From Normal Fear to Pathological Anxiety

Jeffrey B. Rosen  
University of Delaware

Jay Schulkin  
National Institute of Mental Health

In this article the authors address how pathological anxiety may develop from adaptive fear states. Fear responses (e.g., freezing, startle, heart rate and blood pressure changes, and increased vigilance) are functionally adaptive behavioral and perceptual responses elicited during danger to facilitate appropriate defensive responses that can reduce danger or injury (e.g., escape and avoidance). Fear is a central motive state of action tendencies subserved by fear circuits, with the amygdala playing a central role. Pathological anxiety is conceptualized as an exaggerated fear state in which hyperexcitability of fear circuits that include the amygdala and extended amygdala (i.e., bed nucleus of the stria terminalis) is expressed as hypervigilance and increased behavioral responsivity to fearful stimuli. Reduced thresholds for activation and hyperexcitability in fear circuits develop through sensitization- or kindling-like processes that involve neuropeptides, hormones, and other proteins. Hyperexcitability in fear circuits is expressed as pathological anxiety that is manifested in the various anxiety disorders.

Normal fear and anxious apprehension are emotional responses to danger or threat (Epstein, 1972; Ohman, 1993) and motivate the individual to relieve the negative emotional state by spending time in the lecture room before they give their talk. That subsides once the presentation is underway or completed. Some people may actively try to reduce their feelings of threat with public-speaking phobias will have a severe and debilitating symptom of giving a public presentation. The fear is so great that subsides when the aversion diminishes. For instance, public speaking typically elicits some fear or normal anxious behavior that subsides once the presentation is underway or completed. Some people may actively try to reduce their feelings of threat by spending time in the lecture room before they give their talk. This differs from the pathological anxiety disorders in which the emotional responses are chronically dysfunctional. People with public-speaking phobias will have a severe and debilitating autonomic, cognitive, and somatic reaction to even the suggestion of giving a public presentation. The fear is so great that they will avoid speaking at all costs, although it is clearly detrimental to the their job, career, and self-esteem. Fear is one of the major normal precursors for the development of pathological anxiety disorders. The intent of this article is to discuss how a normal, adaptive fear response may develop into a psychopathological disorder.

We use the term normal fear for both adaptive fear and anxiety states and distinguish them from pathological anxiety that is an exaggerated emotional and dysfunctional state. We also make a distinction between fear-related behaviors that occur when danger is first encountered and is still distal and defensive behaviors that occur when the danger is proximal or has been encountered (Blanchard & Blanchard, 1988; Fanselow, 1994; Fanselow & Lester, 1988; Graeff, 1994). Our term fear describes an emotional state during the expectation of or encounter with danger. When danger is imminent, fear can motivate defensive behaviors such as fight or flight.

Fear or normal fear defined by us is a central state similar to that used by many researchers of animal behavior (Bolles & Fanselow, 1980; Davis, Hitchcock, & Rosen, 1987; McAllister & McAllister, 1971) and differs only semantically from the term used by many researchers of animal behavior (Bolles, 1970). However, as we discuss later, the two classes of behavior (fear-related and defensive) can be dissociated from each other behaviorally and neuroanatomically, and defensive behavior can occur in the absence of behavioral signs' of fear. It is our and others (Barlow, 1988; Barlow et al., 1996; Gray, 1982; Gray & McNaughton, 1996) contention that the normal precursors of pathological anxiety lie in the exaggeration of what we call normal fear and not in abnormalities of defensive behavior.

Pathological anxiety is defined as exaggerated fear that manifests itself in the various symptoms of the anxiety disorders...
Pathological anxiety is described primarily by high negative affect associated with a sense of uncontrollability (Barlow, 1988). It is characterized by hypervigilance suggesting a readiness to respond to danger or negative events. Cognitively, it is chronic hypervigilance (Eysenck, 1992) biased to threatening stimuli (Matthews & MacLeod, 1994; McNally, 1996), along with an inability to concentrate on normal daily tasks, that defines much of pathological anxiety. Behaviorally, readiness to respond to danger is increased. Indeed, manifestations of fear-related behaviors, such as exaggerated startle responses, are some symptoms of the anxiety disorders. Pathological anxiety may also involve other emotions such as guilt, shame, or anger (Izard, 1972; Izard & Youngstrom, 1996). The pathological anxiety is typically chronic and so severe that it disrupts one's ability to function in the tasks of daily living for long periods of time. There is also considerable comorbidity of anxiety disorders with major depression (e.g., Rapee & Barlow, 1991).

We hypothesize that pathological anxiety evolves directly from normal fear responses. During normal fear states, activity in the brain's fear circuits increases, but it also subsides when the danger diminishes. However, during and following psychosocial stress the fear circuits may be overactivated and a combination of behavioral and biological processes leads to development of hyperexcitable fear circuits that culminate in turning the normal emotion of fear into pathological anxiety. After elicitation of strong and/or repetitive fear responses, the hyperexcitable fear circuit is more sensitive and more readily activated. Subsequent fearful responses are more easily triggered. Vigilance increases with a selective bias to view stimuli as threatening (Eysenck, 1992; Matthews & MacLeod, 1994). Eventually the activation of the fear circuits becomes independent and autonomous from the triggering stimuli, thus being out of the conscious control of the individual.

Our hypothesis is that the amygdala and its connections play a central role in both normal fear and pathological anxiety and is complementary to that proposed by Joseph LeDoux (1996) in his recent book *The Emotional Brain*. In addition to associative processes that LeDoux emphasizes, we suggest that hyperexcitability occurs by a process of neural sensitization or kindling in which psychosocial stressors initiate changes in the brain's fear circuits that lead to enhanced perception and response to subsequent threat and danger. We suggest that increased release of neuroendocrine hormones (i.e., glucocorticoids) that increase neuropeptides (e.g., corticotropin-releasing hormone) during fear increase the excitability of fear circuits that include structures of the amygdala and extended amygdala. Hyperexcitability in these circuits develops from an increase in a cascade of biomolecular events that include increased gene expression of immediate-early genes.

The fear circuits containing the amygdala and extended amygdala (i.e., bed nucleus of the stria terminalis) play a role in attention and arousal to potentially dangerous stimuli. They also integrate information from the external and internal milieu and have direct output connections to nuclei that control physiologic, autonomic, and fear-induced responses. A common unconscious mechanism may be operative for a variety of qualitatively different fear states (i.e., normal fear and pathological anxiety states). Hyperexcitability in the amygdala and bed nucleus of the stria terminalis would account for the exaggerated fear in pathological anxiety disorders involving cue-specific fear (i.e., specific phobias, posttraumatic stress syndrome, or panic) and nonspecific fear (i.e., generalized anxiety). The amygdala is critical for cue-specific fear conditioning (Davis, 1992; Kapp, Whalen, Supple, & Pascoe, 1992; LeDoux, 1996). Davis and his colleagues have recently suggested that the classic distinction between fear and anxiety (specific vs. nonspecific fear) may be recapitulated neuroanatomically where the central nucleus of the amygdala is involved in cue-specific fear and the bed nucleus of the stria terminalis is involved in nonspecific fear (Davis, Walker, & Lee, 1997). Hyperexcitability in the amygdala, in the bed nucleus of the stria terminalis, or both would contribute to many symptoms of specific and nonspecific pathological anxiety disorders (see the Appendix).

An understanding of how pathological anxiety develops from normal fear lies in our knowledge of the psychological and neuroanatomical substrates of normal fear. We therefore review what is known about normal fear and its neural underpinnings. We then discuss the notion of sensitization and possible neurobiological substrates of sensitization. Finally, some experimental paradigms and hypotheses to study hyperexcitability and neurobiological mechanisms of pathological anxiety are presented.

### Normal Fear

Our view of the emotion of fear is that it evolved as part of animals' adaptive arsenal to use in times of danger. In this context, fear is functional and part of problem-solving mechanisms. This view can be traced back to Aristotle, then Darwin (1872/1965) and was defended by Dewey (1938) and more recently by Arnold (1960) and Frijda (1986) who define emotions as action tendencies. For example, when fear is elicited, the animal acts in characteristic ways that prepare it to flee or defend itself. This includes somatic and autonomic preparation and cognitive or perceptual processing that have their roots in the evolutionary history of the species. This contrasts with a view of emotions, such as fear, in which emotions render one dysfunctional and one's ability to respond and reason about events is compromised (e.g., Freud, 1926/1959; K. Goldstein, 1939/1995; Sabini & Silver, 1996; Sanna, 1987).

Emotions are central states of the brain. In modern times, physiological psychologists such as Lashley (1950/1960), C. T. Morgan and Stellar (1950), and Stellar (1954) formulated this notion, whereas Bard (1939), James (1890/1950), and Jackson (1884/1958) emphasized a hierarchically organized brain that underlies emotions. The circuits for emotions, such as fear, continue to be defined with forebrain circuits interacting with brain stem nuclei during these states (Davis, 1992; Fanselow, 1994; Kapp et al., 1992; LeDoux, 1992). Peripheral mechanisms and inputs such as the kind James (1890/1950) suggested also influence emotions (Damasio, 1994). These include changes in peripheral glucocorticoids and epinephrine secretion that induce neuropeptides that sustain the central state of fear (Schulkin, McEwen, & Gold, 1994). Still, it is the brain that generates the state of fear (Davis et al., 1987). Although the experience of fear can be conscious, the brain mechanisms generating fear and the appraisal of stimuli as fearful are unconscious and automatic (LeDoux, 1996), similar to the workings of any other body organ. Thus, when we write about a perceptual, behavioral, and
motivational state of fear, we are writing about a state that can be experienced but is generated by machinations of unconscious brain mechanisms.

Fear is a perceptual, behavioral, and motivational state. Bindra (1978) and Bolles and Fanselow (1980) argued that fear is not merely a response to stimuli in the classic behavioristic interpretation, but the perception of danger motivates defensive behavior. Thus, the motivational state of fear organizes both perception and behavior (Bolles & Fanselow, 1980). Vigilance is aroused by environmental stimuli that are perceived as potentially dangerous and defensive maneuvers are initiated.

