The Neurobiological Basis of Anxiety and Fear: Circuits, Mechanisms, and Neurochemical Interactions (Part I)

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There have been tremendous advances in our knowledge of the neurobiological basis of human anxiety and fear. This review seeks to highlight how specific neuronal circuits, neural mechanisms, and neuromodulators may play a critical role in anxiety and fear states. It focuses on several brain structures, including the amygdala, locus coeruleus, hippocampus, and various cortical regions and the functional interactions among brain noradrenergic (NE), corticotropin releasing hormone (CRH), and the hypothalamic pituitary adrenal axis (HPA). Particular attention is directed toward results that can lead to a better understanding of the constellation of the symptoms associated with two of the more severe anxiety disorders, panic disorder and posttraumatic stress disorder (PTSD), the persistence of traumatic memories, and the effects of stress, particularly early life adverse experiences, on brain function and clinical outcome. NEUROSCIENTIST 4: 35–44, 1998

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Evidence accumulated from preclinical studies provides a basis for proposing neural circuits underlying anxiety and fear (1). For a proposed circuit to be relevant to human anxiety, there needs to be sufficient afferent sensory input to permit assessment of the fear- or anxiety-producing nature of external or internal stimuli. The neuronal interactions among the brain structures must be capable of incorporating a person's prior experience (memory) into the cognitive appraisal of stimuli so as to attach affective significance to specific stimuli and mobilize adaptive behavioral responses. In addition, the efferent projections from the brain structures should be capable of mediating neuroendocrine, autonomic, and skeletal motor responses to threat that facilitate survival, and they should account for the pathological reactions that result in anxiety-related signs and symptoms.

The exteroceptive sensory systems of the brain (auditory, visual, somatosensory) form an important afferent arm in the circuit through relay channels that convey directly, or through multisynaptic pathways, information relevant to the experience of fear or anxiety. The sensory information contained in a fear- or anxiety-inducing stimulus is transmitted from peripheral receptor cells to the dorsal thalamus. An exception is the olfactory system, which does not relay information through the thalamus, and whose principal targets in the brain are the amygdala and entorhinal cortex (2). Visceral afferent pathways alter the function of the locus coeruleus (LC) and the amygdala, either through direct connections or via the nucleus paragigantocellularis (PGI) and the nucleus tractus solitarius (3–5).

The thalamus relays sensory information to primary sensory receptive areas of the cortex, which, in turn, project to adjacent unimodal and polymodal cortical association areas (6–8). The cortical association areas of visual, auditory, and somatosensory systems send projections to other brain structures, including the amygdala, entorhinal cortex, orbitofrontal cortex, and cingulate gyrus (9–11). The hippocampus receives convergent, integrated inputs from all sensory systems by way of projections from entorhinal cortex (12).

Sensory information that elicits of fear- and anxiety-inducing stimuli is first processed in the sensory cortex prior to transfer to subcortical structures, which are more involved in affective, behavioral, and somatic responses. The amygdala also receives sensory information directly from thalamic nuclei, such as the medial geniculate and thalamic visual areas. These data support a pivotal role for the amygdala in the transmission and interpretation of fear- and anxiety-inducing sensory information because it receives afferents from thalamic and cortical exteroceptive systems, as well as subcortical visceral afferent pathways. The neuronal interactions between the amygdala and cortical regions, such as the orbitofrontal

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cortex, provide a framework for initiation of coping behaviors based upon the nature of the threat and prior experience.

The efferent pathways of the anxiety-fear circuit mediate autonomic, neuroendocrine, and skeletal-motor responses. The structures involved in these responses include the amygdala, bed nucleus of the stria terminalis (BNST), LC, hypothalamus, periaqueductal gray, and striatum. Each of these structures has been strongly implicated in anxiety- and fear-related behaviors.

Many of the autonomic changes produced by anxiety- and fear-inducing stimuli are produced by the sympathetic and parasympathetic neural systems. Stimulation of the lateral hypothalamus results in sympathetic system activation producing increases in blood pressure and heart rate, sweating, piloerection, and pupil dilatation. Activation of the paraventricular nucleus (PVN) of the hypothalamus promotes the release of a variety of hormones and peptides. The sympathetic activation and hormonal release associated with anxiety and fear is probably mediated, in part, by stimulation of the hypothalamus via projections from the amygdala and LC (13). The PGI also plays an important role in regulation of sympathetic function and may account for the parallel activation of the peripheral sympathetic system and the LC.

