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The Sources of Fear and Anxiety in the Brain

Fear produces an agony and anxiety about the heart not to be described; and it may be said to paralyze the soul in such a manner, that it becomes insensible to every thing but to its own misery. . . . When the effects of fear operate powerfully, without any mixture of hope, these passive impressions are predominant but where there is a possibility of escape, the mind re-acts with wonderful energy . . . enabling the sufferer to precipitate his flight, by exertions that would have been impracticable in a more composed state of mind.

T. Cogan, *On the Passions* (1802)

CENTRAL THEME

Contrary to traditional thinking on the topic, which taught that fears simply reflect *learned anticipation* of harmful events, it now appears that the potential for fear is a genetically ingrained function of the nervous system. This should come as no surprise. An organism's ability to perceive and anticipate dangers was of such obvious importance during evolution that it was not simply left to the vagaries of individual learning. Even though learning is essential for animals to utilize their fear systems effectively in the real world, learning does not create fear by pasting together a variety of external experiences. Evolution created several coherently operating neural systems that help orchestrate and coordinate perceptual, behavioral, and physiological changes that promote survival in the face of danger. The emotional experience of fear appears to arise from a conjunction of neural processes that prompt animals to hide (freeze) if danger is distant or inescapable, or to flee when danger is close but can be avoided. To understand the deep experiential nature of fear in humans, we must probe the genetically ingrained neural components that mediate homologous fearful states in other mammals. Our understanding of the neurobiology of human fears has emerged largely from basic research on the brains of "lower" animals. These investigations indicate that the capacity to experience fear, along with fear-typical patterns of autonomic and behavioral arousal, emerges primarily from a FEAR circuit that courses between the central amygdala and the periaqueductal gray of the midbrain. Fear behaviors can be evoked by artificially activating this circuit, and conditioned fears can be developed by pairing neutral stimuli with unconditional stimuli, such as electric shock, that can arouse this emotional system. In other words, conditioned fears emerge by neutral stimuli gaining access to this system via learning. Higher cortical processes are not necessary for the activation of learned fears, although those processes refine the types of perceptions that can instigate fear. The neurochemistries that control this emotional system include excitatory amino acids such as glutamate and a variety of neuropeptides (e.g., CRF, α-MSH, ACTH, CCK, and DBI), each of which may eventually be found to instigate slightly different anxieties—for instance, fear of pain, fear of heights, fear of predators. Minor tranquilizers of the benzodiazepine (BZ) class act by partially dampening activity in this emotional system, through GABA-mediated neural inhibition. Other antianxiety drugs such as buspirone are able to attenuate anxiety in totally different ways, such as by modifying serotonin sensitivity in the brain. New agents—for instance, those that inhibit cholecystokinin (CCK) and other neuropeptide receptor systems (especially CRF) as well as those that stimulate neuropeptide Y and oxytocin systems—show considerable promise of yielding a new generation of antianxiety agents. Others are bound to follow as our knowledge of the FEAR system becomes complete.

On the Characteristics of Fear

One of the most horrible experiences of life is to be stricken by sudden terror. Another is to be continually consumed by the persistent feelings of anxiety that gnaw away at you, destroying your sense of security in the world. It is likely that the affective impact of both

experiences emerges ultimately from the differential arousal of one and the same brain system—a coherently operating FEAR circuit that produces terror when precipitously aroused and chronic anxiety during milder, more sustained arousal. The FEAR system can be activated by various world events, as well as by internal ones. External stimuli that have consistently threatened the survival of a species during evolutionary history often develop the ability to unconditionally arouse brain fear systems. For instance, laboratory rats exhibit fear responses (increased freezing and inhibition of other motivated behaviors) to the smell of cats and other predators (see Figure 1.1), even though they have never encountered such creatures in their lives, having grown up in the safety of a controlled laboratory setting (for more on the underlying neural mechanisms, see the "Afterthought" of this chapter).

In addition to such inborn tendencies, a variety of specific anxieties can be acquired during the life span of each individual. These are usually triggered by specific external events that have been paired with pain or other threatening stimuli, but it is important to recall that feelings of fear can also emerge simply from the internal dynamics of the brain (so-called free-floating anxieties). Internal stimuli that can arouse the FEAR system range from irritative epileptic foci in the limbic system to conscious as well as unconscious memories of past occurrences. Although a neural circuit coursing between the central amygdala and the periaqueductal gray (PAG) of the midbrain has now been well established as a major FEAR circuit, it remains possible, even likely, that there are multiple neural systems that can make us afraid. We do not yet have an accepted neural taxonomy of various fears, but I will address some possibilities.

Although feelings of fear are as hard to define as they are to measure directly, most people have a natural understanding of what it means to be afraid. For those who do not, imagine an archetypal situation. You are alone in the woods, in the darkness of night, lost and with little confidence in your ability to find the way out. The moon filters through racing clouds on the heels of a chilly wind. The branches above sway menacingly. Your imagination runs wild with the archetypal monsters and demons that populated the fantasy landscape of your childhood imagination. Suddenly, a branch cracks and falls behind you. You exhibit a reflexive startle much larger than you would have made to the same sound in the safety of your backyard; this is due to the potentiating effect of the background fear. After this intense reaction, you hold very still for a moment, frozen in one position, as your mind fills with dread, all your senses riveted on the perceived source of the noise. Your cognitive processes are rapidly analyzing sundry imagined and real possibilities. If this analysis attributes the sound to a mythical werewolf or a real mountain lion, you may explode into a vigorous flight pattern, running faster than you thought your legs could ever carry you. If you are fortunate enough to find a momentary place of perceived safety (perhaps an abandoned cabin in the woods), you will hide, tremble, with heart throbbing (not just from your physical exertions); you remain alert for a long time in a cold sweat as you vigilantly evaluate each new environmental stimulus. You may have wet your pants, or worse, along the way.

Fortunately, at daybreak you find your way out. On future occasions you will be more careful not to get lost again. You may dream about the episode for several nights. Had you encountered truly frightful events such as sustained wartime battles, then mixtures of fear and anger would incubate in the neural substrates of your psyche for years to come, until you might develop what is called a post-traumatic stress disorder. Even though many higher cortical perceptions sustained and exacerbated your fears, to the best of our knowledge, the resulting chronic hyperemotional state is created by deep subcortical networks that can become sensitized and can operate independently of your higher cognitive faculties. For this reason, long-lasting fears and anxieties can lead to chronic psychological distress that does not always respond well to standard cognitive therapies.

Experientially, fear is an aversive state of the nervous system, characterized by apprehensive worry, general nervousness, and tension, which tells creatures that their safety is threatened. It is accompanied by specific forms of autonomic and behavioral arousal. The most common clinical symptom of fear is generalized anxiety. The current *Diagnostic and Statistical Manual* (*DSM-IV*) of the American Psychiatric Association offers standard criteria for generalized anxiety that include a variety of psychological symptoms, such as uncontrollable apprehensive expectations, with jumpiness and a tendency for excessive vigilance and fidgeting. The various autonomic symptoms include frequent tendencies for gastrointestinal disturbances, including upset stomach, diarrhea, and frequent urination, as well as other visceral symptoms like tachycardia, chronic dryness of the mouth, and increased but shallow respiration.[1] Some individuals who have anxiety problems complain more about physical symptoms, while for others psychological anguish is the prevailing concern.

Where in the brain is the array of fear responses organized? Obviously, the overall neural control is complex, including many cognitive analyzers as well as autonomic and somatic-motor circuits. Most of the brain is involved. However, there are distinct sites in the brain where electrical stimulation will provoke a full fear response in all mammalian species, and these are locations where the executive system for FEAR is concentrated.[2] These are in the lateral and central zones of the amygdala, the anterior and medial hypothalamus, and, most clearly (and at the lowest current levels), within specific PAG areas of the midbrain. Of course, this highly interconnected network interacts with the many other emotional systems discussed in this book, especially RAGE circuits (which contribute to the bal-

ance between fight and flight reactions), as well as the behaviorally nonspecific chemistries of the brain such as norepinephrine and serotonin. My aim is not to assess all the components of a global fear response but rather to summarize information on what we know of the central FEAR system.[3]

At present, the precise manner in which fears and anxieties are created by brain tissue remains a matter of intense debate and inquiry. But the original idea that captivated psychology—that fear is simply a conditioned response to the cues that predict pain—is no longer tenable. Although pain is an especially effective stimulus for creating fear and generating learned fears, it does not constitute fear itself. To the best of our present knowledge, fear—the subjective experience of dread, along with the characteristic set of bodily changes—emerges from the aforementioned circuit, which interdigitates extensively with the RAGE circuit. In the amygdala, however, the two systems are fairly clearly segregated, with FEAR being more lateral and RAGE more medial. As mentioned, the FEAR circuit courses from the lateral and central nuclei of the amygdala, through the ventral-anterior and medial hypothalamic areas, down to the mesencephalic PAG (Figure 11.1). Freezing, as well as flight behavior and the autonomic indices of fear (e.g., increased heart rate and eliminative behavior), can be evoked along the whole trajectory of this system.[4]

It makes good evolutionary sense for FEAR and RAGE circuits to be intimately related, for one of the functions of anger is to provoke fear in competitors, and one of the functions of fear is to reduce the impact of angry behaviors from threatening opponents. Although it has not been empirically demonstrated, it is reasonable to suppose that at low levels of arousal, the two systems are mutually inhibitory (see Figure 3.5). At very sudden or intense levels of arousal, however, both the fear response and the rage response may be concurrently aroused. Of course, the existence of a major FEAR system does not preclude the existence of other systems that may mediate other forms of alarm and trepidation. Indeed, as we will see in Chapter 14, separation anxiety emerges largely from brain systems other than the FEAR circuit. For clinical reasons detailed there, I have chosen to call it a PANIC system.