Fear is also communicative to others. During belligerent social interaction, species-specific bodily expressions or behavioral gestures (e.g., fearful facial expressions in humans and subservient displays in dogs) may signal to conspecific information about the fear state of the individual so it ceases its attack (Darwin, 1872/1965). Species-specific expressions and vocalizations may also alert other conspecifics about danger (W. J. Smith, 1977). In addition, fear functions to quickly prepare one to behaviorally respond to danger.

Humans and animals display evasive behaviors in the face of danger. The initial response to danger in many species is freezing behavior (Blanchard & Blanchard, 1969, 1989; Fanselow, 1994; Marks, 1987). Freezing or crouching readies the animal for fight or flight if attacked and reduces detection by prey or conspecifics (Blanchard & Blanchard, 1977). Concomitants with freezing are other autonomic, behavioral, and perceptual components including changes in heart rate (can be bradycardia or tachycardia, depending on the species, time of measurement, intensity of aversive stimulus, and whether the animal is free moving or restrained; for example, Iwata & LeDoux, 1988; Kalin, Shelton, Davidson, & Lynn, 1996; Rozendaal, Koolhaas, & Bohus, 1990; Stiedl & Spiess, 1997), blood pressure, respiration, and increased startle and attentiveness. We call this constellation of responses fear (see the Appendix).

It is important to note that all of these responses can occur at times other than during fear. For example, in many animals the cessation of movement and crouching also occurs during predation—a time when the animal is not acting defensively and is probably not fearful. Thus, these behaviors and responses are utilized in many situations associated with different emotional states. To use them as indexes of fear, they must occur within a functional context that is clearly fear inducing. We view the behaviors as linked to a functional central state of fear but that are also available for use during other states.

In addition to the fear-related behaviors discussed earlier, animals utilize defensive behaviors (fight and flight) to diminish harm from an imminent threat or actual attack. These species-specific fear and defense reactions are readily and innately available to the animal (Bolles, 1970) and are expressed on a continuum with different levels of threat (Blanchard & Blanchard, 1988; Fanselow & Lester, 1988). Freezing occurs when a potential threat is encountered. As the danger comes closer, active defensive responses begin to be displayed. Flight is most prominent when the threat becomes more proximal. Eventually, when the threat is very close or it actually causes harm, fight predominates. Tonic immobility can occur with a severe life-threatening attack (Gallup, 1974). Other learned avoidance behaviors (both passive and active) are also incorporated into the behavioral repertoire to use when the danger is confronted again. In our view, the defensive behaviors are different from the fear-related behaviors in that fearful behavior functions to alert and prepare the animal for active defensive responses. The two classes of behavior differ in several ways. First, as discussed earlier, different levels of threat initiate fear and defensive behaviors. Second, defensive behaviors are predominantly active, whereas freezing is a cessation of movement. Potentiated startle may play a transitional role for moving from freezing to escape (Lang, Bradley, & Cuthbert, 1997). Third, each has different, but interacting, neuroanatomical substrates that by necessity counteract each other (Bandler & Shipley, 1994; Fanselow, 1994; see discussion in Fear Circuitry). Fourth, fear is not necessary to elicit defensive displays or to respond to painful stimuli (e.g., Cahill & McGaugh, 1990; Kapp, Frysinger, Gallagher, & Applegate, 1979; Maier et al., 1993; Sananes & Davis, 1992). Nevertheless, the state of fear acts as a motive state to initiate defensive and avoidance behavior in threatening situations (Bolles & Fanselow, 1980; Masterson & Crawford, 1982; McAllister & McAllister, 1991).

During threatening conditions, the rat's fear behaviors of freezing, startle, and cardiac changes have been shown to be fairly well correlated (Leaton & Borszcz, 1985; Young & Leaton, 1994). Humans also have a variety of responses that vary systematically when shown unpleasant or aversive pictures. Facial corrugator muscle responses around the eye increase, heart rate decelerates, and the galvanic skin response and the eye blink startle reflex increase when these pictures are shown (Bradley, Lang, & Cuthbert, 1993). Many responses to pleasurable pictures occur in the opposite direction; facial zygomatic muscle responses increase, heart rate tends to increase, and the startle blink reflex diminishes (Bradley, Lang, & Cuthbert, 1990). Viewing fearful movie clips also induces bradycardia (Fredrickson & Levenson, 1998), which is similar to the orienting response described by Graham and Clifton (1966); for review, see E. Cook & Turpin, 1997), whereas general anxiety and obsessive–compulsive disorder patients respond to self-generated threatening images with a decrease in respiratory-sinus arrhythmia (Borkovec, Lyonfields, Wiset, & Dehl, 1993; Hoehn-Saric, McLeod, & Hipsey, 1995; Thayer, Friedman, & Borkovec, 1996). Although repeated presentation of the same unpleasant pictures elicits habituated responses in many of these physiological responses, the eyeblink startle reflex does not (Bradley et al., 1993). Acoustic startle can be exploited experimentally to probe fear in humans (Lang, 1995). Indeed, fear-conditioned stimuli augment the eyeblink startle response (Grillon, Ameli, Woods, Merikangas, & Davis, 1991). This suggests that similar brain mechanisms and neuroanatomical substrates involved in fear states in mammals such as rats are also utilized in humans (Lang, 1995).

Neural Circuitry of Fear

The Amygdala

The amygdala plays a critical role in many of the components of fear responses (i.e., freezing, heart rate changes, hypoalgesia, and potentiated startle). The amygdala is a structure where input of fear-inducing sensory and autonomic information and output to behavioral response systems converge (Aggleton & Mishkin, 1986; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990). The
central nucleus of the amygdala is an output pathway to activate many of the various components of fear behaviors (Figure 1; Iwata, Chida, & LeDoux, 1987; Kapp, Gallagher, Underwood, McNall, & Whitehorn, 1982; Rosen & Davis, 1988a).

Lesions of the central nucleus and other nuclei of the amygdala (i.e., lateral and basolateral nuclei) disrupt the expression of fear-induced bradycardia, changes in respiration, freezing, startle, and analgesia (Figure 2; for example, Campeau & Davis, 1995a; Hitchcock & Davis, 1986; Kapp et al., 1979; LeDoux, Cicchetti, et al., 1990; Roozendaal et al., 1990; Sananes & Davis, 1992), whereas stimulation of the central nucleus elicits bradycardia, freezing, and enhances acoustic startle responses.

Figure 1. (Top) Schematic drawing of a neuronal fear circuit: information flow through the amygdala. Information from conditioned fear stimuli enters the lateral nucleus of the amygdala (LA) from the medial portion of the medial geniculate nucleus (mMGN), the perirhinal cortex (PR), or both. (Other areas of cortex [CTX] also project to the amygdala; however, they are not considered an intrinsic part of the fear circuit.) Information then travels to the basolateral (BL) and central nucleus (CN) of the amygdala. Efferents of the central nucleus then travel to lower brain structures via the ventral amygdalofugal pathway (VAF). (Bottom) Efferents from the central nucleus (CN) of the amygdala and lateral bed nucleus of the stria terminalis (BNST) project to the periaqueductal gray (PAG) to induce freezing, to the reticularis pontis caudalis (RPC) to potentiate startle, to the parabrachial nucleus (PB) to alter respiration rate, and to the lateral hypothalamus (LH), dorsal motor nucleus of vagus (DMN), and nucleus ambiguus (NA) to influence heart rate and blood pressure.
The central nucleus also receives autonomic information from brain stem nuclei that control heart rate, blood pressure, and respiration (e.g., the dorsal motor nucleus of the vagus, lateral hypothalamus, and the parabrachial nucleus [e.g., Koh & Ricard, 1978; Veening, 1978]). The lateral and basal nuclei of the amygdala receive highly processed sensory information from a rich innervation from polymodal association cortices (Turner, 1981). Sensory (auditory and nociceptive) information from more direct subcortical regions also impinge on the lateral, basolateral, and central nuclei of the amygdala (Aggleton & Mishkin, 1986; Bernard, Alden, & Besson, 1993; LeDoux, Cicchetti, et al., 1990; LeDoux, Sakaguchi, & Reis, 1984; Turner & Herkenham, 1991), suggesting that the amygdala is also involved in the formation of associations between neutral and aversive stimuli (Davis, Rainnie, & Cassell, 1994; LeDoux, Cicchetti, et al., 1990; Maren & Fanselow, 1996; Rogan & LeDoux, 1996; Rogan, Staubli, & LeDoux, 1997). The lateral and basolateral nuclei have many large pyramidal cells, similar to cortical pyramidal cells, the major integrative cells of the cortex (MacDonald, 1982). N-methyl-D-aspartate antagonists, which block various forms of learning, also block fear conditioning when injected into the amygdala at the time conditioning occurs (Fanselow & Kim, 1994; Miserendino, Sananes, Melia, & Davis, 1990). In addition, neurons of the lateral nucleus respond to conditioned fear stimuli (Quirk, Repa, & LeDoux, 1995). There is also evidence that the basolateral–lateral nucleus complex may be a storage site for aversive memories (Maren, Aharonov, & Fanselow, 1996; however, see Parent, West, & McGaugh, 1994).

Although much of our knowledge about the amygdala and fear is derived from conditioned fear, the amygdala is also critical for unconditioned or innate fear. For example, Blanchard and Blanchard (1972) and Fox and Sorenson (1994) demonstrated that lesions of the amygdala completely abolished rats' innate fear-related behavior in the presence of a cat. Thus, the amygdala has a broad role in the emotion of fear and is not just limited to conditional aspects of fear.