The vagus and splanchnic nerves are major projections of the parasympathetic nervous system. Afferents to the vagus include the lateral hypothalamus, PVN, LC, and the amygdala. There are afferent connections to the splanchnic nerves from LC (14, 15). Recent evidence suggests that the connections between Barrington's nucleus and LC may have an important role in the coregulation of pelvic visceral function and forebrain activity (Valentino R, unpublished presentation, 35th Annual Meeting American College of Neuropsychopharmacology, December 1996, San Juan, Puerto Rico). This innervation of the parasympathetic nervous system may relate to visceral symptoms commonly associated with anxiety, such as gastrointestinal and genitourinary disturbances (16).

The regulatory control of skeletal muscle by the brain in response to emotions is complex. Subtle movements involving a few muscle groups (facial muscles), as well as fully integrated responses requiring the entire musculoskeletal system for fight or flight, may be required. Adaptive mobilization of the skeletal motor system to respond to threat probably involves pathways that project between the cortical association areas and motor cortex, cortical association areas and the striatum, and the amygdala and striatum.

The amygdala has strong projections to most areas of the striatum, including the nucleus accumbens, olfactory tubercle, and parts of the caudate and putamen. The portion of the striatum that is innervated by the amygdala also receives efferents from the orbitofrontal cortex and the ventral tegmental area. The amygdalocortical and amygdalostriatal projections are topographically organized and are organized in register. Individual areas of the amygdala and, in some cases, individual amygdaloid neurons, can integrate information from the corticostriatopallidal systems. The dense innervation of the striatum and prefrontal cortex by the amygdala suggests that the amygdala can powerfully regulate both of these systems. These interactions between the amygdala and the extrapyramidal motor system may be important for generating motor responses to threatening stimuli, especially those related to prior adverse experiences (17, 18).

Memories and previously learned behaviors are critical influences on the responses to anxiety- and fear-inducing stimuli via such neural mechanisms as fear conditioning, extinction, and sensitization (see below). Although within the medial temporal lobe memory system, emotional responsiveness (amygdala) and memory (hippocampus) may be separately organized, there is considerable interaction between storage and recall of memory and affect. This is exemplified by the critical role of the amygdala in conditioned fear acquisition, sensitization, extinction, and the attachment of affective significance to neutral stimuli.

The hippocampus and amygdala are sites of convergent reciprocal projections from widespread unimodal and polymodal cortical association areas. It is probably through these interactions, as well as cortical cortical connections, that memories stored in the cortex, which are continually being reinforced by ongoing experience, are intensified and develop greater coherence (19).

The hippocampal memory system is essential to short-term memory. However, it has been suggested that long-term memory may be organized such that, as time passes, with subsequent additional retrieval opportunities and the acquisition of related material, the role of the hippocampus diminishes until it may no longer be necessary for memory. According to this view, long-term memory may reside in the same areas of cortex where the initial sensory impressions take place (20). The shift in memory storage to the cortex may represent a shift from conscious representational memory to unconscious memory processes that indirectly affect behavior.

Therefore, once a fear or anxiety-inducing sensory stimulus is relayed through the thalamus into neural circuits involving the cortex, hippocampus, and the amygdala, relevant memory traces of posttraumatic experiences are stimulated. It is likely that the potency of the cognitive and somatic responses to the stimulus will be strongly correlated with prior experiences because of the strengthening of neural connections within the circuit. These functional neuroanatomical relationships can explain how a single sensory stimulus, such as a sight or sound, can elicit a specific memory. If the sight or sound was associated with a particular traumatic event, a cascade of anxiety- and fear-related symptoms may ensue, probably mediated by the efferent arm of the proposed circuit (Figs. 1 and 2).