Since mild fear is characterized largely by behavioral inhibition components, while intense fear is commonly characterized by active flight, it is important to consider how these diametrically different response tendencies might be elaborated by the FEAR system. By carefully following the behavioral responses evoked by different intensities of stimulation, it has become clear that one can promote freezing during mild arousal of this system and flight at higher stimulation intensities (Figure 11.2). Whether the shift in response tenden-

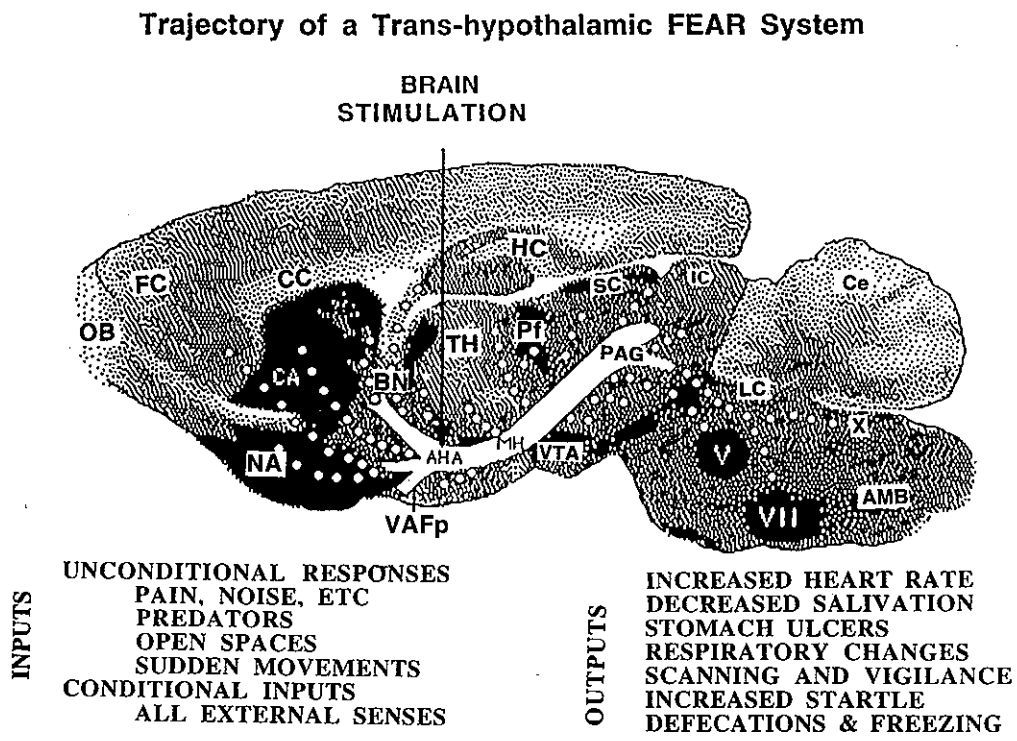

Figure 11.1. Schematic summary of the trajectory of the FEAR system and the various symptoms induced by stimulation of the system. (Adapted from Panksepp, 1990; see n. 2.)

Figure 11.2. Artist's rendition of the type of freezing behavior that can be generated by mild stimulation of the FEAR system. (Adapted from a photograph in Panksepp, 1989; see n. 5.)

cies is organized by different subcomponents of the FEAR system at the stimulation electrode site or the different response characteristics are generated by differential outputs at the aroused synaptic fields downstream from the stimulation is presently unresolved. However, it does seem possible that both of these fear responses are governed by the same basic emotional system within the brain.

Before proceeding with a discussion of the major amygdalo-hypothalamo-mesencephalic FEAR circuit, it will be helpful to present an overview of the vast number of animal models of anxiety that have been developed by behaviorists over the past few decades. Most of the preclinical pharmacological work aimed at identifying and developing new antianxiety agents is emerging from the systematic analysis of such animal models. It is not yet clear how each of these models relates to arousal of the FEAR system versus other negative emotional systems of the brain. The many inconsistencies in the literature may eventually be resolved by an appropriate taxonomy of brain circuits that mediate anxiety. Since this has not yet been achieved, and since most of the available animal models remain to be linked to specific neural circuits, the existing literature may give an impression of chaos and incoherence. But we can at least summarize the diversity of models in a systematic way, and thereby focus on the most promising lines of future inquiry.

Preclinical Models for the Study of Fear

In contrast to the paucity of natural animal models for anger, there is an overabundance of models for fear. This probably reflects the widespread recognition that fear responses are learned readily and that they have distressing consequences for the lives of many people. The various preclinical laboratory models for the study of anxiety can be conveniently broken down into those that use painful stimuli to produce symptoms of anxiety (i.e., via use of punishment procedures) and those that use no explicit punishment. In addition, each of these categories includes several models to analyze changes in learned fears and others to measure unconditional, or instinctual, fear behaviors, yielding four types of models, as summarized in Table 11.1.

Although most of these models are quite sensitive to the effects of minor tranquilizers (which are typically called antianxiety agents), suggesting that they share common affective features, a conceptual problem runs through much of the literature on this topic. Antianxiety effects are generally *assumed* to exist when previously punished behaviors are released from inhibition, but such effects can be explained in several ways: Animals may be less anxious, or they may simply be more impulsive and disinhibited. The second alternative was rarely considered in earlier discussions of how animal models can relate to our understanding of human anxiety.[5]

Another problem is that there are so many differences in formal procedures and drug sensitivities among the various experimental models that it is not yet possible to argue for a common anxiety process that underlies all of them. There are also no accepted guidelines regarding which models are the best predictors for which specific anxiety-related disorders in humans and why. Accordingly, the literature may actually be describing many different types of fears or different ways in which the brain handles one type of fear. Although I

Table 11.1. A Taxonomy of Animal Models of Fear

	With Punishment	No Punishment
Learned	Active avoidance tasks	Partial reinforcement extinction effect
	Conditioned emotional responses	
	Punished behavior tasks	
	Passive avoidance tasks	
Spontaneous	Freezing to shock	Open-field exploration
	Defensive burying	Avoidance of bright lights
	Stimulation of fear circuits	Social-interaction tests
	Responses to loud sounds (startle)	Plus-maze test
		Predatory odors

will not attempt to contrast and compare these models, I will provide a systematic organizational scheme that may help us visualize how the various models interrelate (Table 11.1). The models will be divided into those that use punishment and those that do not, and also according to those that require learning and those that do not.

Quadrant 1 (learned tasks with imposed punishments): The first models that were used to study fear simply measured an animal's tendency to learn new responses to escape and avoid aversive stimuli such as foot shock (which is usually administered through metal rods that constituted the cage flooring). Many of these models were widely implemented by pharmaceutical firms for evaluating the potential antianxiety effects of new drugs. It turned out that these specific models were not especially sensitive to antianxiety agents, probably because, by the time investigators tested their drugs, the learned behavior had become so efficient that test animals no longer experienced much fear. Subsequent models tried to circumvent such problems by establishing stable baselines of learned approach behaviors, on which fears could be imposed via classical conditioning principles (the so-called conditioned emotional response [CER] procedures).[6] Such designs turned out to be much more sensitive to the effects of minor tranquilizers.

Models of this type first conditioned anxiety in experimental animals by systematically pairing environmental cues with aversive events, after which investigators evaluated the effectiveness of those cues in suppressing various appetitive behaviors. For example, the readiness of hungry rats to press levers for food would be measured during baseline periods, as well as during presentation of the fear stimuli. When the danger cue was presented, an internal state of anxiety presumably was produced, and the degree of behavioral inhibition was used as an operational measure of the anxiety. Such CER tasks were most effective when the cue-shock pairings were administered directly upon the appetitive baselines. Eventually such behavioral inhibition tasks were further simplified by using spontaneous consummatory baselines, such as voluntary feeding and drinking, which were periodically accompanied by cue-contingent or even uncontingent administration of foot shock, yielding a very direct measure of the amount of behavior an animal was willing to emit while expecting and receiving mild punishment. If the shock was contingent on an animal making a specific consummatory response, it was considered to be a punishment task. Of course, in this last model the only learning consisted of the animal's presumed realization that it would be punished if it exhibited consummatory behavior.

A variant of this model involved placing animals in well-lit arenas, with immediate administration of shock when they entered an accessible dark hole or, alternatively, when they stepped down from a safe perch. In such circumstances, animals typically exhibit much longer latencies for their spontaneous avoidance behaviors on the second trial if they have already been punished for their efforts on the first trial, yielding "passive avoidance" measures that presumably reflect the behavior-inhibiting effects of anxiety. In other words, a smart animal that has received a shock when stepping to the floor has "second thoughts" about taking such a step the next time. Of course, these models do not readily distinguish between the effects of pharmacological and physiological manipulations on memory processes as opposed to emotional ones. For instance, drugs may evoke amnesia in the animals. A variety of additional controls are needed to evaluate those issues.