The Extended Amygdala

In addition to the amygdala, the bed nucleus of the stria terminalis is beginning to be discussed as having a role in fear and pathological anxiety (Davis et al., 1997). Embryologically, the bed nucleus of the stria terminalis can be considered the rostral extension of the amygdala (Alheid & Heimer, 1988; Alheid, de Olmos, & Beltzmar, 1995; however, see Canteras, Simerly, & Swanson, 1995). The lateral part of the bed nucleus of the stria terminalis is considered the rostral extension of the central nucleus of the amygdala, whereas the medial portion is the rostral extension of the medial nucleus. Additionally, the brain stem projections of the bed nucleus of the stria terminalis innervate many of the same structures as the central nucleus of the amygdala (Alheid et al., 1995; Wallace, Magnuson, & Gray, 1992; see next section). The bed nucleus of the stria terminalis's role in controlling physiological activity of the hypothalamic–pituitary–adrenal axis in response to stress (Herman & Cullinan, 1997) also suggests that it has an important influence on fear and pathological anxiety. Interesting data by Davis and his colleagues suggest that the bed nucleus of the stria terminalis may play a role in nonspecific fear as opposed to cue-specific fear (Davis et al., 1997). Rats are innately fearful of brightly lit environments and startle more in them than in dimly lit chambers (Davis et al., 1997). Lesions of the bed nucleus of the stria terminalis reduce startle levels in the bright light to levels found

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**Figure 2.** Decrease of fear-related behaviors with amygdala lesions. (A) Loss of the fear-induced freezing response in rats to a conditioned auditory fear stimulus after bilateral lesions of the lateral nucleus of the amygdala (From "The Lateral Amygdaloid Nucleus: Sensory Interface of the Amygdala in Fear Conditioning." by J. E. LeDoux, P. Cicchetti, A. Xagoraris, and L. R. Romanski, 1990, Journal of Neuroscience, 10, p. 1067. Copyright 1990 by the Society for Neuroscience). (B) Loss of the fear-induced bradycardia response in rabbits to a conditioned auditory fear stimulus after bilateral lesions of the central nucleus of the amygdala (Reprinted from "Amygdala Central Nucleus Lesions: Effects on Heart Rate Conditioning in the Rabbit," by B. S. Kapp, R. C. Frysinger, M. Gallagher, and C. D. Applegate, 1979, Physiology and Behavior, 23, p. 1113, with permission from Elsevier Science. Copyright 1979 by Elsevier Science.). (C) Loss of fear-potentiated startle in rats after lesions of the central nucleus of the amygdala (From "Lesions of the Amygdala in Fear Conditioning," by J. E. LeDoux, P. Cicchetti, et al., 1990; Maren & Fanselow, 1996; Rogan & LeDoux, 1996; Rogan, Staubli, & LeDoux, 1997). The lateral and basolateral nuclei have many large pyramidal cells, similar to cortical pyramidal cells, the major integrative cells of the cortex (MacDonald, 1982). N-methyl-D-aspartate antagonists, which block various forms of learning, also block fear conditioning when injected into the amygdala at the time conditioning occurs (Fanselow & Kim, 1994; Miserendino, Sananes, Melia, & Davis, 1990). In addition, neurons of the lateral nucleus respond to conditioned fear stimuli (Quirk, Repa, & LeDoux, 1995). There is also evidence that the basolateral–lateral nucleus complex may be a storage site for aversive memories (Maren, Aharonov, & Fanselow, 1996; however, see Parent, West, & McGaugh, 1994).

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(Iwata et al., 1987; Kapp et al., 1979; Rosen & Davis, 1988a).
in a dimly light chamber. Lesions of the central nucleus of the amygdala have no effect on the increased startle. Conversely, amygdala lesions block cue-specific fear potentiated startle, whereas bed nucleus lesions do not (Hitchcock & Davis, 1991). Furthermore, lesion of the basolateral nucleus of the amygdala may block both cue-specific and nonspecific fear. Thus, the central nucleus of the amygdala may be important for cue-specific fear, the bed nucleus of the stria terminalis for nonspecific fear, and the basolateral nucleus of the amygdala for both types of fear.

**Fear Circuit**

The amygdala functions within a circuit. Some of the sensory afferents to the rat amygdala that subserve auditory and visual fear conditioned stimuli have been delineated. These are schematically shown in Figure 1. A pathway from the medial portion of the medial geniculate nucleus, posterior intralaminar nucleus, and suprageniculate nucleus projects directly to the lateral nucleus of the amygdala and carries information about auditory-conditioned stimuli (LeDoux, Farb, & Ruggiero, 1990; LeDoux, Sakaguchi, & Reis, 1984), but not visual-conditioned stimuli (Campeau & Davis, 1995b). Pathways from the temporal auditory and perirhinal cortices also project to the lateral nucleus (Burwell, Witter, & Amaral, 1995; MacDonald & Jackson, 1987; Romanski & LeDoux, 1993; Suzuki, 1996). The temporal auditory cortex can carry information about acoustic-conditioned stimuli (Romanski & LeDoux, 1992), and the perirhinal cortex may participate in fear conditioning of both auditory and visual stimuli (Campeau & Davis, 1995b; Coordinas & LeDoux, 1995; Rosen, Hitchcock, et al., 1992) because it receives sensory information from neocortex and inputs from limbic structures such as the pyriform, entorhinal, insular cortices, and hippocampal structures (Burwell et al., 1995; Suzuki, 1996). However, unlike the amygdala, which is essential for acquisition and performance of conditioned fear, animals with lesions of the perirhinal cortex can easily be conditioned and retrained to be fearful (Campeau & Davis, 1995b; Romanski & LeDoux, 1992), which suggests that it is a transition cortex (LeDoux, 1996) for modulatory sensory information to relay into the amygdala (Burwell et al., 1995; Suzuki, 1996). The basolateral nucleus also receives projections from the hippocampus via the ventral subiculum (Canteras & Swanson, 1992), which may be involved in contextual fear conditioning (Maren & Fanselow, 1996). Basolateral–striatal projections may be important for avoidance behavior (Everitt & Robbins, 1992). Finally, reciprocal basolateral nucleus–basal forebrain projections may be important for attention and vigilance during fear (Gallagher & Holland, 1994; see also the next section).

From the lateral and basolateral nuclei of the amygdala, the fearful information travels either directly to the central nucleus of the amygdala or to the basolateral nucleus of the amygdala and then to the central nucleus of the amygdala (Pitkanen et al., 1995; Stefanacci et al., 1992; Figure 1). The basolateral nucleus may also project to the lateral bed nucleus of the stria terminalis (Deasy, Shi, & Davis, 1997). Both the central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis have extensive projects via the ventral amygdalofugal pathway directly to many diencephalic, midbrain, and brain stem structures, such as the periaqueductal gray (Beitz, 1982; Hopkins & Holstege, 1978; Krettek & Price, 1978; S. Post & Mai, 1980), lateral hypothalamus (Krettek & Price, 1978; Price & Amaral, 1981; Shiosaka et al., 1980), nucleus reticularis pontis caudalis (Rosen et al., 1991), parabrachial nucleus (Hopkins & Holstege, 1978; Veening, Swanson, & Sawchenko, 1984), and dorsal motor nucleus of the vagus and nucleus ambiguous (Hopkins & Holstege, 1978; Veening et al., 1984; Figure 1). The central gray or periaqueductal gray plays a central role as an output pathway in the generation of freezing and escape behavior (Bandler & Shipley, 1994; Carrive, 1993; Fanselow, 1994), whereas the hypothalamus (paraventricular nucleus and lateral hypothalamus) may activate endocrine and autonomic functions (Beaulieu, DiPaolo, Cote, & Barden, 1987; LeDoux, Iwata, Cicchetti, & Reis, 1988). The nucleus reticularis pontis caudalis is part of the startle circuit (Davis, Gendelman, Tischler, & Gendelman, 1982; Lee, Lopez, Meloni, & Davis, 1996) where input from the central nucleus of the amygdala impinges to enhance startle (Rosen & Davis, 1988b, 1990; Rosen et al., 1991). The parabrachial nucleus controls respiration (Von Euler, Martila, Remmers, & Trippenbach, 1976), whereas the dorsal motor nucleus of the vagus and nucleus ambiguous controls the parasym pathetic responses such as bradycardia and respirator-sinus arrhythmia (Porges, 1995).

An important target region of the central nucleus of the amygdala is the periaqueductal gray in the midbrain that controls fear-induced freezing and defensive behaviors (Bandler & Shipley, 1994; Fanselow, 1994; Hostege, 1995). Amygdala projections innervate the ventral periaqueductal gray but not the dorsolateral periaqueductal gray (Hostege, 1995). Lesions of the ventral periaqueductal gray block fear-induced freezing (Fanselow, 1994). In contrast, lesions of the dorsolateral periaqueductal gray have no effect on footshock-induced freezing but decrease the footshock-induced activity burst (Fanselow, 1994). In corroboration, stimulation of lateral regions of the periaqueductal gray produces active defensive aggression, whereas ventral stimulation elicits hypoactivity and bradycardia (Bandler & Shipley, 1994). During low levels of threat when fear-related behaviors like freezing predominate, the dorsal and dorsolateral periaqueductal gray may be inhibited but are released with more threatening stimuli (Graeff, 1994). Similarly, the dorsal periaqueductal gray may inhibit fear-related responses (i.e., attenuation of fear-potentiated startle) under highly threatening situations because lesions of this area release fear-potentiated startle from inhibition (D. L. Walker & Davis, 1997). Thus, although there are neuroanatomic distinctions in the periaqueductal gray between the substrates of fear-related and defensive behaviors, the systems interact with each other so behavior can switch from one to the other when necessary (Fanselow, 1991). Other brain regions also play a role in fear and the expression of fear-related behaviors. The hippocampus plays a role in context-specific processing of fearful information (J. J. Kim & Fanselow, 1992; Phillips & LeDoux, 1992). The septohippocampal region may also be important for behavioral inhibition and vigilation of approach–avoidance behavior during times of risk assessment (Gray & McNaughton, 1996). The prefrontal cortex may play a role in extinction of behavior to fearful stimuli (M. A. Morgan, Romanski, & LeDoux, 1993; however, see Gewirtz, Falls, & Davis, 1997). The amygdala also projects to widespread regions of sensory cortex to influence sensory information processing (Amaral, Price, Pitkanen, & Carmichael,
1992). Obviously the amygdala and its associated fear circuits do not act independently of other brain regions. Theories that integrate the amygdala with many brain regions and systems are necessary for a full understanding of emotions (e.g., Gray & McNaughton, 1996; LeDoux, 1996; Panksepp, Sacks, Crepeau, & Abbott, 1991).

Fear, Attention, Predictability, and the Amygdala

The amygdala adds the emotional coloring to ongoing and remembered events. One function of the amygdala is to maintain stability in the face of uncertainty (Gallagher & Holland, 1994; Schulkin et al., 1994). While the amygdala is linked to anticipatory regulation, the hypothalamus is linked to reactive and homeostatic regulation. Both are fundamental for the regulation of the internal milieu during fear (Schulkin et al., 1994). As environmental conditions change and the world becomes less predictable, the amygdala functions to anticipate and respond to new motivational information (particularly negatively motivating information) from the internal and external environments to set new values to environmental cues, thus making the world more predictable again.