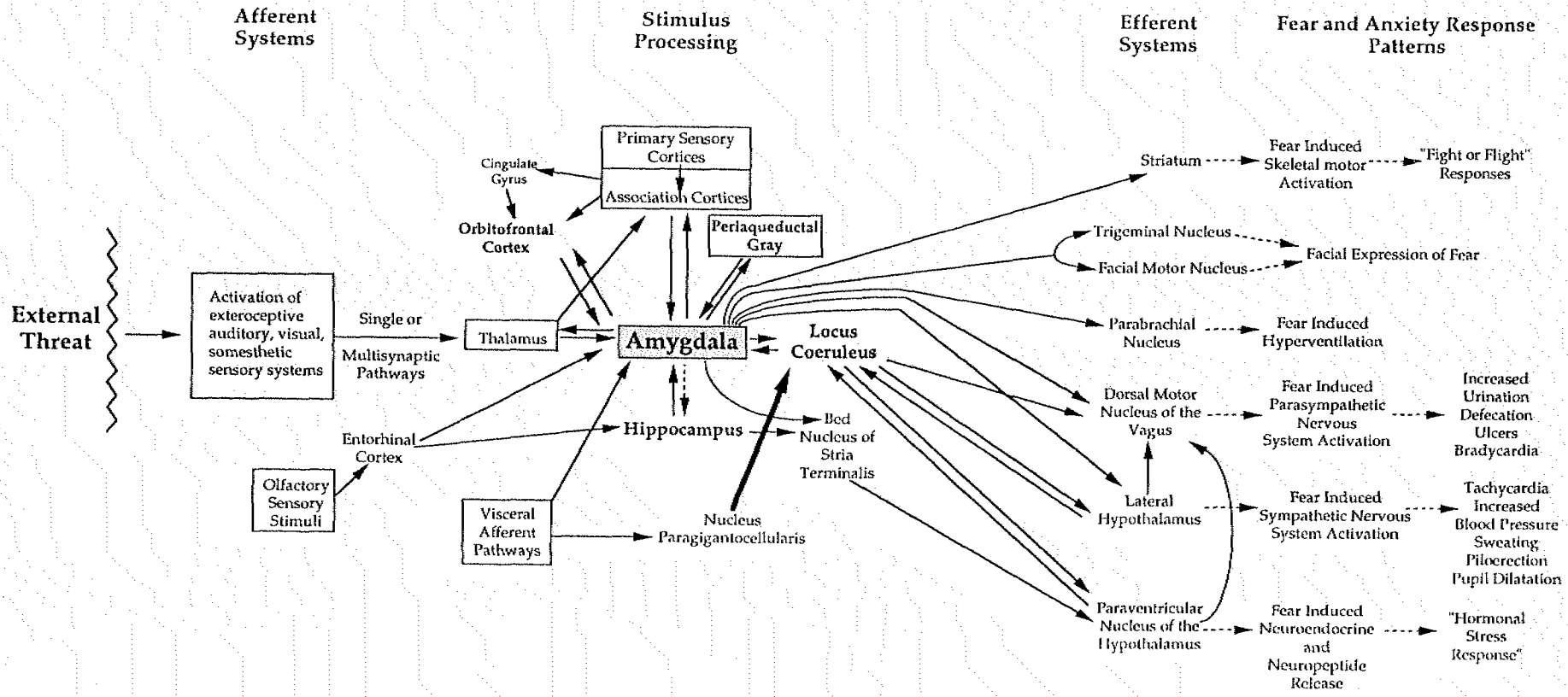

Fig. 1. This figure depicts, in schematic fashion, some of the neural circuits involved in the afferent input of fear- and anxiety-inducing stimuli, the processing of the stimuli utilizing past experience, and the efferent systems that result in the response patterns characteristic of fear and anxiety states. As reviewed in the text, the amygdala appears to play a pivotal role in the assessment of and response to danger. The locus coeruleus is a critical component of the efferent response systems. The subdivisions of the periaqueductal gray have been hypothesized via amygdaloid pathways to coordinate specific response patterns on the basis of the nature of threatening stimuli. The orbitofrontal cortex, also through reciprocal interactions with the amygdala, is involved in determining the significance of fear-producing sensory events, the choice and implementation of behaviors important for survival, and the extinction of conditioned fear responses. The hippocampus is important in traumatic memory consolidation and, with the entorhinal cortex, contextual fear conditioned behaviors. Projections from the hippocampus to the bed nucleus of the stria terminalis (BNST) and projections from the BNST to hypothalamic and brainstem sites may be involved in the expression of contextual fear conditioning. The hypothalamus is a critical site for integration of autonomic and neuroendocrine responses to threat. Modified and reproduced with permission from (1).