Perhaps the most effective model of this type, one that has now been extensively exploited, employs what is called a "potentiated startle." Animals and humans show a characteristic startle response to sudden loud sounds. The vigor of the startle reflex (whose neural details have been worked out and will be discussed later) is increased markedly by concurrent exposure to a classically conditioned fear stimulus (i.e., a light that previously had been paired with electric foot shock). Indeed, the potentiation of the startle response in this manner appears to be elaborated by the FEAR system, which runs from the amygdala to the PAG,[7] and this experimental model can readily be implemented in humans.[8]

Quadrant 1 models were especially prevalent during the initial era of preclinical psychopharmacology in the 1950s to 1970s, but, as mentioned, they were often flawed by their failure to distinguish between antianxiety effects and simple behavioral disinhibition. This noncritical approach produced a long-lived, but questionable, serotonin theory of anxiety.[9] The first neurochemical theory of anxiety ever proposed, was based largely on the observation that serotonin receptor antagonists could increase punished behaviors. However, it is now clear that a reduction of brain serotonin makes animals more manic and impulsive in general, with a very broad pattern of behavioral disinhibition in situations that entail anxiety as well as those that do not. Accordingly, increased behavior in the face of punishment could have simply reflected a generalized release of active behavioral tendencies, not a reduction of anxious feelings. Although some recent data do suggest that certain serotonin receptor subtypes may in fact promote anxiety (especially 5-HT_2 and 5-HT_3), while other receptors for this same amine decrease anxiety,[10] there is presently little empirical reason to believe that serotonin neuronal activity is a major player in producing the actual experience of fear within the brain. Rather, it is clear that the serotonin system modulates the intensity of fear, but to no greater extent than it modulates other negative emotions. In fact, most of the available data is still consistent with the alternative conclusion that an overall increase of serotonin activity decreases anxiety and produces feelings of relaxation. Of course, the vast proliferation of serotonin receptor subtypes discovered

over the past few years (15 are presently known) reveals a level of complexity that is still not well integrated into a solid base of accepted knowledge.

Quadrant 2 (learned tasks with no explicit punishment contingencies): Only one model of anxiety has attempted to utilize a learning task without any explicit punishment. This task is the partial reinforcement extinction effect (PREE), whereby animals exhibit high response rates during extinction because they have presumably become accustomed to frustrative nonreward, which is proposed to resemble a central state of anxiety.[11] Although this model is sensitive to benzodiazepines (BZs) and other antianxiety agents, such as barbiturates, that also block the PREE, it remains more probable that frustration and fear emerge from separate brain mechanisms, in which case these results may not be valid antianxiety effects. Rather, the data may simply indicate that minor tranquilizers diminish the effects of frustration and anger, which is consistent with data presented in the previous chapter and, of course, quite interesting in itself.

Quadrant 3 (instinctual fear behaviors with no explicit punishment): The prototypical model of this type is the "open-field" task in which an animal is placed into an unfamiliar chamber. One then measures exploratory activity (which increases as a function of repeated test sessions), the amount of defecation (which initially is high and diminishes as a function of sessions), and a variety of autonomic indicators of stress and fear, such as elevated heart rate and adrenal glucocorticoid secretion.[12] Perhaps because of the new regulations imposed on animal research in many countries around the world, with restrictions on the use of procedures that may produce distress in experimental animals, a large variety of fear models that do not use punishment have now been developed. All of them rely on the fact that each species has specific sensory and perceptual access routes to fear circuitry. For instance, rodents do not require explicit physical punishment to motivate them to avoid events. They naturally prefer to enter dark holes,[13] yielding *the latency to enter a dark hole task.* When forced to remain under bright light, rats also exhibit reduced social activity, yielding the *diminished social-interaction test*, an anxiety that is effectively counteracted by BZs.[14] They also tend to avoid leaving the security of well-protected (i.e., high-walled) areas for the insecurity of wide-open areas, yielding the *plus-maze test* in which two arms have high walls and two have no walls.[15]

We now also know that rats exhibit an intrinsic fear of the smell of potential predators such as cats and ferrets, yielding various fear-smell tests in which one can measure behavioral disruptions of any of a variety of behavioral baselines (for rough-and-tumble play in juveniles, see Figure 1.1). Most of the preceding measures of fear are diminished by BZs, but it is noteworthy that the plus-maze test and the cat-smell test in rats are not especially sensitive to such drugs.[16] Morphine, which is only moderately effective in these models, strongly counteracts the disruption of play behavior produced by cat smell, suggesting that these models arouse distinct types of trepidation that may need to be differentiated from each other.[17]

Quadrant 4 (instinctual fear behaviors resulting from explicit punishment): The analysis of unconditional (instinctual) responses to punishment is likely to provide the clearest view of the unlearned brain mechanisms mediating fear, since punishment can presumably directly activate instinctual fear behaviors that arise most directly from underlying FEAR circuitries. There are now many such models, including simple ones, such as measuring how long animals "freeze" (show behavioral immobility) in response to "contextual cues" that have been paired with shocks (Figure 11.1),[18] as well as those that measure more complex behaviors, such as rats' tendency to cover up shock prods placed in their living quarters;[19] both of these behaviors can be reduced with BZs. The most compelling model of this type, probably the one that evokes fear most directly, is direct electrical stimulation to specific subcortical locations (including central amygdala, anterior hypothalamus, and PAG) to evoke a central aversive state accompanied by powerful fearlike response patterns.[20] Such brain stimulation induces freezing at low currents and flight at higher current levels, accompanied by intense autonomic indicators of fear such as increases in defecation, urination, heart rate, blood pressure, and adrenal stress responses. This approach provides a direct estimate of the localization of the major unconditional FEAR circuit in the mammalian brain (Figure 11.1) and also permits the dynamics of the underlying circuits to be studied effectively in the fully anesthetized subject.[21] Since some of these fear responses can be evoked under anesthesia, one can presumably study the sources of anxiety without imposing powerful (and no doubt unpleasant) emotional experiences on the experimental animal, but such approaches have not yet become fashionable.

The many models that exist for the analysis of fear suggest that a variety of processes may elaborate anxiety within the brain. Fearful states can be evoked by painful stimuli, cues that have become associated with aversive stimuli, various nonpainful stimuli that have indicated danger in the evolutionary history of a species, and perhaps even certain frustrations. These models are often differentially sensitive to pharmacological manipulations that may reflect the variety of distinct cognitive and motivational controls that interact with a limited set of unconditional anxiety processes that exist in the brain.

Thus, many of the distinct stimuli and situations that can evoke fearful states may derive their motivational impact from shared neural circuits. Indeed, this is how most emotional systems usually appear to operate—by

responding to a multiplicity of inputs and controlling a multiplicity of outputs, all of which can be modulated by ongoing learning processes. It is unlikely that a single FEAR system of the brain can explain how all of the preceding models derive their affective force, but we anticipate that this system will account for a substantial part of the variance. Thus, before discussing the FEAR system in greater detail, let us first summarize some evidence for multiple anxiety systems based on the pharmacological treatment of anxiety disorders in humans.

On the Varieties of Anxiety Systems in the Brain

The abundance of animal models, and the overall clinical complexity of anxiety indicate that we should be cautious in simplifying the issues that confront us as we seek a definitive understanding of anxiety within the mammalian brain. Let me briefly consider some other neuroemotional systems that contribute to aversive brain states related to anxiety. One of these is the system that functions primarily to elaborate separation distress (i.e., the PANIC system discussed in Chapter 14) as indexed by measures of separation calls in species as diverse as primates, rodents, and birds. This circuit is clearly distinct from FEAR and runs from the preoptic area and bed nucleus of the stria terminalis, down through the dorsomedial thalamus to the vicinity of the PAG.[22] This system presumably mediates such negative feelings as loneliness and grief, and may also contribute substantially to the precipitous forms of acute distress known as panic attacks.

Clinically, a distinction between brain mechanisms that control panic attacks and those that control everyday anticipatory anxiety first became apparent when it was found that the best available antianxiety agents (e.g., BZs such as chlordiazepoxide and diazepam) did not quell either panic attacks in humans or separation anxiety in animals. However, tricyclic antidepressants such as imipramine and chlorimipramine, which had no clear effect on simple generalized anxieties, were found to exert clear antipanic effects in humans and to also reduce separation distress in animals.[23] Quite remarkably, people whose panic attacks had been effectively attenuated with tricyclics still feared that the attacks might recur; hence they often did not consciously appreciate the therapeutic effects of the drugs, although they objectively experienced far fewer attacks. In other words, anticipatory anxiety and panic were modulated by different neurochemical systems.

Other symptomatic distinctions can also be made between fearful anxiety and separation anxiety. The former is characterized by generalized apprehensive tension, with a tendency toward various autonomic symptoms such as tachycardia, sweating, gastrointestinal symptoms, and increased muscle tension. The latter, especially in intense forms such as grief, is accompanied by feelings of weakness and depressive lassitude, with autonomic symptoms of a parasympathetic nature, such as strong urges to cry, often accompanied by tightness in the chest and the feeling of having a lump in the throat. While the former emotional state beckons one to escape situations that intensify the anxiety, the latter tends to motivate thoughts about the lost object of affection and impels one to seek the company of special loved ones.[24]

Recently, a strong case has been put forward claiming that panic attacks emerge from primitive suffocation-alarm systems of the brain, which may be closely coupled with separation-distress systems.[25] Thus, although PANIC and FEAR systems can be distinguished in the brain (also see Chapter 14), it is to be expected that they can also operate synergistically: Chronic anxiety can increase the incidence of panic attacks, and panic attacks can lead to chronic anxiety. The effectiveness of some new antianxiety agents, such as alprazolam, in reducing panic[26] may also indicate that the two emotional systems share some common neurochemical influences, perhaps because of shared nonspecific influences such as increased serotonin and reduced norepinephrine (NE) activity.