Attention, vigilance, and arousal have played an important role in theoretical discussions of fear and pathological anxiety. Several attentional—pathological anxiety models have been proposed (see Eysenck, 1992). Activation of attentional processes is important for focusing on stimuli. Increased activation of regions involved in attentional processes may also potentiate responses to sensory stimulation by lowering the thresholds and by increasing receptive fields of neuronal populations. Neurons in sensory cortices that initially do not fire to a sensory stimulus will respond to the stimulus following fear conditioning (Weinberger & Diamond, 1987). Work over many years has demonstrated that stimulation of the amygdala increases vigilance, arousal, and attentiveness in many species. In elegant studies performed by Flynn (1972) several years ago, stimulation of the amygdala elicited fear and modulated defensive attack induced by stimulation of the hypothalamus in cats (Siegel, Schubert, & Shaikh, 1995) and increased the receptive fields around the mouth. Thus, not only were the cats more aroused and acted more fearfully following amygdala stimulation, but the larger receptive fields around the mouth and whiskers made the cats more sensitive to touch. Enhanced responsivity (i.e., startle) to acoustic stimuli when the amygdala is electrically stimulated also indicates that activation of the amygdala can facilitate reflexive responses by increasing excitability in the sensorimotor circuit subserving startle (Koch & Ebert, 1993; Rosen & Davis, 1988a; Figure 3).

Conditioning of fear behaviors and attentional processing are intertwined (Kapp, Supple, & Whalen, 1994; Kapp et al., 1992). Electroencephalograms recorded from frontal cortex in rabbits respond to novel stimuli (e.g., a tone) with low-voltage fast activity that habituates with repetitive presentation. However, during pairing of the same tone with an electric shock to the nictitating membrane of the eye, the low-voltage fast activity returns with presentation of the tone. This conditioned electroencephalogram activity occurs concomitantly with the appearance of conditioned fear responses (i.e., bradycardia). During fear the central nucleus of the amygdala may function in the acquisition of an increased state of nonspecific attention or arousal manifested in a number of conditioned emotional bodily responses (Kapp et al., 1992). This combination of increased attention and a coordinated pattern of responses during conditioned fear, such as bradycardia, piloerection, or freezing behavior, functions to enhance sensory processing.

Holland and Gallagher (1993) have also examined the role of the amygdala in attention and prediction. Lesions of the central nucleus of the amygdala were shown to disrupt the normal increased attention given to a stimulus with inconsistent predictive value. It was also shown that learning about stimuli that did not predict subsequent presentation of a stimulus (produced by a latent inhibition paradigm) was not different in amygdala-lesioned rats compared with normal rats. Gallagher

**Figure 3.** Enhancement of acoustic startle by stimulation of the central nucleus of the amygdala in naive rats. (Top) Location of the stimulating electrode in the central nucleus of the amygdala (as indicated by arrow). (Bottom) Effects of different levels of electrical stimulation (25-ms train of 0.1-ms pulses) of the amygdala on the acoustic startle response in rats. Amygdala stimulation onset was 25 ms before the presentation of a 40-ms acoustic startle stimulus. Low levels of amygdala stimulation current did not affect acoustic startle. Only current above a particular threshold enhanced the acoustic startle response (*). From "Enhancement of Acoustic Startle by Electrical Stimulation of the Amygdala," by J. B. Rosen and M. Davis, 1988, Behavioral Neuroscience, 102, p. 199. Copyright 1988 by the American Psychological Association.
and Holland (1994) concluded that the central nucleus of the amygdala plays a role in attention to stimuli associated with increased unpredictability but not to stimuli that predict subsequent event or non-event occurrences. Recent experiments have demonstrated further behavioral distinctions between the central and basolateral nuclei of the amygdala, where lesions of the basolateral nucleus of the amygdala block the acquisition to conditioned positive incentives, but central nucleus lesions do not (Hatfield, Han, Conley, Gallagher, & Holland, 1996). In summary, the data demonstrate that the central nucleus of the amygdala is central to the processing of anticipation that is important in attentional aspects of fear.

As discussed earlier, the human eyeblink startle reflex is modulated by the emotional significance of stimuli and not only by their attention inducing properties (Lang et al., 1990). Whether the amygdala also plays a role in emotional and attentional mechanisms that increase human eyeblink startle reflex by negatively valanced stimuli can only be speculated at this time. Nevertheless, recent demonstrations have shown that patients with selective bilateral lesions of the amygdala lack the ability to recognize specific facial and vocal expressions of fear (Adolphs, Tranel, Damasio, & Damasio, 1994, 1995; Scott et al., 1997). Moreover, patients with selective damage to the amygdala do not display emotion responses (i.e., increased skin conductance) to conditioned aversive stimuli (Bechara et al., 1995; LaBar, LeDoux, Spencer, & Phelps, 1995). These data strongly suggest that the amygdala is critical for perception of many types of fear-provoking or aversive stimuli in humans and is necessary for behavioral expressions of fear. Indeed, in normal humans, regional cerebral blood flow is increased in the amygdala during free recall of emotional information (Cahill et al., 1996) while viewing fearful faces, and is decreased with pictures of happy faces (Morris et al., 1996; Figure 4).

The amygdala is involved in the perceptual or appraisal mechanisms that are activated during fear. These mechanisms are unconscious (LeDoux, 1996) and finite in processing capacity, but they are constrained by the amount of neural tissue and thus by processors that can be allocated to a particular task. Generalized anxiety disorder patients are unconscious of positively valanced stimuli and are constrained by the emotional significance of stimuli and not only by their attention inducing properties (Pashler, 1997; Treisman, 1954), and learning (G. A. Miller, 1956) have been known for a long time (James, 1890/1950). Many examples of limited attentional capacities in animals have also been shown, in which presentation of a novel stimulus is known to distract the animal and disrupt the expression of a previously conditioned response. This limited capacity for computation may also occur during fear. An example of this is that presentation of a novel stimulus can reduce the expression of fear-potentiated startle that is normally provoked by a known, conditioned fearful stimulus (Davis, Fails, Campeau, & Kim, 1993). Experience with unpredictable events leads to an increase in attentional allocation for processing unpredictable and possibly dangerous stimuli. Unpredictability of aversive events has been postulated to be important for the development of chronic fear or pathological anxiety (Peterson, Maier, & Seligman, 1993; Seligman, 1968) and may be a factor in the etiology of generalized anxiety disorder (Mineka & Zinberg, 1996). Uncontrollable and unpredictable aversive stimuli delivered in learned helplessness (Mineka, 1985) and experimental neurosis paradigms (Mineka & Kihlstrom, 1978) have been shown to increase fear-related behavior and decrease successful avoidance conditioning. In a limited-capacity system, such as the fear system, severe, repeated, or both, unpredictable and uncontrollable aversive events may promote a long-lasting, chronic hypervigilant state and hyperexcitability in the neural structures that subserve vigilance to potentially dangerous stimuli.

From Normal Fear to Pathological Anxiety

Many theories of anxiety and panic disorders have made distinctions between the psychology and neuroanatomy of anxious apprehension on the one hand and the panic, escape, and avoidance behavior on the other (e.g., Barlow, 1988; Barlow et al., 1996; Graeff, 1994; Gray, 1982; Gray & McNaughton, 1996). In these theories, the psychological construct of exaggeration of the anxious apprehension (fear), and not the panic or escape (defensive) behavior, is the root of the pathology. Neuroanatomically, it is the circuits subserving fear, and not those subserving defensive behavior, that are critical for pathological anxiety. Most researchers think, including us, that the amygdala, and possibly the bed nucleus of the stria terminalis, is the core of this fear circuit (e.g., Davis, 1992; LeDoux, 1996; however, see Gray & McNaughton, 1996, for a different view).

We contend that clues for understanding human anxiety disorders lie in the study of normal fear and its associated behaviors. This not only includes the fear-related autonomic and behavioral responses that are activated during pathological anxiety but, importantly, the perceptual fear response of greater vigilance. Unraveling the mechanisms of the perceptual fear response may lead researchers to greater understanding of pathological anxiety because dysfunction or overactivation of the perception of
fear leads to anxious thought and maladaptive behavior (see the Appendix).

Animals are ready to respond to external stimuli and in many cases in a prepotent or fixed manner (Lorenz, 1981; Tinbergen, 1951). This seems particularly true of fear responses (Bolles, 1970). If the perceptual-response system is primed and more sensitive or excitable, then there is a greater action tendency. Frijda’s (1986) and Arnold’s (1960) notion of emotions is that there is an increased tendency or readiness to respond to stimuli that elicit particular responses. Increases in the readiness to respond would produce greater or exaggerated responses to stimulation and would allow for these responses to be elicited with lower intensity stimulation. The various cognitive biases (e.g., interpretive, attentional, or memorial; reviewed in Eysenck, 1992, and Matthews & MacLeod, 1994) and increased startle responses (Grillon, Ameli, Foot, & Davis, 1993; Grillon, Ameli, Goddard, Woods, & Davis, 1994; C. A. Morgan, Grillon, Southwick, Davis, & Charney, 1995) demonstrated in anxiety disorder patients toward threatening stimuli indicate that neural fear systems are hyperexcitable in anxiety disorders. Neurologically, this can be conceptualized as hyperexcitability of brain structures that evaluate exteroceptive, interoceptive, and proprioceptive stimuli as dangerous. Thus, external, as well as internal, autonomic and muscular events are evaluated more readily as signaling danger in a hyperexcitable fear evaluation system.

Etiology of Hyperexcitability

Hyperexcitability of neural circuits that are responsible for normal adaptive fear states and behaviors may lead to exaggeration or persistence of these states and behaviors. How may chronic hyperexcitability develop? There are three general variables that may contribute to the development of hyperexcitability: genetic factors, experience during critical stages in development, and physical or psychological trauma at any age.