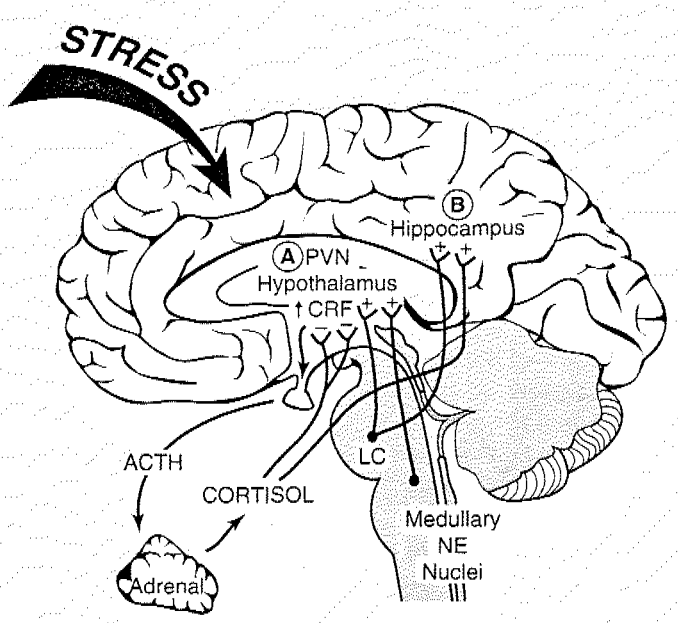

Fig. 2. The functional interactions among cortisol, CRH, and noradrenergic systems represent remarkable adaptive mechanisms. Stressful and fear inducing stimuli increase CRH, HPA axis, and noradrenergic system functions. CRH increases LC firing and NE release in projection areas, including the PVN of the hypothalamus. Norepinephrine increases CRH in the PVN. The CRH stimulates adrenocorticotropic hormone release from the pituitary, which results in enhanced release of cortisol from the adrenal gland. High levels of cortisol, through negative feedback, decrease both CRF and NE synthesis at the level of PVN, and thereby probably serve to retrain the stress-induced neuroendocrine and cardiovascular effects mediated by the PVN (*A*). In contrast, at the level of the hippocampus, cortisol and norepinephrine act in concert to enhance memory and are probably key mediators of traumatic remembrance (*B*).

Brain Imaging Studies Relevant to the Neural Circuitry of Anxiety and Fear

Neuroimaging has begun to examine neural correlates of fear and anxiety in patients with panic disorder (Box 1) and PTSD (Box 2). As described later, magnetic resonance imaging has revealed hippocampal atrophy in patients with PTSD (21) and childhood physical and sexual abuse (22–23). Considering the role of the hippocampus in the integration of memory elements, the findings suggest a possible neural correlate for symptoms of memory fragmentation and dysfunction in PTSD. Positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) have been used to assess brain function during active states of fear and anxiety. Patients with panic disorder have been shown to have a relative decrease from baseline in the ratio of frontal cortex to cerebellar blood flow measured with SPECT [^{99m}Tc]HMPAO following administration of yohimbine in comparison to healthy subjects (24). Patients with panic disorder who had a panic attack during lactate infusion had a blunted occipital blood flow response to lactate relative to controls and non-panicking patients as measured with SPECT [^{99m}Tc]HMPAO (25). PET studies found decreases in left inferior parietal lobule metabolism and decreased left hippocampal/right hippocampal ratio of metabolism in panic disorder patients in comparison to controls (26). In a recent investigation, the cerebral metabolic response to yohimbine administration (which increases brain NE release and results in symptoms of PTSD and fear and anxiety in PTSD patients) was decreased in prefrontal, temporal, orbitofrontal, and parietal cortex in patients with Vietnam combat-related PTSD compared with healthy subjects (27). Considering the dose-dependent effects of norepinephrine on brain metabolism (low doses increasing metabolism, and high doses decrease metabolism) these findings are consistent with the hypothesis of an increase in NE brain function in PTSD.

PET $H_2[^{15}O]$ studies in Vietnam veterans with PTSD have been completed measuring changes in cerebral blood flow in response to combat-related stimuli (23–30). These preliminary investigations have identified roles for limbic and paralimbic brain structures in the reexperiencing symptoms associated with PTSD. For example, the ventral anterior cingulate gyrus and right amygdala may mediate responses to mental images of combat-related scenes (29). In a recent study, relatively larger increases in blood flow were observed in PTSD patients in comparison to combat controls exposed to both combat slides and sounds in left parietal cortex, left motor cortex, right cerebellum/dorsal pons, right occipital posterior parahippocampus (lingual gyrus), and mid cingulate. These regions are involved in spatial (parietal) and motor (cerebellum and motor cortex) memory, emotion (cingulate and posterior parahippocampus) and memory for faces (post parahippocampus-lingual gyrus). The blood flow response in the orbitofrontal cortex was markedly different in PTSD patients, suggesting a neuroanatomical correlate of failure of extinction (extinction to conditioned fear response is mediated by orbitofrontal inhibition of amygdala function) (30) (Fig. 3).

Neural Mechanisms of Anxiety and Fear

Fear Conditioning

In many patients with anxiety disorders, such as panic disorder with agoraphobia, simple phobias, and PTSD, vivid memories of a traumatic event, autonomic arousal, and even flashbacks can be elicited by sensory and cognitive stimuli that have been associated with the original panic attack or trauma (Table 1). Consequently, patients begin to avoid these stimuli in their everyday life or a numbing of general emotional responsiveness occurs.

