same stress-free conditions.[276]

On the other hand, enhancement of the startle reflex, either by infusion of CRH intraventricularly (CRH-enhanced startle) or by conditioned fear, does not seem to depend on activation of CRH receptors in the amygdala, at least not in its central nucleus. Although large electrolytic lesions of the amygdala were found to block CRH-enhanced startle,[277] local infusion of CRH into the amygdala failed to increase startle in this study involving a large number of animals and several placements within the amygdala. Moreover, recent experiments using fiber-sparing lesions of the central and/or basolateral nuclei of the amygdala failed to block CRH-enhanced startle.[278] In contrast, neurotoxic lesions of the bed nucleus of the stria terminalis completely block CRH-enhanced startle, and direct infusion of CRH into this nucleus increases acoustic startle.[278] In addition, local infusion of alpha-helical CRH [9-41] into the central nucleus of the amygdala did not block fear-potentiated startle.[278]

Other Compounds: On the basis of a series of observations, Deakin and Graeff[279] hypothesized that serotonin (5-hydroxytryptamine; 5-HT) enhances fear or anxiety in the amygdala, whereas it has the opposite effect in the dorsal central gray. A great deal of evidence supports the anti-anxiety effects of 5-HT in the dorsal central gray (see review[12]), although fewer direct data are

available concerning the role of 5-HT in the amygdala. Local infusion of 5-HT or the 5-HT_{1A} agonist 8-hydroxydipropylaminotetralin (8-OH-DPAT) into the amygdala have been reported to produce anxiogenic effects in the conflict test,[251,267] whereas infusion of the 5-HT_2 antagonist ketanserin has an anxiolytic effect.[251] On the other hand, infusion into the amygdala of the 5-HT_{1A} agonists 8-OH-DPAT, buspirone, or ipsapirone reduced shock-induced vocalization.[280] In this case, however, the 5-HT_{1A} agonists were infused into the posteromedial cortical amygdaloid nucleus rather than the basolateral nucleus[251] or the central nucleus.[267] Interestingly, the corticomedial nucleus, rather than the central or basolateral nuclei, was also the most effective site for morphine analgesia in the shock-induced jump response tested in freely moving rats[281,282] (see the next section).

Compounds acting as 5-HT_3 receptor subtype antagonists have been reported to produce anxiolytic effects after local infusion into the amygdala.[283,284] Such infusions also can block some of the signs of withdrawal following subchronic administration of diazepam, ethanol, nicotine, or cocaine[285] or increases in levels of dopamine or the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the amygdala after activation of dopamine neurons in the ventral tegmental area.[286] In addition, local infusion of a 5-HT_{1A} antagonist into the central nucleus has been reported to have an anticonflict effect.[267]

Activation of neuropeptide Y_1 receptors in the central nucleus has been reported to produce selective anxiolytic effects in the conflict test,[287] and this effect could be blocked by prior intraventricular administration of antisense inhibition of Y_1 receptor expression,[288] which itself produced an anxiogenic effect.[288,289] Local infusions of opiate agonists in the central nucleus were reported to have anxiolytic effects in the social interaction test.[290]

Hypoalgesia

Infusion of morphine,[281,282,291] enkephalinase inhibitors,[292] or mu opioid agonists[293] into the amygdala has antinociceptive effects, although this has not always been found.[294] Morphine and mu agonists seem to be most effective in the basolateral nucleus when the tail-flick test is measured in anesthetized rats.[291,293] In waking rats, when jump threshold is used as a measure, the most sensitive placements seem to occur in the corticomedial nucleus and not in the basolateral or central nucleus.[281,282] Morphine infused into the corticomedial nucleus also reduced open field defecation but had no effect on tail-flick latency.[282] Antinociception also occurs after injection of neurotensin[295] into the central nucleus of the amygdala or carbachol into the basolateral or medial amygdala nuclei.[296] Unilateral local infusion of morphine into the central nucleus of the amygdala attenuated both the acquisition and expression of inhibitory avoidance and conditioned hypoalgesia measured with the formalin test,[297] which is sensitive to naloxone. These effects of morphine in the amygdala could be reversed by coadministration of naloxone into the amygdala, and the effects on acquisition could not be explained by state-dependent learning. Interestingly, morphine infusions did not block conditioned analgesia when rats were tested on the heated floor, a naloxone-insensitive form of hypoalgesia. Hence, the amygdala did not seem critical for all types of conditioned analgesia. Although Good and Westbrook[297] did not find effective sites for morphine in the basolateral amygdala, Harris and Westbrook[298] did see an attenuation of both hypoalgesia and inhibitory avoidance after infusion of midazolam in the basolateral nucleus.