Another anxious state that may result from distinct neural activity is post-traumatic stress disorder (PTSD), which is characterized by chronic negative feelings, including mixtures of anger and anxiety. The severity of PTSD can be diminished with antiseizure medications, such as carbamazepine, an agent that is not consistently effective in the control of either panic attacks or anticipatory anxiety.[27] In addition to facilitating GABA activity, carbamazepine has a spectrum of other neurochemical effects. This drug also blocks "kindling," which is the experimental induction of chronic epileptic potentials in the brain via the periodic application of brief electrical stimulation to seizure-prone areas of the temporal lobe such as the amygdala (see "Afterthought," Chapter 5). It is not unusual for kindled animals to exhibit chronic emotional changes (increases in irritability as well as heightened sexuality), further suggesting that similarities may exist between this type of evoked brain change and PTSD.[28] Kindled animals also startle more easily than controls.[29]

A variety of other psychiatric disorders are commonly accompanied by anxiety. For instance, obsessive-compulsive behaviors and rituals often reflect an attempt to ward off encroaching anxieties. We do not know whether such incipient anxieties are mediated by any of the systems discussed earlier. It is noteworthy, however, that the serotonin-reuptake inhibitors such as chlorimipramine, which are effective antipanic agents, are also highly effective in controlling obsessive-compulsive behaviors,[30] suggesting a shared neurochemical substrate for both. Selective serotonin reuptake inhibitors (SSRIs) are also effective in reducing separation distress in animals, although their efficacy in generalized anxiety disorders is more modest.[31] However, since sero-

tonin modulates all emotional systems (see Chapter 6), such lines of investigation are not going to be especially useful for distinguishing emotional processes.

It seems likely that brain systems that mediate anticipatory and chronic generalized anxiety can be differentiated from those that mediate panic attacks, separation anxiety, and PTSDs in terms of the specific brain mechanisms involved, even though they also share many neural components. For instance, all may share a hypersensitized "alarm" component, reflecting an initial alerting response when threatening stimuli first appear on the psychological horizon; this response may arise, in part, from generalized cerebral arousal/attentional systems such as cholinergic and noradrenergic alerting circuits of the brain stem (see Figure 6.5). Many anxieties may also share arousal of the pituitary-adrenal stress responses,[32] although, surprisingly, this response system is not vigorously engaged during panic attacks.[33]

During the past few decades, several brain systems have been proposed as basic substrates for anxiety, including noradrenergic arousal from the locus coeruleus,[34] serotonergic arousal from midbrain raphe cell groups,[35] and a hippocampal-septal behavioral inhibition system.[36] Each of these theories remains controversial, with considerable contradictory data. Perhaps the most serious problem is the simple fact that animals still appear able to experience a great deal of fear after these systems have been experimentally damaged. Animals with damage to the brain areas mentioned above can learn to avoid foot shock and continue to exhibit anxious behaviors in many of the models discussed here. Accordingly, these systems probably contribute to fear in nonspecific ways. Indeed, they contribute substantially to practically every behavior an animal exhibits.

The Basic FEAR System

Brain-stimulation studies have long suggested that a coherently operating FEAR system exists in the brain. As mentioned previously, it extends from the temporal lobe (from central and lateral areas of the amygdala) through the anterior and medial hypothalamus to the lower brain stem (through the periventricular gray substance of the diencephalon and mesencephalon) and then down to specific autonomic and behavioral output components of the lower brain stem and spinal cord, which control the physiological symptoms of fear (including increases in heart rate, blood pressure, the startle response, elimination, and perspiration; for a summary see Figure 11.1). A growing consensus is emerging that this neural system mediates a fundamental form of unconditional fear.[37] Minor tranquilizers exert part of their antianxiety effect by reducing arousal of this brain system.[38]

When this system is activated by electrical stimulation of the brain (ESB), animals exhibit a variety of fearlike behaviors, ranging from an initial freezing response at low current levels to an increasingly precipitous flight response at higher current intensities. These, of course, reflect the types of fear responses animals normally exhibit when dangers are either far or close. In other words, the responses evoked artificially by ESB look very similar to the behavior of animals that have either noticed a predator at a distance or are being pursued by one. Likewise, the behaviors resemble those of animals that either have received foot shock recently or are in the midst of being shocked. Even though such animals appear to be severely distressed, it seems unlikely that the brain stimulation is activating a pain pathway, since the stimulated animals normally do not squeal or exhibit other apparent symptoms associated with pain. For some time, investigators believed that this kind of brain stimulation did not evoke a subjective state of fear. They were wrong.

As in the case of rage described in the previous chapter, the fearlike behaviors evoked with brain stimulation have commonly been considered to simply reflect motor control mechanisms for flight. The failure to more fully consider the possible role of this emotional response system in affective experience arose from a single peculiar fact: Even though animals exhibit flight when this system is stimulated, they do not readily learn to avoid the brain stimulation that evoked the fearful behaviors. In other words, a neutral cue predicting the onset of ESB in the FEAR system does not readily become a conditional source of fear that is sufficient to motivate the learning of discrete avoidance responses. By comparison, peripheral pain (e.g., foot shock) does so readily. Accordingly, investigators concluded that only somatic and visceral motor output systems had been activated rather than the emotional integration system for fear itself. We now know that this conclusion is incorrect: Animals will exhibit conditioned fear to this kind of ESB, as long as sufficiently sensitive behavioral tests are used (Figure 11.3).[39] It is possible that animals did not avoid the centrally evoked fear state in earlier studies because ESB-induced emotions are simply too pervasive and cannot be effectively linked to discrete external cues. Also, it is possible that the fear outlasted the ESB to such an extent that normal reinforcement processes could not be properly engaged.

Although we cannot directly measure subjective experience, the behavioral evidence from all mammals that have been studied strongly suggests that a powerful internal state of dread is elaborated by the FEAR system. First, all animals readily learn to escape such stimulation, implying that this type of ESB is highly aversive. The more closely the requisite learned response resembles the ESB-induced flight, the more rapidly the animal learns. Thus, the act of running away is learned more rapidly than a lever-press response.

If given the opportunity, animals will avoid environments where they have received such stimulation in the past, and if no avenue of escape is provided, they

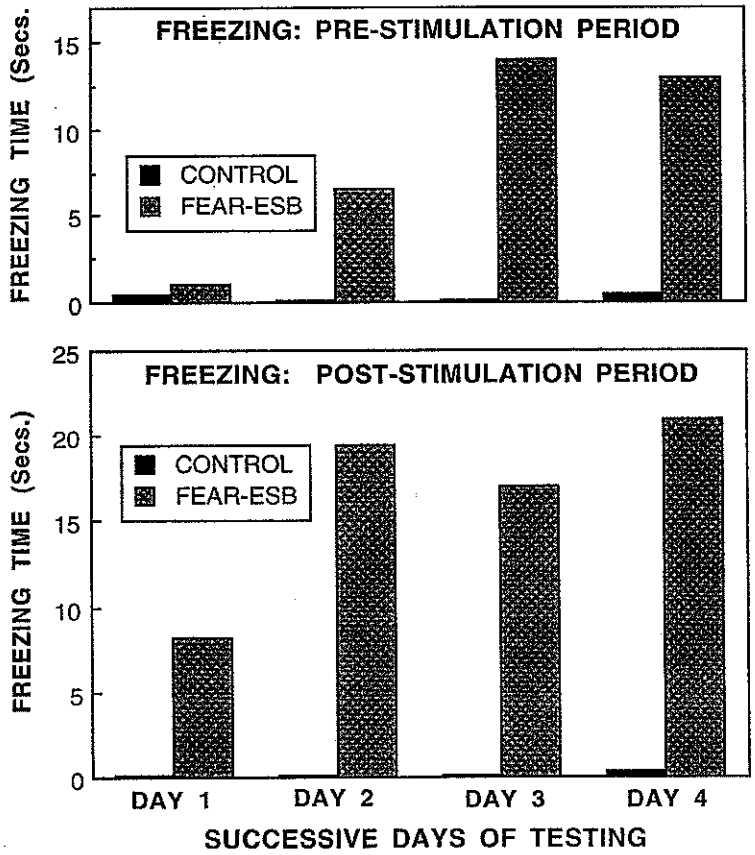

Figure 11.3. Freezing time during the minutes prior to and after electrical stimulation of the FEAR system on four successive days of testing. (Unpublished data, Sacks & Panksepp; adapted from Panksepp, 1996; see n. 40.)

will freeze as if in the presence of a predator.[40] Thus, although it is certainly difficult to train animals to avoid (i.e., anticipate) this kind of brain stimulation using traditional behavioral procedures (such as shuttle boxes and lever presses), animals do exhibit clear conditional responses if one utilizes simpler measures of learned behavior. Indeed, during stimulation of this system at very low current levels, the first response animals exhibit is an increase in freezing. Only when current levels increase does one begin to see a dramatic flight response. Perhaps most important, humans verbally report powerful feelings of foreboding during stimulation applied to these brain sites. The subjective fear responses are usually described in metaphoric terms.[41] For instance, one patient said, "Somebody is now chasing me, I am trying to escape from him." To another, onset of stimulation produced "an abrupt feeling of uncertainty just like entering into a long, dark tunnel." Another experienced a sense of being by the sea with "surf coming from all directions."