Substantial evidence indicates that neural plasticity within the amygdala is crucial for conditioned fear. Fear conditioning mechanisms are mediated through the amygdala and dependent upon the processing that sensory stimuli undergo before entering the amygdala. As noted above, the amygdala receives modality-specific input from polymodal association cortex and modality-independent inputs

Box 1: Diagnostic Criteria for Panic Disorder

A. Both 1) and 2):
   1) Recurrent, unexpected panic attacks.
   2) At least one of the attacks has been followed by 1 month (or more) of one (or more) of the following:
      a) Persistent concern about having additional attacks
      b) Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, "going crazy")
      c) Significant change in behavior related to the attacks
B. Absence of agoraphobia
C. The panic attacks are not due to the direct physiological effects of a substance (e.g., a drug of abuse or a medication) or to a general medical condition (e.g., hyperthyroidism).
D. The panic attacks are not accounted for better by another mental disorder, such as social phobia (e.g., occurring on exposure to feared social situations), specific phobia (e.g., on exposure to a specific phobic situation), obsessive-compulsive disorder (e.g., on exposure to dirt in someone with an obsession about contamination), posttraumatic stress disorder (e.g., in response to stimuli associated with a severe stressor), or separation anxiety disorder (e.g., in response to being away from home or close relatives).

from the hippocampus via the entorhinal cortex and subiculum (31). A critical role for the amygdala in conditioned fear is supported by the observation that patients with bilateral amygdala damage due to Urbach-Wiethe disease, a rare hereditary disorder, or amygdala resection for intractable epilepsy, fail to fear condition (32, 33).

These anatomical connections suggest that sensory information relayed to the amygdala has received substantial higher level processing, thereby making it possible to assign significance, based upon prior experience, to complex stimuli. Cortical pathways that influence fear conditioning may be clinically relevant because they suggest a mechanism by which cognitive factors may be important in the etiology and treatment of phobic anxiety disorders.

In addition to the thalamo-cortico-amygdala connections, a subcortical thalamo-amygdala pathway provides a cruder and more superficial analysis of stimuli, suggesting that fear conditioned responses can be elicited without awareness of the cause of the fearful response (34–36). This pathway may be relevant to "spontaneous" attacks of anxiety.

Many patients with anxiety disorders, especially panic disorder and PTSD, have persistent symptoms reflective of a continuous perception of threat. This is suggestive that contextual fear conditioning may model some of the chronic symptoms of anxiety (37).

Separate mechanisms may mediate conditioned fear to explicit cues and contextual fear conditioning. The amygdala is involved in both cue-specific conditioned fear and contextual fear conditioning. The hippocampus and periaqueductal grey play a role in contextual but not cue-specific fear conditioning (38,39). The bed nucleus of the stria terminalis (BNST) has been found to mediate contextual fear conditioning but not conditioning in response to explicit cues (40).

There is evidence that the function of brain NE and CRH systems is relevant to conditioning to explicit and contextual cues. Reductions in forebrain NE (41) impair fear conditioning to explicit cues, while enhancing contextual fear conditioning. Neutral stimuli paired with shock produce increases in brain NE metabolism and behavioral deficits similar to those elicited by the shock (42). In the freely moving cat, the firing rate of cells in the LC can be increased by presenting a neutral acoustic stimulus previously paired with an air puff to the whiskers, which also increases firing and is aversive to the cat (43). Also, a body of evidence indicates that an intact NE system may be necessary for the acquisition of fear conditioned responses. (44). CRH activates the BNST via mechanisms different from conditioned fear, possibly related to contextual fear (45).

Extinction

A possible failure of extinction has been proposed to account for the persistence of intrusive trauma memories in response to reminders of the original trauma in patients with PTSD or the persistence of panic attacks in response to reminders of the original setting of the initial panic attack. Theoretically, when a conditioned fear stimulus is no longer associated with a painful or otherwise aversive outcome, the conditioned fear response should gradually disappear. However, although extinction suppresses the signs of fear, it does not necessarily erase the original learning (e.g., the traumatic memories). In fact, extinction is thought to be an active process involving the formation of new memories that mask or compete with the memory of conditioned fear (46). The brain mechanisms underlying extinction are only partially understood. Recent findings suggest that a similar plasticity in the amygdala may underlie conditioned fear and extinction. NMDA receptor antagonists prevent extinction of fear-potentiated startle, indicating that an NMDA-dependent type of plasticity might be involved (47). Extinction could result from increases in the synaptic efficacy of inhibitory neurons within the amygdala (48). Alternatively, because lesions of auditory, visual, and prefrontal cortex interfere with extinction, it is possible that extinction involves the suppression of subcortical emotional memories by cortical inputs (48–51).