Genetic factors most likely play a role in pathological anxiety. Twin studies on anxiety disorders suggest that genetic factors do play a role in the etiology of pathological anxiety (e.g., Kendler et al., 1995; Torgersen, 1997). The specific anxiety disorders do not seem to be genetically homogenous, but at the same time there is not a discrete set of genetic factors for each disorder (Kendler et al., 1995). Kagan, Reznick, and Snidman, (1988) have found that about 10–15% of children seem to be born excessively shy with heightened levels of arousal and a propensity for exaggerated social wariness and behaviorally inhibited responses that persist at least into later childhood. This proneness to fear is stable over time and throughout development stages (Kagan, 1994). Several rat and mouse strains have exaggerated fear and avoidance responses in various tests of fear and pathological anxiety (Boissy, 1995; Caldarone, Saavedra, Tartaglia, Wein, & Flaherty, 1997; Flint et al., 1995; Gershenfeld & Paul, 1997; C.-D. Walker, Aubert, Meaney, & Driscoll, 1992), suggesting that genetic factors may play a role in the etiology of anxiety disorders.

Exaggerated fearfulness and possibly hyperexcitability of the neural circuits of fear develop in adults as a consequence of a major traumatic experience. A well-documented consequence of war or rape is the development of posttraumatic stress disorder (e.g., Choy & de-Bosset, 1992; Kuch & Cox, 1992; Resnick, Yehuda, Pitman, & Foy, 1995; Yehuda, Boisoneau, et al., 1995). These individuals not only have vivid, terrifying recurrent memories of the specific traumatic incident but are chronically hyperexcitable as evidenced by generalized exaggerated startle reflexes. Interestingly, although holocaust survivors and combat veterans with posttraumatic stress disorder have chronic low levels of cortisol compared with nonposttraumatic stress disorder survivors and veterans (Yehuda, Boisoneau, et al., 1995; Yehuda, Kahana, et al., 1996), an increased sensitivity of the hypothalamic-pituitary-adrenal system has been found in combat veterans with posttraumatic stress disorder (Yehuda et al., 1996; Yehuda, Boisoneau, Lowry, & Gil, 1995). This suggests that even though these participants seem to have depressed basal stress response systems, they are in actuality more hyperresponsive to stressful challenges (Yehuda, 1997). The low basal levels may be a unique feature of posttraumatic stress disorder, which surprisingly (Pitman, 1997) differs from the chronic stress response first described by Seyle (1956/1976).

Trauma at an early age, particularly infant–mother separations, have a detrimental effect on emotional development (Bowby, 1973). Numerous animal studies have demonstrated that maternal separation or deprivation can have prolonged effects on behavior and physiology. Short repeated separations may actually be immunizing for later stress, whereas longer periods of maternal deprivation can increase later responses to stress (e.g., Levine, 1993; Meaney et al., 1993). Interestingly, studies throughout several decades demonstrate that maternal behavior can ameliorate the effects of early stress on later behavioral and physiological responses to stress (Levine, 1957, 1967; Liu et al., 1997; Van Oers, De Kloet, & Levine, 1997). Lack of this maternal behavior may sensitize the pups to stressors. Human studies suggest that child-rearing practices may contribute to the development of pathological anxiety (Rapee, 1997).

Other psychosocial events may also precipitate the development of pathological anxiety. The majority of social phobic persons are reported to recall a socially aversive event associated with the onset of their social phobia (Ost & Hugdahl, 1981; Townsley, 1992 and see in Mineka & Zinbarg, 1996). The fact that social phobias typically develop during adolescence and young adulthood suggests that there is a critical period for the development of social phobias (Ohman, 1986). Shyness may also interact with aversive episodes to facilitate the development of social phobias (Stemberger, Turner, Beidel, & Calhoun, 1995). Whether these phobic persons actually experienced traumatic social events or merely perceived normal ones as being traumatic is unclear. It may not be the life event per se that is important, but the perception of its being aversive that may contribute to the development of the disorder.

Conclusions about the number and type of life events as precipitating factors in panic disorders are equivocal. Some researchers suggest that panic disorder patients have had more stressful recent life events than normal participants (e.g., Faravelli & Pallanti, 1989). Other researchers found that panic disorder patients have had a greater number of these events (e.g., Manfredo et al., 1996; Rapee, Litwin, & Barlow, 1990; Roy-Byrne, Geraci, & Uhde, 1986) but report more stressors impacting personally on them (Roy-Byrne et al., 1986). Other researchers found that the number of events was not greater, but the panic patients retrospectively interpreted life events as more significant than a normal control group (Rapee et al., 1990). Thus, it does not seem that recent life events per se precipitate the develop-
Biological Underpinnings of Hyperexcitability

Biological stress responses, whether as a result of trauma, early stressful experience, or a genetic predisposition, may be important for the development of hyperexcitability. It is well-known that endocrine events during critical stages in development have long-term consequences for both brain organization and behavioral expression (Goy & McEwen, 1980). Recently, researchers found that infant monkeys reared by mothers experiencing unpredictable foraging conditions had higher corticotropin-releasing hormone in cerebrospinal fluid in adulthood than infant monkeys reared by mothers that had either a predictable overabundance or a scarcity of food (Coplan et al., 1996). The study showed that unpredictability in early life, and not just chronic hardship, led to persistently higher hormone levels in adulthood. Heightened levels of arousal and fear responses to strangers and novel situations found in shy human infants also persist at least into later childhood. These children may have exaggerated cortisol and autonomic physiological responses (Gunnar, Mangelsdorf, Larson, & Hertsgaard, 1989; Kagan et al., 1988; Schmidt et al., 1997). Indeed, excessively shy children display both exaggerated startle responses and high salivary cortisol levels (Schmidt et al., 1997).

Similarly, high levels of cortisol are linked to exaggerated fear responses in monkeys. For example, rhesus monkeys with high cortisol levels freeze for longer periods of time during fearful situations than monkeys with lower levels (Kalin, Selton, Rickman, & Davidson, 1998; Champoux, Coe, Shankberg, Kihn, & Soumi, 1989). Raising corticosterone levels with exogenous administration can also potentiate fear-induced freezing in rats (Figure 5; Coordimas, LeDoux, Gold, & Schulkin, 1994) and fowls (Jones et al., 1988). Adrenalectomy, on the other hand, decreases contextual fear conditioning in rats (Pugh, Fleshner, Fleshner, Tremblay, & Rudy, 1997).

Corticosterone levels during critical stages of development have profound effects on the organization of the brain and the expression of fear-related behaviors (Takahashi, 1994). Early life events, such as maternal deprivation, which increases corticosterone levels, have long-term consequences for both brain and behavior (e.g., Levine, 1993; Meany et al., 1993). For example, rats deprived of maternal closeness for 3 hr a day for a 2-week period as pups were found to have higher levels of corticotropic-releasing hormone mRNA expression in the hypothalamus and central nucleus of the amygdala as adults than rats separated only 15 min a day (Plotsky, unpublished observations; Plotsky & Meany, 1993). These maternally deprived rats were also more likely to develop helpless behavior in uncontrollable aversive contexts, suggesting that these rats were excessively stressed or fearful. Interestingly, their systemic levels of corticosterone as adults were not different than normal rats, but the central state of exaggerated fear induced by the early experience was long lasting.

Much work over the years done primarily by McGaugh (McGaugh et al., 1993; Roozendaal, Quirarte, & McGaugh, 1997), Izquierdo (Izquierdo et al., 1993), and Gold (1988) has shown that with various learning tasks, posttrial peripheral administration of epinephrine, glucocorticoids, and glucose can potentiate memory and consolidation and can increase the resistance to extinction of conditioned responses. Conversely, adrenergic antagonists interfere with the memory of the learned behavior (McGaugh et al., 1993). Because the potentiating and inhibiting properties of these manipulations are done subsequent to training, but well before the testing sessions, it has been hypothesized that they facilitate or interfere with memory consolidation processes (McGaugh et al., 1993). In human subjects, the noradrenergic beta-blocker propranolol was shown to impair the memory of an aversive story more than the memory of an emotionally neutral story, suggesting that noradrenergic activation preferentially enhances emotional experiences (Cahill,
Facilitation of Conditioned Freezing by Glucocorticoids

Facilitation of CRH-Enhanced Acoustic Startle by Glucocorticoids

Facilitation of CRH-Induced Seizures by Glucocorticoids


Prins, Weber, & McGaugh, 1994). These findings have led to the notion that the pathogenesis of posttraumatic stress disorder may be due to overstimulation of endogenous stress systems during traumatic events that potentiate overconsolidation of the memory of the trauma and thus lead to intrusive recall and emotional responses that are hallmarks of posttraumatic stress disorder (Pitman, 1989).

Perhaps elevated cortisol, epinephrine, and norepinephrine induce greater activation of amygdala through the memory-enhancing mechanisms similar to those just described and thereby increase the level of vigilance and the expectation of adversity (Schulkin et al., 1994). Lesions of the central nucleus of the amygdala have been shown to block the integration of behavioral, neurochemical, and neuroendocrine responses to a conditioned fear stimulus (L. E. Goldstein, Rasrussom, Bunney, & Roth, 1996). The amygdala plays an important role in central nervous system mediation of the potentiating effects of peripheral stress-responsive factors (McGaugh et al., 1993). Glucocorticoid receptor agonists and antagonists injected into basolateral amygdala modulate memory storage (Roozendaal & McGaugh, 1997). Injection of noradrenergic antagonists into the amygdala block the memory potentiating effects of peripheral administration of epinephrine and other compounds. Gamma-amino butyric acid and acetylcholine are also included with norepinephrine in a neuromodulator pathway in the amygdala that is important for the memory-enhancing effects of peripheral stress hormones (McGaugh et al., 1993).