Whether the subjective experience of fear is mediated directly by this circuit or in conjunction with other brain areas will have to be addressed in further research. A modest amount of evidence favors the explanation that affective experience is an intrinsic subcortical function, since decorticate animals still exhibit escape and fear behaviors when these circuits are stimulated. To resolve how specific emotions are subjectively felt may require clarification of the primordial neural substrates elaborating affective experience, which may be organized at levels as low as the midbrain (see Chapter 16). At present, we do not have a detailed understanding of how affective experience is actually generated by such emotional circuits, but an understanding of the relevant behavioral substrates opens up a provocative avenue for determining how the conscious aspects of human and animal anxieties are created. Although precise neural evidence concerning the connectivities of the FEAR system remains modest, as will be summarized later, substantial progress is being made in defining how

learned inputs enter the circuit in the amygdala and how unconditional ones such as pain come to enter the circuit in the PAG.[42]

Relationships between Pain and Fear

In addition to various forms of anxiety, there are many other types of aversive internal feelings—ranging from pain to hunger, thirst, and other bodily needs that may modulate the intensity of fear. It is especially important to consider the role of pain in the genesis of anxiety, since that has been the traditional way of producing fear conditioning in animal models. Animals readily learn to escape from and avoid places where they have been hurt. Current evidence suggests that pain and fear systems can be dissociated even though they interact strongly at various locations within the neuroaxis (including the lowest reaches in the PAG, as well as the highest reaches in the amygdala).[43]

Perhaps the clearest evidence for the dissociation is that fearlike behaviors in animals and fear states in humans are not readily produced by electrical stimulation of the classic spinothalamic pain systems. It is only at midbrain levels, where the classic pain systems diverge into reticular fields, that localized ESB begins to yield such fearful behaviors as freezing and flight. Further, humans who have been stimulated in these latter brain areas typically report fear rather than pain, and animals exhibit flight and escape with no vocal expressions of pain. Likewise, lesions in brain areas containing fear circuitry do not typically affect pain thresholds in animals.[44] Thus, even though pain systems do send inputs into areas of the brain that mediate fear (especially at the PAG of the mesencephalon), electrical activation of the FEAR system does not appear to readily evoke the sensation of pain in either humans or animals.

However, it is also clear that the FEAR system does control pain sensitivity. It is commonly observed that animals and humans do not focus on their bodily injuries when they are scared,[45] and fear-induced analgesia emerges, at least in part, from arousal of pain-inhibition pathways such as serotonin and endogenous opioids, near the PAG of the mesencephalon.[46]

Learning within Fear Systems

Learning mechanisms allow organisms to effectively channel their specific fears into environmentally appropriate responses. The FEAR system contains certain intrinsic sensitivities, in that it responds unconditionally to pain and the smell of predators and other intrinsically scary stimuli, but it can also establish new input components that function through learning to inform the organism about cues that predict threats. Some environmental circumstances lead to rapid conditioning, presumably because certain perceptions have ready access to the FEAR system, while neutral stimuli take longer to condition. For instance, it has been found that in humans autonomic fear responses condition more rapidly when a mild electric shock is paired with images of angry faces than when it is paired with smiling faces.[47] In other words, the brain is predisposed to associate fear with the potentially threatening configuration of anger more readily than with a pleasant face. Neural assemblies at the base of the temporal lobes decode the facial patterns of emotions, and from there they probably transmit information along evolutionarily prepared input channels to the FEAR system, as well as to other emotional circuits of the amygdala.[48]

There are bound to be several preferential input channels to the FEAR system, reflecting the different intrinsic fears of different species. Thus, humans readily exhibit fears of dark places, high places, approaching strangers (especially those with angry faces), and sudden sounds, as well as snakes and spiders.[49] Rats are especially apt to fear well-illuminated areas, open spaces, and the smell of cats and other potential predators. But completely neutral stimuli can also access the FEAR system of the brain. During the past few years, great progress has been made in unraveling the manner in which this system becomes classically conditioned when neutral cues are paired with shock.

One of the first breakthroughs in the field was the finding that conditioned fears access the FEAR system at the central nucleus of the amygdala.[50] When this area is lesioned on both sides of the brain, animals no longer exhibit increased heart rates to stimuli they had learned to fear.[51] It is now becoming clear that the central nucleus is one major brain area where conditional synaptic control of fear is created. This provides a precise neurogeographical end point for analyzing how neurotic behaviors might be generated through learning.

Several intensely focused research programs have now revealed the precise mechanisms that allow simple conditioned fears to access the unconditional FEAR system. Effective models have been derived from studies of fearful responses to lights and tones paired with the administration of electric shock. Consider a situation in which a tone is followed by shock: The sound enters the eighth cranial nerve, and after synapsing in the cochlear nucleus, the information moves on to the inferior colliculus of the midbrain, then to the lateral geniculate of the thalamus, and then to the auditory cortex in the brain's temporal area (Figure 11.4). One can ask whether damage to any of these areas diminishes the conditioned fear response, and the answer is a clear yes for all auditory relay areas below the cortex.[52] This makes sense because the animal has been rendered deaf. However, the conditioned fear remains intact if only the auditory cortex is removed. In other words, the highest levels of auditory processing are not necessary for conditioned fears to be exhibited to simple sounds. This implies that a conditional linkage to the FEAR system has emerged at some subcortical location.

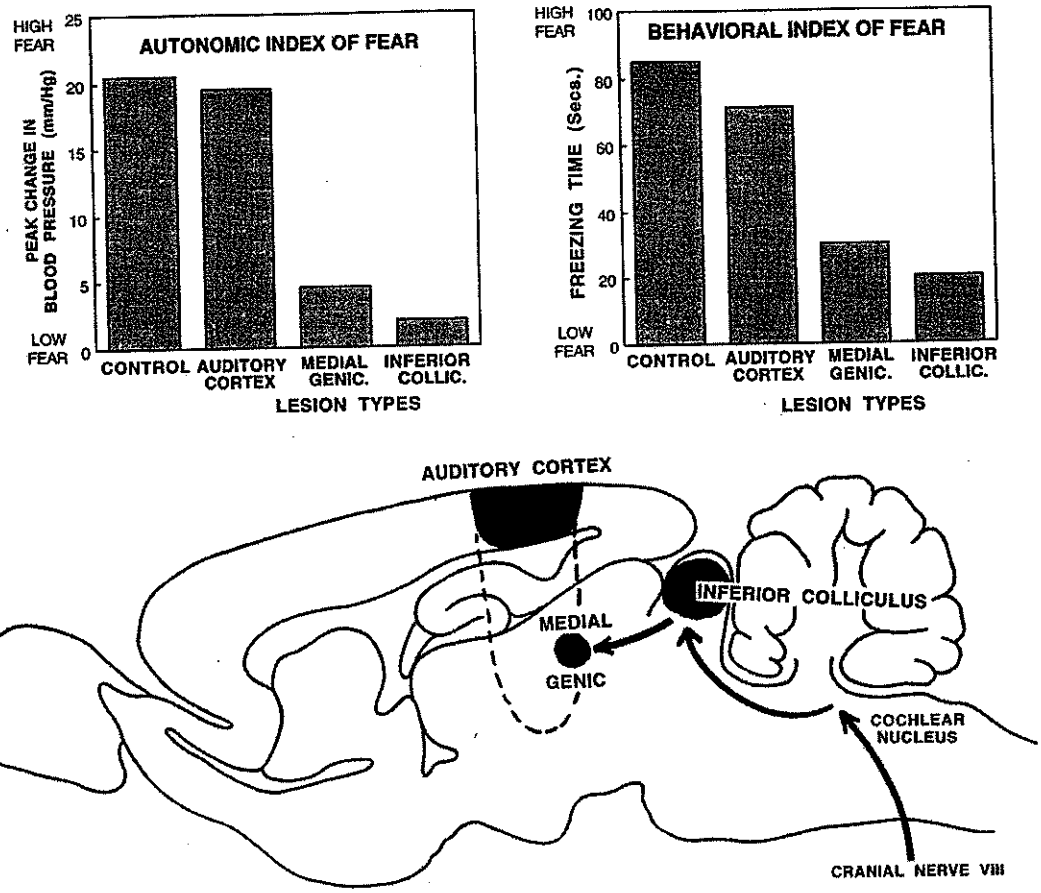

Figure 11.4. Lesions of subcortical but not cortical auditory processing areas disrupt conditioning of fear response to acoustic stimuli paired with foot shock. (Results adapted from Le Doux, 1993; see n. 53.) Behavioral data on top, and locations of lesions on bottom. The damage to the auditory cortex was on the lateral surface of the brain, depicted by dotted lines.

This important finding did not mean, of course, that cortical processing is irrelevant for fear learning. Complex fearful perceptions probably do require input from the cortex, but the finding did encourage investigators to search for a direct connection from thalamic auditory relays to the highest reaches of the FEAR circuit in the amygdala. Indeed, retrogradely labeled neurons were found in the thalamic auditory nucleus, the ventral part of the medial geniculate body, after placement of retrograde tracers into the headwaters of the FEAR system in the lateral amygdala.[53]

Although the analysis of amygdalopedal connections from the auditory thalamus did not yield powerful connections to the central amygdala as was initially expected, there were strong connections from the medial geniculate to the lateral and basolateral parts of the amygdala—areas which earlier ESB studies had implicated as FEAR circuits of the temporal lobes.[54] These lateral amygdaloid areas connect directly to the central amygdaloid nucleus, which then sends axons down to the lower reaches of the hypothalamus and midbrain, where the information is distributed to various, hormonal, autonomic, and somatic output channels that characterize the overall fear response.[55]

In other words, a direct thalamic-amygdaloid connection can convey low-level auditory information directly into the FEAR system without cortical participation.[56] However, additional work indicates that higher cortical processing is necessary for more complex auditory information to access the FEAR system.[57] By extrapolating these results to humans, we might hypothesize that the cortex decodes the affective lexical content of what is said as opposed to decoding the angry or fearful way something is said, but detailed evidence for this at the human level is nonexistent.