Several lines of evidence suggest that the original associations are intact following extinction. Representation

Box 2: Diagnostic Criteria for Posttraumatic Stress Disorder

A. The person has been exposed to a traumatic event in which both of the following were present:
   1) The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others.
   2) The person's response involved intense fear, helplessness, or horror.

B. The traumatic event is persistently reexperienced in one (or more) of the following ways:
   1) Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.
   2) Recurrent distressing dreams of the event.
   3) Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated).
   4) Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
   5) Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:
   1) Efforts to avoid thoughts, feelings, or conversations associated with the trauma
   2) Efforts to avoid activities, places, or people that arouse recollections of the trauma
   3) Inability to recall an important aspect of the trauma
   4) Markedly diminished interest or participation in significant activities
   5) Feeling of detachment or estrangement from others
   6) Restricted range of affect (e.g., unable to have loving feelings)
   7) Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal lifespan)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:
   1) Difficulty falling or staying asleep
   2) Irritability or outbursts of anger
   3) Difficulty concentrating
   4) Hypervigilance
   5) Exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C, and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

of the unconditioned stimulus even up to 1 year after extinction is sufficient for reinstating extinguished responding to a preextinction level (52). These data demonstrate the essentially permanent nature of conditioned fear and the apparent fragility of extinction. This phenomenon may help to explain the common clinical observation that traumatic memories may remain dormant for many years, only to be elicited by a subsequent stressor or unexpectedly by a stimulus long ago associated with the original trauma (53).

Behavioral Sensitization

Many patients with anxiety disorders experience chronic symptoms of increased arousal, and an increased susceptibility to psychosocial stress in general. Several features of behavioral sensitization suggest this hyperresponsiveness may account for these clinical phenomena.

The behavioral hyperresponsiveness of individuals with anxiety disorders is not restricted to trauma or phobia-related stimuli. PTSD patients exhibit exaggerated startle and bursts of anger, and are sensitive to various psychosocial stressors (54). In addition, PTSD can have a delayed onset, with symptoms increasing over time. Behavioral sensitization has been proposed as a model for such characteristics. Single or repeated exposure to physical stimuli or pharmacological agents sensitize an animal to subsequent stressors. Similarly, PTSD can result from different types of catastrophic events, and prior trauma enhances the likelihood of developing PTSD. The response of the sensitized animal can be behavioral, neurophysiological, or pharmacological and can occur to stressors that are of the same or different nature (cross-sensitization) relative to the original stressor. Some reports suggest that, in patients with PTSD, the response to subsequent nonspecific stressors is increased; the stimuli that evoke intrusive memories, flashbacks, and related symptoms in patients with PTSD are often difficult to determine and may bear only a distant association to the original evoking stimuli. Sensitization can be dose-related; the relationship between the severity of the trauma and the risk of developing PTSD has been well documented. Similar to PTSD symptoms, sensitization can be context-dependent or context-independent. Sensitization is context-dependent following exposure to a single stressor, but context-independent with repeated