THE ROLE OF CONNECTIONS BETWEEN THE AMYGDALA AND THE CORTEX IN FEAR AND ANXIETY

Thus far we have concentrated on connections between the central nucleus of the amygdala and brain areas related to the expression of fear and anxiety. It is also the case, however, that the amygdala, especially the basolateral amygdala, has extensive connections to many cortical areas such as the frontal cortex (see Amaral et al.[299] for review of primate data) that could be involved in the experience or perception of fear and anxiety. As outlined earlier, only in humans is it possible to directly measure the experience of fear because this can be understood only through verbal report. Moreover, to actually determine if changes in the experience or perception of emotion result from a disconnection of the amygdala from a given cortical structure, cases would have to be found that included an intact amygdala on one side of the brain combined with unilateral damage to a cortical region on the other side of the brain known to receive amygdala input. To my knowledge, such an analysis has not been systematically carried out in humans. However, exactly this approach is being used experimentally in monkeys to study the role of amygdala–frontal connections in an appetitive memory task.[300] It would thus be extremely interesting to know how such disconnections might affect fear-related behaviors in monkeys and other species.

Recently, connections between the prefrontal cortex and the amygdala have been implicated in extinction of fear, with freezing in rats used as a measure of conditioned fear. Lesions of the ventral medial prefrontal

cortex slowed the rate of extinction,[301,302] whereas repeated presentation of a conditioned fear stimulus normally leads to a loss of the fear reaction to that stimulus. In these same animals, extinction of conditioned fear to contextual cues was not impaired,[302] suggesting that the role of the medial prefrontal cortex in fear inhibition must be highly specific. However, in an extensive series of experiments, we have found normal rates of extinction of conditioned fear (using both freezing and fear-potentiated startle) to both explicit and contextual cues after total removal of the ventral medial prefrontal cortex.[303] Moreover, lesions of the ventral medial prefrontal cortex did not interfere with conditioned inhibition, which is a more direct measure of fear inhibition than is extinction.

Because the lesions in the studies by Morgan et al.[301,302] were performed before fear conditioning, the apparent blockade of extinction following ventral medial prefrontal cortex lesions may have been produced by an increase in the strength of original fear conditioning rather than by interference with the process of extinction. Although the two groups did not differ significantly in their level of freezing before the initiation of the extinction sessions, freezing to explicit cues often becomes maximal after a very few training trials, so that ceiling effects might well have been operating. Because rate of extinction can be a more sensitive index of the strength of original conditioning than the terminal level of performance prior to the initiation of extinction (see, for example, Annau and Kamin[304]), the slower rate of extinction in the lesioned animals may have simply reflected a stronger degree of original learning. The fact 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. Moreover, when ventral prefrontal cortex lesions are made after fear conditioning, but before extinction, the lesions have no effect on the rate of extinction.[305] These results indicate that the ventral medial prefrontal cortex is not essential for the inhibition of fear under a variety of circumstances. Clearly, further work needs to be done regarding the role of the cortex in fear and inhibition of fear.

CONCLUSIONS

An impressive amount of evidence from many different laboratories using a variety of experimental techniques indicates that the amygdala plays a crucial role in conditioned fear and anxiety, as well as attention. Many of the amygdaloid projection areas are critically involved in specific signs that are used to measure fear and anxiety. Electrical stimulation of the amygdala elicits a pattern of behaviors that mimic natural or conditioned states of fear. Lesions of the amygdala block innate or conditioned fear, as well as various measures of attention, and local infusion of drugs into the amygdala has anxiolytic effects in several behavioral tests. It is possible that long-term potentiation in the amygdala may mediate the development of fear conditioning. An NMDA-dependent form of long-term potentiation has been observed in the amygdala, and local infusion of NMDA antagonists into the amygdala blocks the formation of conditioned fear memories, as measured with several different tests of fear. A better understanding of brain systems that inhibit the amygdala, as well as the role of its very high levels of peptides, may eventually lead to the development of more effective pharmacological strategies for treating clinical anxiety disorders, and perhaps memory disorders as well.

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