Much of the conditioning that occurs in the amyg-

dala is mediated by glutamate synapses, since the conditioning process can be prevented by placement of antagonists to n-methyl-d-aspartate (NMDA) glutamate receptors directly into the lateral amygdala.[58] The acquisition of fear can also be modulated by ascending NE systems, since blockade of ß-adrenergic synapses concentrated within the amygdala tends to diminish consolidation and retention of fearful information.[59] It is to be expected that many other amines and neuropeptides localized in the amygdala will also prove to be influential in the overall integration of fear responses. It may well be that different peptides here help elaborate the various types of fearful sensations and perceptions.

In any event, the preceding results affirm that emotional learning can occur without the intervention of the highest reaches of the cognitive brain. There are direct anatomical entry points from the thalamus into the relevant amygdaloid circuits, but it is clear that the more indirect cortical and hippocampal connections also provide information about external threats. For instance, the hippocampus informs animals about threatening aspects of their spatial environments, but it does not process discrete fear stimuli as does the amygdala.[60] Conditioning, as well as affective experience, can probably also be elaborated at lower levels of the fear circuit (i.e., at hypothalamic and mesencephalic levels), but such important issues remain to be empirically evaluated.

Once all the details of the learning mechanisms have been worked out, it should be possible to specify how new pharmacological maneuvers might facilitate the deconditioning of long-lasting learned fears. Glutamate antagonists have already been evaluated and found to block not only the acquisition of conditioned fears but also their extinction.[61] Thus, since glutamate facilitates both learning and unlearning of fears, as well as most other forms of learning, such information is unlikely to yield any useful clinical interventions.

A vast number of cognitive studies have now demonstrated that glutamate participates in virtually every form of memory and cognitive information processing imaginable. All cortical information descends onto the basal ganglia via glutamate synapses (see Figure 4.9). As we will see in the next section, glutamate receptors control not only fear conditioning but also control unconditioned fear responses. Thus, drugs that modify glutamate receptors will be useful in the clinical control of anxiety only if we are fortunate enough to find variants of such receptors that will allow specific modulation of deconditioning processes. This presently seems improbable.

It is more likely that pharmacological modulation of a variety of neuropeptides, including CRF, α-MSH, ACTH, NPY, and others, will provide more specific neurochemical control of anxiety than does glutamate. These systems are constituents of the FEAR system[62] and afford excellent routes for new drug development. Indeed, our understanding of how minor tranquilizers (i.e., antianxiety agents) work in the brain by interacting with BZ receptors has so far provided the most abundant information for understanding how anxiety is produced and how it can be controlled.

The Neurochemistry and Pharmacology of FEAR

For medical purposes, the most useful knowledge about fear and anxiety will emerge from an understanding of the neurochemical systems that mediate fearful impulses. An extensive body of evidence has already been assembled on the brain systems that are sensitive to BZs.[63] BZ receptors are concentrated along the trajectory of the FEAR circuit, from the central amygdala, downward via the ventral amygdalofugal pathway, through the anterior and medial hypothalamus, and down across the substantia nigra to the PAG and the nucleus reticularis pontis caudalis (the RPC), where fear modulation of the startle reflex occurs.[64] BZ receptors are closely coupled to gamma-aminobutyric acid (GABA) function in the brain. Just as glutamate is the brain's most prolific excitatory transmitter, its metabolic product GABA, via one decarboxylation step, is the most pervasive inhibitory transmitter and is capable of suppressing fear as well as many other emotional and motivational processes.[65] In short, BZs reduce fear by facilitating GABA activity in many parts of the brain, including by directly inhibiting the FEAR circuit.

The discovery of this BZ-GABA receptor complex has been the single most important development for explaining how BZs and the older antianxiety agents (alcohol and barbiturates) inhibit fearfulness. The BZ receptors promote GABA binding, which then increases neuronal inhibition in the FEAR system by facilitating chloride influx into neurons.[66] In other words, anxiety is quelled by BZs through the hyperpolarization of the neuronal elements that pass anxiety messages through the neuroaxis. While agonists for the BZ receptor, such as the many variants of BZ-type minor tranquilizers, suppress activity in the FEAR circuit, they may also modulate higher cognitive processing of the relevant information (anxious thoughts and appraisals), perhaps via effects on the relatively abundant BZ receptors in the neocortex.

Antagonists for the BZ receptor (such as flumazenil) are usually behaviorally inactive by themselves,[67] suggesting that endogenous anxiety signals are not tonically present at BZ receptor sites. Of course, such BZ receptor antagonists can block the antianxiety effects of exogenously administered BZs, as well as the anxiety provoked by a class of drugs known as "inverse agonists" for BZ receptors, which *decrease* inhibition within the FEAR circuit and can produce chronic anxiety disorders.[68] This "inverse agonist" concept was first generated by the discovery of various ß-carboline drugs that produced effects opposite to those of BZs; they

actively inhibited chloride entry into neurons via interaction with the BZ-GABA complex, thereby promoting anxiety in both humans and animals.[69]

One key task has been to discover what type of endogenous brain molecule normally acts on the BZ receptor. Even though definitive evidence is not available, and many natural brain metabolites have some effect on BZ receptors, a key candidate for some time has been an endogenous neuropeptide called diazepam binding inhibitor (DBI), which appears to promote anxiety when released onto BZ receptors, perhaps via an inverse-agonist effect.[70] As yet there is no conclusive evidence that DBI is in fact the major anxiety-generating transmitter of the brain, although most agree that if there is one that acts on the BZ receptor, it is likely to be an inverse agonist. In any event, existing data suggest that BZs promote serenity, in part, by promoting GABA-mediated inhibition within the FEAR system.

Which, then, are the neurotransmitters that directly convey the signal of fear through the neuroaxis? There are several possible candidates. Although NE and serotonin (5-HT) were once touted as specific anxiety transmitters, those early hypotheses have seemed improbable for some time, since biogenic amines operate as nonspecific control systems for all behavior.[71] Although increasing NE and 5-HT activity with drugs such as yohimbine and m-chlorophenylpiperazine (MCPP), respectively, can promote the experience of anxiety in humans,[72] such effects may be nonspecific. They may simply reflect general arousal effects that amplify whatever tendencies already exist in the nervous system, rather than reflecting any specific type of emotional arousal. Certainly, several other neuropeptides and amino acids modulate anxious behaviors more specifically and powerfully, at least in the animal models in which they have been studied. They will figure prominently in our future understanding of the neurochemical substrates of fear.

As indicated, one compelling option is that the simple amino acid neurotransmitter glutamate, which, as already noted, mediates the learning of fears, is also a key transmitter for generating the unconditioned response of fear.[73] A powerful fear syndrome can be evoked by administering the glutamate agonists kainic acid and also the specific agonist NMDA into the PAG or lower and higher areas near the ventricular system. Within minutes after placement of these agents into the brain, animals begin to exhibit spontaneous bouts of flight (often in a semicrouched posture) accompanied by an apparent psychic anguish. Visually oriented animals such as birds exhibit rapid head scanning, persistent vocalization, and bulging eyes suggestive of profound terror. These episodes can be inhibited by appropriate glutamate receptor antagonists (those that block kainate or NMDA receptors).[74] However, as already mentioned, such glutamate receptors are widespread in the brain, and only with remarkable luck (e.g., the discovery of unique emotion-specific variants of glutamate receptor antagonists or modulators) could we ever hope to develop antianxiety agents based on such knowledge. At present, the neuropeptides are more promising targets for pharmacological development in the ongoing search for new and useful ways to control anxiety.

In addition to DBI, several other anxiogenic neuropeptides have anatomical pathways along the trajectory of the FEAR system. Central administration of the neuropeptides CRF, α-MSH, ACTH, and CCK can promote an array of anxiety symptoms in animals.[75] CRF (see Figure 6.7), for example, causes agitated arousal and can reduce a variety of positively motivated behaviors, including feeding, sexual, and other positive social activities. Animals also tend to freeze in environments where they previously received CRF. Conversely, foot shock–induced freezing is diminished by CRF receptor antagonists.[76] Parenthetically, it should be reiterated that CRF arising from the paraventricular nucleus of the hypothalamus also controls the pituitary-adrenal stress response (see Figure 6.9) that accompanies virtually all emotions and many psychiatric disturbances, especially depression. Thus, it is generally believed that CRF receptor antagonists will eventually yield potent antianxiety and antistress agents. Nonpeptide CRF antagonists are already being developed for oral use.[77]

The neuropeptide α-MSH promotes camouflage-type pigmentary changes in many fish and reptiles. When such animals are scared, their skin tends to turn black. Although this peptide does not control skin pigmentation in higher vertebrates, a vigorous freezing/hiding pattern can be evoked in chicks by central administration of this peptide. ACTH, which comes from the same segment of the proopiomelanocortin (POMC) gene as α-MSH, has similar effects. Although there is little comparable information on mammalian behavior patterns, microinjections of high doses of ACTH into the PAG can precipitate vigorous flight, as well as freezing, in rats and other animals.[78] The affective effects of such treatments remain to be evaluated using conditioned freezing and place-avoidance paradigms, but it is anticipated that centrally effective antagonists of these neuropeptide receptor systems may reduce fearful behavioral inhibition.