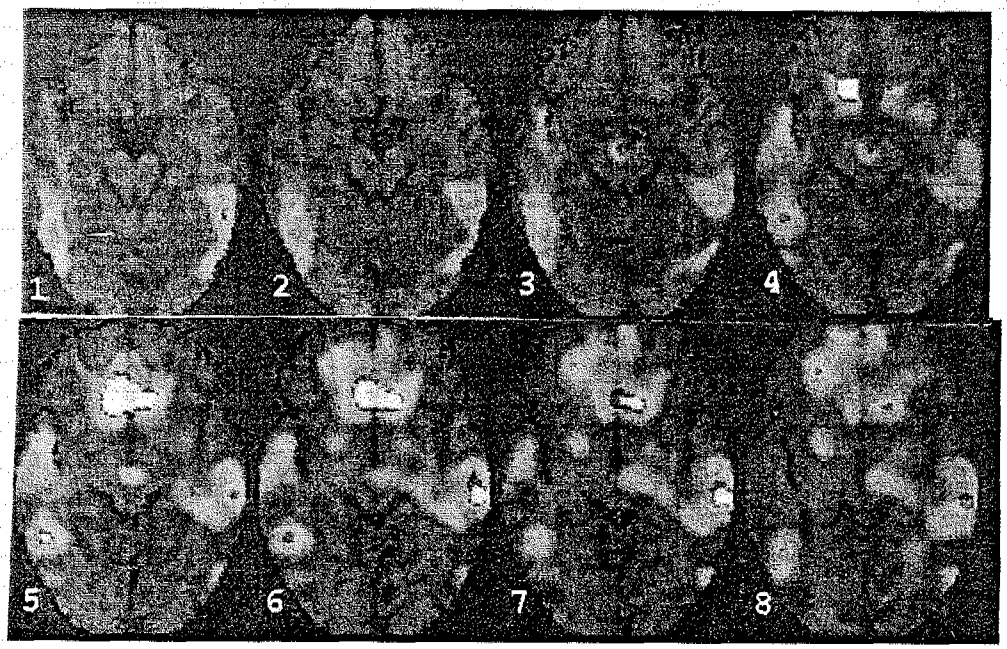

Fig. 3. Statistical parametric map overlaid on an MR image of areas showing different cerebral blood flow response following exposure to combat-related slides and sounds in veterans with combat-related PTSD relative to veterans without PTSD (z score >3.00; P <0.001). The large white area is in the orbitofrontal cortex; smaller areas include the auditory cortex. These regions are involved in inhibition of amygdala function, which results in extinction to fear responding. A failure of orbitofrontal and auditory cortex function may represent a neural correlate of a failure of extinction to fear in PTSD and may translate into the increased fearfulness seen in these patients following exposure to combat-related pictures and sounds.

stressors. Finally, sensitization is subject to genetic factors, developmental phase, and gender, each of which seems to play a role in PTSD (54).

Behavioral sensitization to stress may involve alterations in NE function. Limited shock exposure that does not increase NE utilization in control rats does increase NE release in animals previously exposed to the stressor (55). Moreover, changes in NE function in animals subjected to long-term shock require lower shock currents than under acute conditions (56). An in vivo study observed augmented extracellular NE concentrations in the hippocampus, whereas ex vivo measurements of noradrenergic metabolites in response to chronic stress indicated a sensitized response in the hypothalamus but not hippocampus (57). It is not clear to what degree this reflects differences in metabolic disposition of NE in the two regions, as opposed to actual differences in sensitization processes. Nonetheless, regional specificity in biochemical indexes of the expression of sensitization may be important. A recent in vivo dialysis investigation demonstrated stress-induced sensitization of NE release in the medial prefrontal cortex (58).

Clinical Studies of Fear Conditioning, Extinction, and Sensitization

Empirical studies of conditioning in humans have had difficulties demonstrating the operation of reflexive, unconscious emotional processes as opposed to processes that are more under voluntary control and subject to conscious awareness. Without a dissociation between these two processes, empirical studies of fear conditioning have had limited relevance to anxiety disorders.

Recent developments have renewed interest in clinical conditioning studies. One of these developments is the report of a dissociation between declarative knowledge and conditioned autonomic responses in patients with brain lesions. Bechera and others (59) reported that damage to the amygdala did not prevent patients from learning the relationship between the conditioned (CS) and the unconditioned (US), but abolished conditioned autonomic responses. In contrast, damage to the hippocampus did not affect conditioned autonomic responses, but prevented learning the CS-US association. This suggests that unconscious emotional processes are involved in fear conditioning.

Further evidence for such processes has come from studies using backward masking techniques, which prevents conscious awareness of a stimulus. Using such a technique, Ohman reported that fear conditioning, to fear-relevant stimuli (e.g., spiders and snakes), was mediated by preattentive automatic information processing mechanisms (60). These automatic mechanisms, which might be involved in maintaining conditioned fear responses, are believed to be associated with subcortical pathways. Two separate pathways appear to be involved in fear conditioning, a thalamo-cortico-amygdala pathway and a thalamo-amygdala pathway (35). It has been proposed that the former route provides a detailed cognitive appraisal of sensory information, whereas the second is involved in a faster, but superficial and crude

Table 1. Neural Mechanisms Related to the Pathophysiology and Treatment of Anxiety Disorders

Mechanism	Description	Neurochemical systems	Brain regions	Pathophysiology	Treatment
Fear conditioning	Animals exposed to emotionally neutral stimulus (CS) in conjunction with an aversive stimulus (US) will subsequently exhibit a CR of fear to the CS in the absence of the UCS.	NMDA receptors, noradrenergic, opiate	Sensory cortex Amygdala Locus Coeruleus Thalamus Hypothalamus Hippocampus Entorhinal cortex Bed nucleus of stria terminalis	May account for common clinical observation in panic disorder, PTSD, and phobias, in that sensory and cognitive stimuli associated with or resembling the original freightening experience elicit panic attacks, flashbacks, and a variety of autonomic symptoms. Chronic anxiety symptoms may relate to the effects of contextual fear conditioning.	Psychotherapies designed to reverse the effects of fear conditioning are very effective. The development of drugs that act selectively on the sensory pathways afferent to the anxiety circuit may decrease conditioned fear.
Extinction	There is a reduction in the CR when the CS is presented repeatedly in the absence of the UCS; this may result from learning a new inhibitory memory that opposes the original memory.	NMDA receptors	Sensory cortex Amygdala Orbitofrontal cortex	A failure in the neural mechanisms underlying extinction may relate to treatment-resistant phobias. In PTSD, it may relate to persistence in recalling traumatic memories.	Psychotherapies need to be developed that facilitate extinction through the use of conditioned inhibitors and learning of "new memories."
Sensitization	Increase in response magnitude after repeated administration of a stimulus or presentation of a different strong stimulus.	Dopaminergic, noradrenergic, NMDA receptors	Nucleus accumbens Amygdala Striatum Hypothalamus	May explain the adverse effects of early life trauma on subsequent responses to stressful like events. May play a role in the chronic course of many anxiety disorders and, in some cases, the worsening of the illness over time.	Suggests the efficacy of treatment may vary according to the stage of evolution of the disease process. Emphasizes the importance of early treatment intervention.