Corticotropin-releasing hormone and corticotropin-releasing hormone mRNA expression in the central nucleus of the amygdala and the bed nucleus of the stria terminalis may also be positively affected by peripherally administered corticosterone while corticotropin-releasing hormone and its mRNA in the paraventricular nucleus of the hypothalamus are decreased (Makino, Gold, & Schulkin, 1994; Swanson & Simmons, 1989; Watts & Sanchez-Watts, 1995). Regulation of the corticotropin-releasing hormone receptor in the hypothalamus and amygdala and bed nucleus of the stria terminalis may also have different sensitivities to corticosterone (Makino et al., 1994, 1995). The corticotropin-releasing hormone plays a significant role in fear and pathologial anxiety in both extrahypothalamic and hypothalamic brain regions (Koob et al., 1993). Corticotropin-releasing hormone injected into the lateral ventricles increases freezing to fearful stimuli and potentiates acoustic startle in rats (Koob et al., 1993; Liang, Melia, Miserendino, et al., 1992). Anatomically specific injections of corticotropin-releasing hormone into the bed nucleus of the stria terminalis, but not in the amygdala, septum, or ventral hippocampus, potentiate startle (Lee & Davis, 1997a, 1997b). Conversely, intracerebroventricular administration of a corticotropin-releasing hormone antagonist reduces freezing and anxious behavior on several tests of fear and anxiety (Koob et al., 1993; Swiergiel, Takahashi, & Kalin, 1993) and attenuates fear-potentiated startle (Swerdlov, Britton, & Koob, 1989). The antagonist injected into the bed nucleus of the stria terminalis also blocks startle potentiated by the intracerebroventricularly administered corticotropin-releasing hormone (Lee & Davis, 1997b). The amygdala plays an important, but indirect, role in these effects of the corticotropin-releasing hormone on fear behavior (Liang, Melia, Campeau, et al., 1992; Swiergiel et al., 1993).

Corticosterone can also influence the effects of the corticotropin-releasing hormone on acoustic startle (Lee, Schulkin, & Davis, 1994; Figure 5). If low doses of the corticotropin-releasing hormone that do not affect startle by themselves are given in combination with corticosterone, the startle response is en-
hanced. Corticosterone can also act synergistically with corticotropin-releasing hormone to facilitate limbic seizures (Rosen, Pishevar, Weiss, Smith, Kling, Gold, & Schulkin, 1994; Figure 5). Experimentally induced hypercortisolemia may act synergistically with stress-related molecules, such as the corticotropin-releasing hormone, in brain areas related to fear to induce exaggerated fear responses and seizures.

**Sensitization Processes**

The ability of stress hormones and preexposure to psychosocial stressors in animals to precipitate greater fear and stress responses indicates that sensitization processes play a major role in turning normal fear responses into abnormal behavior (Marks & Tobena, 1990; R. M. Post, 1992). By definition sensitization implies that the threshold for activation of the system is lower following presentation of a stimulus. In other words, the system becomes hyperexcitable.

The role of sensitization in the development of pathological anxiety is not well understood or studied (Marks & Tobena, 1990). Theoretically, sensitization is an important factor in the etiology of hyperexcitability of the fear-circuit because experiencing unpredictable stressors may lead to some psychopathological disorders (R. M. Post, 1992). Experimental paradigms, in which inescapable footshock is delivered to rats, increase generalized anxious symptoms (Peterson et al., 1993) and facilitate fear conditioning (Servatius & Shors, 1994). Early experience with unpredictable stress during development may sensitize the fear circuits and may facilitate fearful responding later in life (Coplan et al., 1996; Rosenblum et al., 1994). Other paradigms suggest that the effects of a single stressful exposure can incubate and become greater over time, even when subsequent direct encounters with the aversive environment is prevented (Pynoos et al., 1997). The results of sensitization to stressors (i.e., hyperexcitability and pathological anxiety) become long lasting and difficult to treat (Marks & Tobena, 1990). Indelible fearful and anxious engrams are thus formed in the brain.

Sensitization may produce hyperexcitability by itself or in combination with various learning processes. Facilitation of fear conditioning and memory consolidation by glucocorticoids and epinephrine has already been discussed. Simple associative conditioning is unable to explain the development of pathological anxiety (e.g., Mineka & Zinbarg, 1996). Mineka and Zinbarg have made a strong case that simple conditioning mechanisms when viewed in a dynamic context may explain some of the etiology of anxiety disorders. Several factors, including one’s history of exposure to uncontrollable and unpredictable stressors, the nature of the stressors and conditioned stimuli (how conditionable they are), and one’s temperament, influence learning processes (Mineka & Zinbarg, 1996). These factors may sensitize neural fear circuits to associative conditioning processes and thus facilitate responses to threatening stimuli. For example, experience with uncontrollable or unpredictable stressors can increase subsequent fear conditioning (Peterson et al., 1993; Servatius & Shors, 1994). Fear conditioning is also easier with stimuli considered having an intrinsic potency for eliciting fear. Naive monkeys learn to be afraid of snakes by observing monkeys acting afraid of snakes (M. Cook, Mineka, Wolkenstein, & Laitsch, 1985). However, they do not become afraid of flowers by viewing other monkeys displaying fear of flowers (M. Cook & Mineka, 1990).

Sensitization can also enhance previously learned associations. For example, fear responses to a conditioned tone paired to a weak footshock can be strengthened or inflated by subsequent random exposure to a more intense footshock (Rescorla, 1974). The greater the time interval between the conditioning and the exposure to the higher intensity shock, the greater the effect of the intense shock (Henderson, 1985). It is as if the memory of the fearful event becomes more intense over time.

**Neurobiology of Sensitization**

What are the molecular mechanisms of sensitization that can turn the normal fear response into pathological anxiety? Although these are unclear, it may be heuristically useful to sketch a neurobiological framework that may facilitate thinking about ways sensitization can affect the brain (Figure 6).

Most of researchers’ knowledge about the long-term molecular effects of repetitive activation of mammalian brain comes from two models: long-term potentiation (LTP) and kindling (Cain, 1992; Collingridge & Bliss, 1995). Both use repetitive electrical stimulation of discrete areas of the brain or specific pathways to induce a long-lasting hyperexcitability. LTP paradigms typically induce hyperexcitability in one session and use an increased response to single electrical pulses as a measure of hyperexcitability. Although LTP is used as a model for associative learning (e.g., Laroche, Doyere, Redini-Del Negro, & Buret, 1995; McKernan & Shinnack-Gallagher, 1997; Rogan et al., 1997), it may also model nonassociative sensitization (Shors & Matzel, in press). Although some neurobehavioral models of pathological anxiety stress the associative nature of LTP and its similarity to classical conditioning (e.g., LeDoux, 1996), we are emphasizing nonassociative mechanisms of LTP and kindling.

Kindling models nonassociative sensitization and refers to the slow develop of increased seizure activity following repeated stimulation given once daily. Kindling produces a decrease in threshold and engages the same neural mechanisms in the first few stimulations as LTP does, but it then recruits additional mechanisms as kindling further proceeds (Sutula & Steward, 1987). Thus, both LTP and the early stages of kindling may induce similar molecular changes that are important for hyperexcitability. Induction of hyperexcitability from repeated exposure to activation may induce a cascade of genetic events that includes the expression of immediate-early genes, like Fos, that may activate other genes, such as peptides and structural proteins that render the tissue more sensitive to subsequent stimulation (R. M. Post, 1992).

Glutamate receptors, particularly the N-methyl-D-aspartate type, are important for the development of LTP and hyperexcitability in the hippocampus (Collingridge & Bliss, 1995; McNamara, 1993) and the amygdala (Maren, 1996). Footshock-induced sensitization and facilitation of a fear-conditioned response require N-methyl-D-aspartate activation (Shors & Servatius, 1995). Glutamate, mediated through activation of various second messengers (e.g., calcium and cyclic adenosine monophosphate [AMP]), is also important for inducing a cascade of genetic transcriptional events, such as the induction of
immediate-early genes (e.g., Fos, nerve growth factor induced factor A [NGFI-A], cAMP responsive element binding protein [CREB]; Labiner et al., 1993; Mayford, Abel, & Kandel, 1995). Kindling can also induce the expression of a number of neuro-peptides, possibly through mechanisms involving the immediate-early genes (Rosen, Abramowitz, & Post, 1993; Rosen, Cain, Weiss, & Post, 1992). Finally, structural changes also occur in synapses following LTP (e.g., Chang & Greenough, 1984; Desmond & Levy, 1986) and kindling (Geinisman, Morrell, & deToledo-Morrell, 1988; Sutula, Xiao-Xian, Cavazos, & Scott, 1988).

Glutamate receptors are also important for fear. Injections of N-methyl-d-aspartate antagonists directly into the amygdala block fear conditioning (Fanselow & Kim, 1994; Miserendino et al., 1990), whereas non-N-methyl-d-aspartate antagonists can block the expression of previously learned fear (M. Kim, Campeau, Falls, & Davis, 1993). Immediate-early genes, such as Fos, which have very low basal levels, are transiently expressed in the amygdala and related limbic structures following stress and conditioned and unconditioned fear (Beck & Fibiger, 1995; Campeau, Hayward, Hope, Rosen, & Davis, 1991; Pezzone, Lee, Hoffman, & Rabin, 1992; M. A. Smith, Banerjee, Gold, & Glowa, 1992). Another immediate-early gene, NGFI-A, was also found to be significantly increased in the lateral nucleus of the amygdala in rats that displayed conditioned freezing following footshocks, whereas it was not in rats that were shocked but did not freeze (Rosen, Fanselow, Young, Sitcoske, & Maren, 1998). Kindling also induces the expression of immediate-early genes in the amygdala and related limbic structures (Clark, Post, Weiss, & Nakajima, 1991; Shin, McNamara, Morgan, Curran, & Cohen, 1990).

These immediate-early genes act as transcriptional factors to induce transcription of other genes such as neuropeptides that affect behavior and modulate neurotransmission and other processes in the brain. A number of neuropeptides and their mRNAs, which also are not normally expressed in fear-related limbic regions or have low levels in these areas, are transiently expressed following kindling (Gall, 1993; Rosen, Cain, et al., 1992; Rosen, Kim, & Post, 1994; Zhang et al., 1996; Figure 7). These include peptides that are thought to play roles in pathological anxiety and affect (e.g., corticotropin-releasing hormone, cholecystokinin, thyrotropin-releasing hormone, and neuropeptide Y; Bradwejn & Koszycki, 1994; Heilig, Koob, & Britton, 1994; Marangell et al., 1997). We have already written extensively about corticotropin-releasing hormone. Neuropeptide Y is thought to counteract the actions of corticotropin-releasing hormone, possibly in the amygdala (Heilig et al., 1994), and may therefore have anti-anxiety properties. Thyrotropin-releasing hormone injections into the amygdala produce gastric ulcer, suggesting that it is a stress-inducing agent (Henke, 1992). Interestingly, a corticotropin release inhibiting factor has been found to be encoded within the gene for thyrotropin-releasing hormone (Redei, Hilderbrand, & Aird, 1995). Thus, when the gene for thyrotropin-releasing hormone is expressed it would also express a factor that may antagonize the actions of corticotropin-releasing hormone. Finally, cholecystokinin is a known
Panic-inducing agent in humans (Bradwejn & Koszycki, 1994) and enhances fear-potentiated startle in rats (Frankland, Josselyn, Bradwejn, Vaccarino, & Yeomans, 1997). Speculatively, through sensitization, levels of these peptides would be increased and cause alterations in hyperexcitability in fear circuits and, thus, pathological fear responses.