An especially well-studied anxiogenic peptide is cholecystokinin (CCK). It, and various CCK fragments, can precipitate panic attacks in humans and a broad spectrum of anxiogenic symptoms in animals with the use of a variety of anxiety models described previously. Thus, from animal studies, it is to be expected that a CCK antagonist should have powerful antipanic and/or antianxiety effects, but preliminary clinical work has not been promising.[79]

A variety of other neuropeptides and neuropeptide antagonists appear to reduce anxiety symptoms following central administration. Centrally administered opioids (acting at *mu* sites), as well as oxytocin and somatostatin, are very effective agents for reducing separation dis-

tress vocalization (see Chapter 14). Recent work with putative neuropeptide Y (NPY) antagonists has suggested that they can evoke anxiety in animal models.[80] If such findings are supported by further research, it may eventually yield an especially useful category of drugs: In addition to reducing aspects of fear, an NPY agonist would be expected to markedly increase appetite, since this is the most powerful appetite-promoting peptide presently known.[81] Also, a number of steroids can modulate anxiety.[82] An especially important dimension of future research is to specify more precisely how these various neurochemical vectors mediate inputs and outputs of the FEAR system. Do certain neurochemistries convey specific fears, while others are indirect modulators (e.g., providing gain settings and duration controls) within the FEAR system? Future research should be able to tease apart the distinct functions of the many chemistries that control the diverse aspects of the anxiety/fear response and provide more precise avenues for the pharmacological control of various anxiety disorders.

Current Treatment of Anxiety in Clinical Practice

Progress in the treatment of anxiety was a matter of chance and exceptional good fortune during the early days of biological psychiatry. Until the development of benzodiazepine-type minor tranquilizers, the only drugs that could successfully control human anxiety were opioids, alcohol, barbiturates, and meprobamate.[83] Unfortunately, these drugs had many side effects, the worst of which was a poor safety margin, where the difference between the clinically effective dose and the lethal dose (ED/LD ratio) was rather small, increasing the probability of accidental death or suicide. The treatment of anxiety was revolutionized by the serendipitous discovery of the drug chlordiazepoxide (CDP). The efficacy of CDP was identified in 1960 during the final phase of research just prior to the scheduled termination of a relatively unfruitful research program on BZs at Hoffman-LaRoche labs. Almost as a last resort, it was found that one of the BZ molecules, CDP, was very effective in taming wild animals at a local zoo.[84] CDP rapidly became a great success in controlling various anxiety disorders, but for many years no one knew what it, and related BZs, did in the brain. As already summarized, now we do.

The entry of CDP into pharmaceutical practice, under the trade name Librium®, was rapid because of the drug's remarkable specificity and safety margin as compared with anything used previously. CDP could reduce anxiety at less than a hundredth of the lethal dose, which was a remarkable improvement over any other antianxiety agent, and soon many more potent BZs such as diazepam (Valium®) became available. The mild sedative effects commonly observed at the beginning of BZ therapy exhibit rapid tolerance, while antianxiety effects are sustained during long-term use. Initially, these drugs seemed to produce no apparent physical dependence during modest use. However, long-term use of high doses, which became a common practice, eventually was found to yield dependence and a withdrawal syndrome resembling the delirium tremens (DTs) of alcohol withdrawal.[85] This suggested that both agents work upon common substrates in the brain, and it is now well established that both promote GABA activity.

As BZs rapidly supplanted all other antianxiety medications on the market, several additional medical uses were discovered, including inhibition of muscular spasms and effective control of certain types of seizures, especially those that emanate from the limbic system.[86] BZs also found a receptive market as sleep-promoting agents and, because of their cross-tolerance (but relative lack of toxic effects), became effective medications for the alleviation of symptoms of alcohol withdrawal. In other words, subjects who were well habituated to taking high doses of alcohol could be placed on BZs without having to experience the harsh DT symptoms of alcohol withdrawal.[87] Of course, as long as people continued to take the BZs, the addictive state/process was sustained in their brains.

It was also anticipated that molecules of this class might be capable of being developed that would reverse some of the symptoms of drunkenness. Indeed, BZ receptor antagonists, such as flumazenil, can alleviate some of the symptoms of drunkenness, but not the toxic effects of alcohol. Such drugs will probably never be marketed because they do not reduce blood alcohol levels, and the manufacturers might be liable for accidents caused by people who have taken such drugs.[88]

A great variety of BZs eventually came on the market, but it was not until 1979 that the BZ receptor was finally identified in the brain; later, a different type of BZ receptor, which can control involuntary muscle spasms, was identified in the periphery. BZs are now tailor-made and marketed for specific disorders, even though the basic neuronal action is the same for all of them. The practice of using specific agents for each disorder is not based on any fundamental differences in their mode of action but rather on differences in potency and speed of entry into and exit from the brain. Thus, fast-acting BZs are used for sleep disorders, and longer-acting BZs are used for alcohol withdrawal and anxiety.[89]

Even though BZs turned out to be remarkably safe medicinal agents, the main shortcoming has been the previously mentioned dependence syndrome during long-term use. Other side effects include increased appetite, disorientation and memory loss (especially in the elderly), and the release of aggressive tendencies in passive-aggressive individuals.[90] Presumably this latter effect, which is somewhat paradoxical from the perspective that BZs can reduce affective attack (see Chapter 10), reflects release of an underlying irritability that

has been kept in check by overriding anxieties or other social inhibitions. By reducing the impact of such concerns, the underlying aggressive impulses may be temporarily released. Because of the shortcomings of BZs, as well as the intense profit motives of pharmaceutical firms, there has been a concerted effort to develop additional antianxiety agents.

Many antianxiety candidates are now in the wings, but the only item that has reached the center stage of the pharmaceutical market is buspirone (Buspar®), which has a profile of action quite distinct from that of the BZs. The therapeutic effect of this agent appears to be based on anxiety modulation through the 5-HT system. Buspirone has the relatively selective effect of stimulating 5-HT-1A receptors, which are predominantly concentrated on serotonin cell bodies. At this site, buspirone reduces 5-HT neuronal activity in the brain and hence diminishes serotonin release in higher brain areas.[91] Although many investigators believe that buspirone alleviates anxiety by reducing 5-HT activity, it should be remembered that there are also postsynaptic 5-HT-1A receptors in the brain (see Figure 10.7), and it presently remains possible that the postsynaptic effects of buspirone, which act to facilitate 5-HT activity, are more important in the control of anxiety than the presynaptic ones, which reduce serotonin activity. Since the reduction of 5-HT release occurs promptly upon buspirone administration, while effective control of anxiety takes up to several weeks, it also remains likely that the effects of buspirone emerge from a long-term regulatory effect of the drug, perhaps upon the postsynaptic sensitivity of the 5-HT system. Thus, the antianxiety effects of buspirone could well be due to a long-term facilitation of 5-HT sensitivity in the brain.

Once therapeutic effects are obtained with buspirone, they tend to be milder than those obtained with BZs, but fewer side effects are encountered. Buspirone does not produce any sedative effects, does not produce any desirable short-term psychic effects (hence it is not subject to abuse), and does not produce dependence or withdrawal upon discontinuation. Unfortunately, buspirone provides little benefit to those individuals who have already used Bzs for a long time.[92] Thus, buspirone is now the best initial treatment option at the outset of any long-term pharmacotherapy for excessive anxiety. Unlike some of the newer BZs such as alprazolam, however, buspirone has exhibited no efficacy as an antipanic agent.[93]

For common physiological symptoms of anxiety, such as palpitations and sweating, ß-noradrenergic blockers, such as propranolol, still appear to be the drugs of choice. "ß-Blockers" are generally deemed to be useful medication for the symptomatic control of anxiety that accompanies certain activities such as public presentations and performances.[94] Finally, it is noteworthy that MAO inhibitors such as phenelzine have been found to be highly effective for the control of social phobias and other neurotic personality disorders.[95] On the other hand, tricyclic drugs that are effective in reducing the incidence of panic attacks are also useful for reducing childhood anxiety-related disorders such as school phobias and enuresis, which may arise from overactive separation distress systems of the brain (see Chapter 14).

An Overview of the Complexity of Fears and Anxieties in the Brain

There remains little doubt that there exists a highly coherent FEAR system in the brain that contributes substantially to the overall emotional response that we typically call anxiety, as well as to more intense forms of terror and dread. Although it is not yet known how the FEAR system helps create the phenomenological experience of anxiety,[96] we can be reasonably certain that it does, leading perhaps to the remarkably widespread manifestations of fear in the brain as revealed by Fos immunohistochemistry.[97] As mentioned earlier, the whole brain seems to be involved.

In addition to real-world threats and dangers, ESB along the FEAR circuit generates powerful fear responses and the corresponding negative affective states in experimental animals and humans. Pharmacological and surgical dampening of activity along this system can make both animals and humans placid. In short, many expressions of fear emerge directly from this neural system, and it is only a matter of time before the many subjective feelings of fears will be understood with the tools of modern neuroscience.

The definitive data concerning the sources of affective experiences must come from human subjective reports following various brain manipulations, as well as from scans of brain activity during emotional episodes. Although data from the available imaging technologies at times can be misleading[98] and also rather insensitive when it comes to deeper brain stem structures such as those we have focused on here, recent work does indicate that the amygdala is aroused when anxiety is precipitated in various ways.[99]

Also, during the past few years, a number of neuropsychological studies have demonstrated that damage to the amygdala can reduce fear conditioning in humans just as it does in animals, and that such brain-damaged individuals are no longer able to recognize the facial expressions of emotions.[100] In a recent single-case study, a young man with massive bilateral temporal lobe damage extending far beyond the amygdala has exhibited unconscious emotional conditioning, and still exhibits preferences for individuals who had treated him especially well.[101] Whether and how such preconscious affective information can influence consciousness remains an unstudied issue.