CR, conditioned response.

analysis of stimuli (36). This latter pathway is thought to trigger conditioned responses before the stimulus reaches full awareness. Unconscious conditioned phobic responses to fear-relevant stimuli are believed to be mediated by the thalamo-amygdala pathway (60).

Clinical studies that have examined whether patients with PTSD exhibit a biological vulnerability to associate conditioned fear with fear-relevant stimuli have been conflicting. Pitman and Orr (61) reported greater resistance to extinction of conditioned responses to angry facial expressions, but not to neutral facial expressions, in patients with anxiety disorders other than PTSD, compared with controls.

The startle reflex is a cross-species response to intense stimuli that is potentiated by fear. Startle is a promising measure of individual differences in conditionability for several reasons. Its use allows very similar procedures to be performed in humans and animals. In addition, the neural circuitry underlying "fear-potentiated startle" is fairly well understood in animals (62), suggesting that startle can inform on human neurobiological function and dysfunction during fear conditioning.

A recent startle investigation in PTSD has identified several areas of impairment in fear conditioning (63). The study examined fear conditioning to explicit (i.e., the CS) and contextual (i.e., the experimental room) cues in veterans with and without PTSD using a differential conditioning procedure. Subjects in the two groups were able to verbalize correctly the CS-US relationship (i.e., subjects knew which CS was associated with the shock). However, only veterans without PTSD exhibited differential startle responses during the CS+ and the CS−, suggesting that declarative and emotional learning was dissociated in veterans with PTSD. Further, the failure of the PTSD group to show a differential conditioned startle response resulted from an increased response to the CS−, suggesting that fear to the CS+ generalized to the CS− in this group. This generalization of fear to what should be considered a safety signal (i.e., the CS−) suggests that fear inhibitory mechanisms were impaired

in PTSD. This pattern of responses in veterans with PTSD contrasts with the one described in patients who have undergone unilateral surgical lobectomy. LaBar et al. (64) reported that patients with extensive lesions of the amygdala also fail to show differential conditioning. However unlike the veterans with PTSD, this failure resulted from a lack of response to the CS+, not to an excess response to the CS−. Preclinical data suggest that increased responding to CS− results from hippocampal dysfunction (65, 66).

Contextual fear conditioning involving the startle reflex also appears to be enhanced in veterans with PTSD. Preclinical studies suggest that different brain structures mediate fear conditioning to explicit and contextual cues. In particular, the BNST, but not the amygdala, appears to be involved in the potentiation of startle by contextual cues. The increased sensitivity of veterans with PTSD to contextual cues might explain their tendency to be hypervigilant and to be in a chronic state of generalized anxiety (67). In light of studies showing abnormal NE function in PTSD, it is interesting that the BNST has some of the densest noradrenergic innervation of any area in the brain (68).

PET studies during challenge with pharmacological and cognitive stressors support a role for abnormal function of orbitofrontal cortex in symptoms of failure of extinction in PTSD. Preclinical studies showed that lesions of orbitofrontal cortex result in a failure of extinction, probably because of the loss of orbitofrontal inhibition of amygdala responsiveness (51). Pharmacological challenge with yohimbine resulted in the greatest differences between PTSD patients and controls in orbitofrontal cortex. A blunted metabolic response to yohimbine in the PTSD patients suggested a failure of the normal adaptive mechanism of orbitofrontal activation with stressors (in this case, pharmacological stressors) (27). Consistent with this hypothesis, exposure of PTSD patients to cognitive stressors in the form of combat-related slides and sounds resulted in a failure of orbitofrontal cortical activation as measured with PET $H_2[^{15}O]$ relative to combat-exposed controls (29). These findings are consistent with orbitofrontal dysfunction in PTSD and suggest a neural mechanism for the failure of extinction that characterizes PTSD patients.

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