Changes in the expression of other molecules (e.g., growth and neurotrophin factors) that are important for growth and maintenance of neurons (Thoenen, 1995) may also be affected by fear, stress, and sensitization. Both inescapable stress (restraint) and kindling alter the expression of mRNAs for a number of growth factors, including nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3 (M. A. Smith, Makino, Kvetnansky, & Post, 1995). These factors may be important for neuronal death that may be caused by stress (Sapolsky, 1992).

Probably the best research on molecular aspects of sensitization is done in the sea slug, aplysia, in which single cells can be stimulated and analyzed. Sensitization involves the repeated release of serotonin, increased levels of second messengers, and activation and suppression of gene transcription (Abel, Martin, Bartsch, & Kandel, 1998). Serotonin can also modulate fear in mammals (e.g., Graeff, Guimaraes, DeAndrade, & Deakin, 1996; Inoue, Tsuchiya, & Koyama, 1996), and medications that block serotonin reuptake are effective antipanic and agoraphobic agents (e.g., Klein, 1996).

Although the role and induction of these and other types of molecular events are just beginning to be explored in fear and pathological anxiety, a conceptual view is that molecules that are not normally expressed in the neuronal fear circuits are activated during high levels of stress and activation and, therefore, change the excitability characteristics of the circuit. Other molecules that are functionally inhibitory may be diminished following stress. Stress-related hormones that facilitate these processes may play a role in enhancing the activation of cascades of molecular events that may lead to changes in brain that underlie long-lasting hyperexcitability (i.e., Schulkin et al., 1994).

**Experimental Animal Paradigms to Study Hyperexcitability in Fear and Pathological Anxiety**

Although research on human pathological anxiety suggests that hyperexcitability and hypervigilance are important underlying mechanisms of pathological anxiety (Barlow, 1988; Eysenck, 1994),...
there are very few experimental models to study the neuro-behavioral processes that distinguish fear from pathological anxiety (however, see Davis et al., 1997). In pharmacological studies researchers examine the effects of anxiolytics on changes of normal behavioral adaptation in fear- and anxiety-provoking situations. Although these have been used successfully for years as behavioral assays for anxiolytic drug screens, they do not distinguish between fear and pathological anxiety (File, 1992).

This problem may be attacked from several approaches. Experiments in which animals are exposed to inescapable stress can facilitate fear and fear conditioning (Mineka, Cook, & Miller, 1984; Peterson et al., 1993; Servatius & Shors, 1994). Social defeat stress subsequently facilitates fear conditioning (e.g., Meerlo et al., 1997; Williams & Scott, 1989). Neurodevelopmental approaches in which animals are stressed during development may be particularly germane to early brain changes and the later expression of exaggerated fear in adulthood. Consequences of these manipulations may impinge on the amygdala-centered fear circuit and alter its level of excitability.

We have taken the approach to produce hyperexcitability in the neural circuits subserving fear by directly stimulating the circuit and then independently measuring the consequences on conditioned fear. It is important to emphasize that the stimulation method is not our model of pathological anxiety but is only a way of inducing a sensitized fear circuit. Pathological anxiety is modeled by exaggerated fear responses found in animals with an hyperexcitable fear circuit. In our initial studies we have chosen to induce sensitization in the fear circuit by delivering electrical stimulation to the amygdala that evokes localized electrical seizure activity (partial kindling stimulation), but with no behavioral manifestation of seizures. This stimulation will produce a lowered threshold for subsequent activation (Racine, 1972).

Experimentally, kindling increases sensitivity of the brain after repeated stimulation and eventually produces generalized seizures (Goddard, McIntyre, & Leech, 1969; Racine, 1972). If stimulation is given only a few times (partial kindling), the tissue around the stimulation site will become more excitable, but generalized seizures will not develop. The hyperexcitability produced is long lasting or permanent (Dennison, Teskey, & Cain, 1995; Racine, 1972), and many molecular consequences of kindling have been revealed (McNamara, 1993). The molecular changes found with kindling may lead researchers to some of the biochemical events that are important for the development of hyperexcitability in fear circuits. Stimulation can be localized to particular regions of the brain, and it has an advantage over behaviorally induced stress when one wants to look at the neuro-anatomy of hyperexcitability. Stress induced by behavioral means (e.g., inescapable footshock) activates many regions of the brain, some that may mediate fear and others that do not. Activation of a brain region by direct stimulation is more circumscribed and confined to brain structures synaptically linked to the area stimulated. Whether kindling is directly comparable to sensitization after exposure to psychosocial stress is unclear at present. Other stimulation methods that produce hyperexcitability but not seizure activity (e.g., LTP) can also be utilized. Results from studies of localized stimulation of brain and those using psychogenic stressors (e.g., inescapable shock and repeated social defeat) should complement each other to provide a better understanding of the neurobiology of pathological anxiety. In addition, kindling can be used as a theoretical framework to understand the etiology of some psychological disorders in which repeated episodes of hyperexcitability increase the likelihood that subsequent pathological episodes will occur (Pitman, 1989, 1997; Pitman et al., 1993; R. M. Post, 1992).

### Exaggerated Fear-Potentiated Startle Produced by Partial Amygdala Kindling

Initial experiments demonstrated that partial kindling of the amygdala (only two stimulations), but not partial hippocampus kindling, can produce rats that have exaggerated fear-potentiated startle when using a light as a conditioned fear stimulus (Figure 8; Rosen, Hamerman, Sitcoske, Glowa, & Schulkin, 1996). Rats were initially presented with acoustic startle stimuli and were assigned to groups that had identical startle amplitudes. Importantly, the rats were then conditioned to be fearful of a light 1 day prior to the partial amygdala kindling stimulation but were tested for fear conditioning 1 day following the kindling. In other words, the kindling did not enhance the fear conditioning per se but increased the responsivity of the circuits responsible for the expression of fear-potentiated startle. In addition, baseline startle (noise-alone trials) was not enhanced, suggesting that the rats were not merely more jumpy or responsive but were hyperresponsive to the startle stimuli only in the presence of the fear-conditioned stimulus. Other researchers also found that acoustic startle without a fear stimulus is not enhanced following amygdala kindling (Ebert & Koch, 1996), indicating that the brain stem acoustic startle circuit (Davis et al., 1982) is not directly sensitized by the kindling and that sensitization of the amygdala may produce an attentional bias toward threatening stimuli similar to that found in general anxiety disorder patients (Eysenck, 1992; Matthews & MacLeod, 1994).

Why hippocampal kindling did not produce exaggerated fear-potentiated startle is probably because the hippocampus does not seem to be part of the fear circuit for cue-specific fear conditioning, but it is part of the circuit for fear conditioning in which contextual cues are used (J. J. Kim & Fanselow, 1992; Phillips & LeDoux, 1992). This neuroanatomical interpretation was further supported by using the expression of c-fos mRNA as a marker for neuronal activation (Rosen et al., 1996). c-fos mRNA expression following partial amygdala kindling was found to be detectable in limbic cortices known to be important for fear-potentiated startle (e.g., amygdala and perirhinal cortex); whereas hippocampus kindling, which had no effect on fear-potentiated startle, induced c-fos mRNA expression confined to the dentate gyrus and cornus ammonis of the hippocampus (Figure 9).

Other researchers have also linked kindling of the amygdala to fear (Adamec, 1997; Depaulis, Hefler, Deransart, & Marescaux, 1997). Adamec (1978) demonstrated that partial amygdala kindling renders aggressive cats less aggressive but more defensively fearful. Full amygdala kindling, in which generalized seizures are induced, also seems to increase fear- and anxiety-like responses in rats as measured on the elevated plus-maze (Adamec, 1990; Adamec & Morgan, 1994; Nieminen et al., 1992). Others have also found alterations in emotionality in animals after amygdala kindling (Boast & McIntyre, 1977; Helfer, Deransart, Marescaux, & Depaulis, 1996; McIntyre & Molino, 1972). In humans, fear is the most prominent affect after temporal lobe epileptic discharges (Gloor, 1978). Interest-
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subserving fear that may lead to pathological anxiety. We have suggested that hyperexcitability in fear circuits, particularly in the amygdala and extended amygdala, may not only produce exaggerated fear behavior but also states of hypervigilance. This would include exaggerated conditioned and some innate types of fear, but, perhaps, not all states of fear (Gonzalez, Andrews, & File, 1996; Kagan & Schulkin, 1995; Treit, Pesold, & Rotzinger, 1993). The same circuitry that mediates normal attention, perception, and behavior to detect and respond to danger or at times of uncertainty (Gallagher & Holland, 1994; Schulkin et al., 1994) would also mediate these processes during pathological conditions of hypervigilance. With overstimulation of the fear circuits, thresholds for activation are lowered—fearful behavior and worry are accentuated. The sensitized fear circuits would produce an emotive bias (Pitman et al., 1993). In this context

Figure 8. Exaggerated fear-potentiated startle as a result of partial amygdala kindling. (Top) Rats were conditioned to be fearful of a light (light-footshock pairing). Rats received two amygdala kindling stimulation or sham stimulation over the next 2 days. Fear-potentiated startle was tested 24 hr after partial amygdala kindling was significantly increased compared with sham-kindled rats (*p < .03). There were no differences between the groups when baseline startle was elicited in the absence of the fear-conditioned stimulus (noise alone). Differences between the groups were found only when fear was induced (i.e., acoustic startle stimulus was presented while the fear-conditioned stimulus was on [light noise]). (Bottom) Exaggeration of fear-potentiated startle was not produced by partial kindling of the hippocampus. Although both groups displayed fear-potentiated startle, the hippocampus-kindled group was no different than the sham-kindled group. Error bars represent standard error of the mean. From “Hyperexcitability: Exaggerated Fear-Potentiated Startle Produced by Partial Amygdala Kindling,” by R. B. Rosen, E. Hamerman, M. Sitcoske, J. R. Glowa, and J. Schulkin, 1996, Behavioral Neuroscience, 110, p. 46. Copyright 1996 by the American Psychological Association.