Although many believe that the conscious readout of affective experiences is mediated by fairly high regions of the brain such as the amygdala and frontal

cortex, the position taken here is that the whole continuum of each emotional command system is important for contributing to the feeling of anxiety. To anyone who has studied decorticate animals, it is clear that they can still exhibit a great deal of fearful behavior,[102] and the affect of fear is probably a primitive state of consciousness that can be elaborated by ancient reaches of the brain stem such as the PAG (see Chapter 16). Even though the anxiety experiences of normal adults may be critically dependent on neural processing at the highest levels of the FEAR circuit,[103] the likelihood that young animals who have lost the higher reaches of the system can still experience fearful affect through the lower levels of the FEAR circuit remains a clear possibility that has not been adequately evaluated. If such low subcortical levels of affective processing do exist, we should be able to demonstrate some fear conditioning, especially changes in conditioned fears and place preference,[104] during stimulation of the lower reaches of the FEAR system in animals whose lateral and central amygdaloid nuclei have been completely destroyed at an early age (as in Figure 11.3). Clearly, much work remains to be done.

Just over a century ago, Freud bemoaned the fact that we knew practically nothing about the creation of anxiety in the brain. Now we have a mountain of important evidence that points to specific circuits in primitive parts of the brain that must have evolved long before organisms developed substantial cognitive abilities. This adds special meaning to that famous bit of wisdom from President Franklin D. Roosevelt during World War II, that "the only thing we have to fear is fear itself." In essence, the brain's capacity for fear is an evolved process that arises ultimately from internal neural causes rather than simply from the terrors of the environment.

The existence of this primitive state of fearfulness has been noted by many thoughtful observers down through the ages. My favorite is Jack London's description of how the instinct of fear begins to develop in his canine protagonist, White Fang,[105] The young wolf had never "encountered anything of which to be afraid. Yet fear was in him. It had come down to him from a remote ancestry through a thousand lives. It was a heritage he had received directly . . . through all the generations of wolves that had gone before. Fear!—that legacy of the Wild which no animal may escape." This fictional portrayal contains more than a grain of truth for humans as well. Because we share such ancestral emotions, animal brain research can finally clarify how we come to experience fear in our interactions with the world.[106]

AFTERTHOUGHT: Innate Fears—The Smell of Predators

Psychology has typically focused on how animals learn fearful behaviors, but now that we recognize that some fears represent the innate potentials of the brain, we can begin to ask how innate fears might be elaborated. Presumably, certain patterns of sensory stimulation have direct access to FEAR circuitry. This is affirmed to some extent by the patterns of fear development in human children. Children under 2 years typically exhibit the greatest fear in response to sudden noises, strange objects, pain, and loss of physical support, but all these fears decline steadily with age.[107] Other fears develop only as the child matures. For instance, only gradually do children become afraid of animals, strangers, the dark, and specific thoughts such as fears of drowning and death. Unfortunately, it is next to impossible to study the biological sources of these fears in the human brain.

By comparison, we can easily study some innate fears of animals. For instance, as exemplified in Figure 1.1, rats exhibit an innate fear of the smell of predators. When a very tiny sample of cat hair (a few milligrams will do) is placed in its cage, a rat exhibits dramatic changes in behavior—it plays less, eats less, and demonstrates an elevated level of wary attention. Such animals do not simply freeze (even though that behavior is elevated) but outwardly appear to be in a confused state, full of trepidation about something, although they do not appear to be afraid of the hair itself. Although most will eventually avoid the hair, individual animals will come very close, smelling and investigating it furtively. How does this olfactory stimulus actually enter the FEAR circuitry of the rat's brain?

Like all mammals, the rat has a *main olfactory system* (MOS) that transmits information from the olfactory epithelium to the olfactory bulb, which then distributes the information into various areas of the brain, including many circuits of the amygdala and hypothalamus. This system is designed primarily to sample odors from a distant source. The other olfactory system, called the *vomeronasal complex*, also known as the *accessory olfactory system* (*AOS*), tends to collect information from more nearby objects.[108] The animal actually has to be very close to the source to properly sample objects (indeed, when a snake flicks its forked tongue in and out of its mouth, it is sampling the air by depositing molecules directly into the accessory olfactory system at the roof of the reptilian mouth).

Which of these systems is the rat using when it exhibits trepidation in response to the smell of predators? This question has been answered by selectively damaging the MOS, by topical application of zinc sulfate, in one group of animals and eliminating the AOS input, by snipping the vomeronasal nerve as it enters the brain on the medial surface of the MOS, in another group.[109] We originally did these experiments anticipating that the smell of a cat was exerting its emotional effects via the distal olfactory system (i.e., input via the MOS). This would allow the rat to sense an approaching predator in order to effectively hide or flee. Quite surprisingly, the anxiety-provoking smell reached the

brain via the AOS! This was measured by the ability of MOS and AOS destruction to reduce or eliminate the play-reducing effect of cat smell. Accordingly, the evidence indicated that the short-range rather than the long-range olfactory system was mediating the aversive effects of cat smell. This adaptation would mainly allow rats to avoid locations where predators have been, and presumably where they are likely to be again, since most predators are territorial. The olfactory fear of cats is apparently not an evolutionary design that allows rats to detect predators that are prowling at a distance.

Do humans have a similar dual olfactory system? For a long time, investigators thought these structures were vestigial, with only some children still having a functional system. But now it appears that most adults do, in fact, have a functional AOS.[110] There is an increasing amount of evidence that it might act upon our level of sexual arousal—the topic of the next chapter. This is also a pervasive function of the AOS in animals. Already companies are trying to develop new perfumes targeted for this primitive system that helps make subliminal judgments about the pleasantness and erotic potentials of our social world. Whether the AOS also mediates some human fears remains unknown.

Suggested Readings

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PART III

The Social Emotions

Substantive understanding of social emotions has begun to emerge only recently. The first chapter of this part is devoted to the most primitive and exciting form of social engagement, sexual behavior, which is obviously already well represented in the reptilian brain. During the long course of mammalian evolution, driven partly by the sexual recombination of genes, a variety of behavioral strategies have emerged by which organisms select mates, and the existing diversity of sexual strategies is enormous. As summarized in Chapter 12, we now know that there are distinct LUST circuits for male and female sexuality, even though they also share many processes.

As we will see in Chapter 13, sexuality also established the possibility for nurturance. The emotional tendency to provide special care to the young, so impressive in mammals, is seen only in rudimentary forms in reptiles. Still, a primitive tendency to provide maternal care probably evolved before the divergence of mammalian and avian stock from their common ancestor. This is suggested by the strong parental urges of most avian species and by recent paleontological evidence suggesting that some dinosaurs may also have exhibited maternal tendencies. However, maternal devotion, through the evolution of CARE systems, has vastly expanded within the mammalian brain, while remaining rooted in the sociosexual processes that had evolved earlier.

Complex social feelings in mammals emerged hand in hand with the evolution of the limbic system. As summarized in Chapter 14, one of the most poignant advances in the evolution of emotionality was the capacity of the young to value social support. This social sense is closely linked to vocalization circuitry in the brain. Just as FEAR and RAGE systems allow organisms to cope with archetypal emergency situations that threaten survival, the separation-distress, or PANIC, system provides mammals with a sensitive emotional barometer to monitor the level of social support they are receiving. If social contact is lost, organisms experience a painful feeling of separation, and the young protest (cry) vigorously in an attempt to reestablish contact and care. The neuroscientific analysis of this system will have many implications for understanding everyday loneliness, as well as various psychiatric disorders, such as childhood depression and the emergence of panic attacks.

In the last chapter on a specific emotional system, I will delve into the subcortical circuits that generate playfulness. The rough-and-tumble PLAY system, described in Chapter 15, is important for learning various emotional and cognitive skills, including aspirations for social dominance and cooperation, which influence behavior with different intensities throughout the life span of each animal. The PLAY system promotes the establishment of social structures and helps ensure

the learning of social skills, which can facilitate reproductive success. It is one of the major systems in the brain that can generate happiness and joy.

Finally, in Chapter 16, I will consider a variety of critical issues concerning higher brain mechanisms in emotionality, including such fundamental aspects of brain organization as the nature of "the self," which must be addressed by neuroscience if we are ever to understand how emotional feelings are actually generated by the brain. I will attempt to clarify some of the most difficult and important issues in neuroscience, but unfortunately they are ones that have barely been touched empirically. To scientifically consider such topics, we must work concurrently at high theoretical and basic empirical levels. Many have suggested that there is probably no coherent neural representation of "the self" within the brain, but here I will advocate the position that there is such a neural entity, and that it elaborates a basic motor representation of the organism as an active creature in the world. This neural representation may be essential for an animal to have affective feelings. To help us talk about such a complex function of the brain, I will refer to its primordial neural substrates, deep in the brain stem, as the SELF (Simple Ego-type Life Form). I will develop the idea that this mechanism is multiply rerepresented in the brain during development and that it provides the center of gravity for the emergence of affective consciousness in brain evolution. Although adult human emotional experience also relies on higher brain representations of emotional systems, the position advocated here is that those higher functions could not subsist without the integrity of the lower functions.