Figure 9. Neuronal activation by unilateral kindling stimulation in the left amygdala (top) and left hippocampus (bottom) as visualized by c-fos mRNA expression 30 min after kindling stimulation. Because partial amygdala kindling produced exaggerated fear-potentiated startle while partial hippocampus kindling did not, hyperexcitability in fear circuit structures (AMY and PC) activated by the amygdala stimulation were most likely responsible for the exaggerated fear response. AMY = amygdala; PC = perirhinal cortex; DG = dentate gyrus. From “Hyperexcitability: Exaggerated Fear-Potentiated Startle Produced by Partial Amygdala Kindling,” by R. B. Rosen, E. Hamerman, M. Sitcoske, J. R. Glowa, and J. Schulkin, 1996, Behavioral Neuroscience, 110, p. 47. Copyright 1996 by the American Psychological Association.

Figure 8.

Figure 9.

Conclusions: Fear Circuits, Hyperexcitability, and Pathological Anxiety

We have presented both a theoretical framework and an experimental paradigm to study hyperexcitability in neural circuits...
individuals with hyperexcitable fear circuits are more likely to freeze, withdraw, and interpret their world as dangerous and fearful.

Hyperexcitability in fear circuits may be a common core abnormality in all anxiety disorders. Exaggerated responses to specific cues, such as selective interoceptive cues in panic disorders or external cues in specific phobias, may develop from associative conditioning with sensitized, hyperexcitable fear circuits. Involvement of additional neuroanatomical circuits, different genetic vulnerabilities, and the influence of various social and psychological factors may lead to one anxiety disorder or another.

Fear-related behaviors, particularly startle, are used to study fear in normal and anxiety disorders patients. The blink startle response increases in amplitude during the presentation of aversive pictures or in anticipation of an aversive event (Grillon et al., 1991; Lang, 1995; Lang et al., 1990). Patients with posttraumatic stress or panic disorders, display exaggerated fear-potentiated startle responses (Grillon et al., 1994; C. A. Morgan et al., 1995). Shy, fearful, and inhibited young children with high levels of cortisol also have high levels of startle (Schmidt et al., 1997). Interestingly, in many of these studies, the startle response is exaggerated to the anticipation of threatening stimuli but not to baseline startle stimuli. This parallels the effects of amygdala kindling on fear-potentiated startle in rats (Figure 8; Rosen et al., 1996) and suggests that pathological anxiety is not simply an increase in responsivity to all stimuli but is a state of hyperexcitability or lowered threshold specifically for threatening stimuli (Eysenck, 1992).

Our hypothesis suggests that the amygdala would be hyperactive in anxiety disorder patients in the midst of an anxious episode but is not necessarily hyperactive during basal conditions. This would be most evident in disorders that oscillate or are precipitated by particular stimuli or situations. Several recent brain imaging studies (Breiter et al., 1996; Ketter et al., 1996; Rauch et al., 1996) demonstrated that the amygdala is activated during precipitated fear states in normal participants and during posttraumatic stress and obsessive-compulsive episodes in anxiety disorder patients. The increased blood flow in these regions was found only during the precipitated anxious episodes. These studies suggest that the amygdala is normally not in a hyperactivated state but is hyperexcitable when activated by fearful stimuli. This parallels the stress hormone response data in posttraumatic stress disorder patients discussed earlier (Yehuda, 1997).

Conversely, chronic increased activity in the amygdala may be a trait marker for unipolar depression (Drevets et al., 1992). It will be interesting to see whether patients with more chronic and nonstimulus-specific anxious disorders (e.g., generalized anxiety) will have increased and more sustained activity in the amygdala and bed nucleus of the stria terminalis, suggesting a chronic hyperexcitable and hyperactive state.

Our hypothesis and paradigm suggest that direct activation of the amygdala, extended amygdala, or both, by kindling or LTP stimulation should produce similar increases in neuronal activity during fear that are found in anxiety disorder patients. In animals, this can be measured by immediate-early gene expression during the testing and measuring of fear. Furthermore, experimentally induced hyperexcitability should facilitate the expression of neuromolecules, such as neuropeptides, during fear states and should allow inferences to be made about the molecular underpinnings of pathological anxiety.

Performance on fear-related vigilance tasks should also be better in animals after kindling or LTP-like stimulation. Kindled animals should also display broader generalization gradients to fear-inducing stimuli. In addition, other manipulations that increase sensitization in the amygdala, such as glucocorticoid and epinephrine administration, should produce similar enhancing effects on fear-related vigilance tasks (McGaugh et al., 1993). On the other hand, manipulations that inhibit or reverse kindling should produce diminished fear responses. A recently reported amygdala stimulation procedure that "quenches" kindled seizures (Weiss et al., 1995) may be an interesting model to study biological changes that decrease fear.

Our hypothesis also suggests that psychosocial stressors will sensitize the fear circuit. Researchers using inescapable shock, social defeat, and early maternal separation should activate fear circuits (e.g., Matsuda et al., 1996). When animals subjected to these stressors are subsequently put in new fear-inducing situations, they should have more activity in fear circuits than animals that are challenged but that did not have the earlier stressful experiences. As a corollary, animals that receive stress-reducing treatments should have reduced expressions of fear and less amygdala activity during a later aversive challenge. Previous experience of control over aversive stimuli should also decrease amygdala activity in fearful situations. Psychosocial intervention and exposure therapies should produce less sensitive fear circuits.

The idea of a hyperexcitable amygdala and extended amygdala as a biological substrate for pathological anxiety leads to interesting notions about accessibility to fear circuits and the organization, development, and formation of connectivity in the fear circuits with pathological fear and anxiety. Through experience, or experimentally through kindling, the amygdala becomes hyperexcitable, suggesting that the synaptic connections in fear circuits have lowered thresholds for activation and thus the connectivity within these circuits is stronger. With repeated strong activation, these hyperexcitable connections may become relatively permanent.

This occurs with kindling; once rats are kindled they can be left alone for months and then, once stimulated again, they will display seizures at the same strength they had when last stimulated months ago. In addition, with continued repeated stimulation, kindled seizures may become spontaneous and independent of the triggering stimulation (Pinel & Rovner, 1978). In an analogous fashion, repetitive activation of the amygdala by repeated episodes of excessive fear may produce chronic hyperexcitability in the amygdala that eventually becomes functionally autonomous. Fear-related responses may eventually become independent of a triggering stimulus. Thus, anxious feelings and behavior, and the associated hypervigilance, develop lives of their own. The mechanisms responsible for hypervigilance and the attentional bias toward interpretation of the environment as threatening are inappropriately regulated. Although there may be an awareness of the anxious state, there is a feeling of a loss of control.

This type of inaccessibility can be seen in anxiety disorder patients. Patients often claim that the worry and anxiousness always seem to be there, or they may appear on their own, and make them feel uncontrollable. The chronic state of hyperexcitability of excitatory mechanisms within fear circuits is not dampened properly by normal inhibitory processes. This constant uncontrollable
worry would expend large amounts of energy, with costly psychological and biological consequences (e.g., McEwen & Mendelson, 1993). Finding out what these excitatory and inhibitory mechanisms for developing and sustaining hyperexcitability are, and finding out how they change the characteristics of normal, adaptive fear-related behaviors into exaggerated responses, have promise for developing a better understanding of the etiology and pathology of clinical anxiety disorders.

References


amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction (pp. 401–430). New York: Wiley.


LeDoux, J.E., Iwata, J., Cicchetti, E, & Reis, D. J. (1988). Different
Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman,
Levine, S. (1967). Maternal and environmental influences on adrenal
Levine, S. (1957). Infantile experience and resistance to physiological
Topographic organization of neurons in the acoustic thalamus that project
to the amygdala. Journal of Neuroscience, 10, 1043–1054.
projections of the central amygdaloid nucleus mediate autonomic and
behavioral correlates of conditioned fear. Journal of Neuroscience, 8,
17–29.
projections of the medial geniculate nucleus mediate emotional re-
sponses conditioned to acoustic stimuli. Journal of Neuroscience, 4,
683–698.
dermatopituitary-adrenal responses to stress. Behavioral Neuro-
and the paraventricular nucleus of the hypothalamus.
Matsuda, S., Peng, H., Yoshimura, H., Wen, T.-C., Fukuda, T., & Saka-
Matthews, A., & MacLeod, C. (1994). Cognitive approaches to emotion
of conditioned fear. In F. R. Brush (Ed.), Aversion conditioning and
sively motivated behavior: Some controversial issues. In M. R. Denny
(Ed.), Fear, avoidance, and phobias (pp. 135–164). Hillsdale, NJ:
Erlbaum.
chemistry and morphology of the brain: Counterregulation versus damage.
In L. Goldberger & S. Bretzinit (Eds.), Handbook of stress: Theoretical
McGaugh, J. L., Intrione-Collison, I. B., Cahill, L. F., Castellano, C.,
Dalmaz, C., Parent, M. B., & Williams, C. L. (1993). Neuromodula-
tory systems and memory storage: Role of the amygdala. Behavioral
Brain Research, 58, 81–90.


Rosen, J. B., & Davis, M. (1988b). Temporal characteristics of enhance-


Dose–response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. *Archives of General Psychiatry, 52,* 583–593.


Appendix

Common Features of Fear in Rats and Anxiety in Humans

<table>
<thead>
<tr>
<th>Animal</th>
<th>Fear/anxiety</th>
<th>Perceptual</th>
<th>Defensive</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Increased startle, freezing, heart rate changes, hypoalgesia, and defecation and urination</td>
<td>Vigilance</td>
<td>Fighting, biting, escape (flight or jumping), and avoidance (passive, active, and defensive burying)</td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>Exaggerated startle reflex, worry (apprehensive expectation), heart rate changes, feeling numb, and diarrhea and urinary frequency</td>
<td>Hypervigilance</td>
<td>Irritability, outburst of anger, and persistent avoidance</td>
<td>Difficulty sleeping and sleep disturbances</td>
</tr>
</tbody>
</table>

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