# Neurobiology of Anxiety Disorders and Implications for Treatment

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## Abstract

The neurobiology of the anxiety disorders, which include panic disorder, post-traumatic stress disorder (PTSD), and specific phobias, among others, has been clarified by advances in the field of classical or Pavlovian conditioning, and in our understanding of basic mechanisms of memory and learning. Fear conditioning occurs when a neutral conditioned stimulus (such as a tone) is paired with an aversive, or unconditioned stimulus (such as a footshock), and then in the absence of the unconditioned stimulus, causes a conditioned fear response. Preclinical studies have shown that the amygdala plays a key role in fear circuitry, and that abnormalities in amygdala pathways can affect the acquisition and expression of fear conditioning. Drugs such as glutamate *N*-methyl-D-aspartate (NMDA) antagonists, and blockers of voltage-gated calcium channels, in the amygdala, may block these effects. There is also preliminary evidence for the use of centrally acting beta-adrenergic antagonists, like propranolol, to inhibit consolidation of traumatic memories in PTSD. Finally, fear extinction, which entails new learning of fear inhibition, is central to the mechanism of effective anti-anxiety treatments. Several pharmacological manipulations, such as D-cycloserine, a partial NMDA agonist, have been found to facilitate extinction. Combining these medication approaches with psychotherapies that promote extinction, such as cognitive behavioral therapy (CBT), may offer patients with anxiety disorders a rapid and robust treatment with good durability of effect.

**Key Words:** Phobia, PTSD, panic, reconsolidation, extinction, amygdala, prefrontal cortex, fear, classical conditioning, Pavlov.

## Introduction

ANXIETY DISORDERS are the most common type of psychiatric disorders, with an incidence of 18.1% and a lifetime prevalence of 28.8% (1, 2). They account for a $42.3 billion annual cost in the United States, with over 50% of the total sum directed towards nonpsychiatric medical treatment costs (3). According to the National Comorbidity Survey Replication, in a given year, only about 37% of patients with anxiety disorders utilize any form of health services, including visits with psychiatrists (13%), other mental health practitioners (16%), or general medical doctors (24.3%) (4). Patients with anxiety disorders also have a high comorbidity with mood disorders, with up to 90% of patients experiencing some form of depression in their lifetime (5).

Our understanding of anxiety disorders, such as phobias, panic disorder and PTSD, has benefited from research on the neurobiology of fear and fear conditioning. This article will review this research and examine its implications for these anxiety disorders, with a focus on identifying potential therapeutic strategies.

Below is a brief summary of the diagnostic features from the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) for the major "fear-based" anxiety disorders, which have been associated with pathological fear response (6).

**Panic disorder (PD)** (prevalence: 4.7%) is a syndrome in which a person experiences recurrent and unexpected attacks, of sudden onset and short duration (10–15 minutes), which consist of the following symptoms: shortness of breath, palpitations, chest pain, sweating, chills, nausea, trembling, fear of dying or losing control, numbness, and a feeling of detachment or unreality. PD may or may not be accompanied by agoraphobia, an avoidance of situations where a person may feel trapped and unable to escape (e.g., trains, large crowds) (6). **Post-traumatic stress disorder** (prevalence: 6.8%) is a potentially debilitating

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chronic illness, caused by witnessing or experiencing a serious traumatic event, in which the person feels a threat to his/her life or the life of others, and experiences intense fear and horror. Typically, patients re-experience the traumatic event (e.g., nightmares, flashbacks), engage in avoidance of stimuli associated with the sentinel trauma (e.g., impaired recall of events related to the trauma, anhedonia, restricted affect), and experience increased autonomic reactivity (e.g., hypervigilance, irritability, insomnia, heightened startle response) (6). **Phobias**, among the most common psychiatric disorders, were previously classified as social phobia, now called **social anxiety disorder (SAD)** (prevalence: 12.1%), or specific phobia. SAD is defined as persistent fear of showing anxiety symptoms when exposed to unfamiliar situations or people and potential scrutiny, which result in humiliation and avoidance. Affected persons show avoidance of such social or performance situations, and when forced, will experience intense anxiety, and possibly even panic attacks (6). **Specific phobias** (prevalence: 12.5%) are marked by a persistent, excessive fear of a specific object or situation (classified as animal type, natural environment type, blood-injection injury type, situational type, and other type). This causes a potentially maladaptive avoidance of the phobic stimulus, and a severe anxiety reaction, such as a panic attack, when exposed to it (6).

Although anxiety disorders present with different symptoms, severity and natural histories, the therapeutic interventions for all these disorder are similar. For PD, the Food and Drug Administration (FDA)-approved medication treatments are either a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine; sertraline; paroxetine or paroxetine controlled release; or venlafaxine XR, a selective serotonin-norepinephrine reuptake inhibitor (SNRI) (7). The other recommended treatment for PD is cognitive behavioral therapy (CBT), or specifically, panic control therapy, a 12-week psychotherapy treatment that involves addressing cognitive distortions, psychoeducation, breathing exercises, progressive muscle relaxation, and progressive exposure (8). Both CBT and medication treatment have been shown to be equally effective, although evidence that combination treatment is better has been disputed. For PTSD, the evidence-based, first-line treatments are SSRIs (sertraline and paroxetine), and CBT using prolonged exposure (PE). In PE, the patient imagines the traumatic event out loud to reduce anxiety related to talking about it, and then is exposed to the places or things that trigger distressing thoughts or feelings. For SAD, the approved medication treatments are SSRIs (sertraline and paroxetine, including paroxetine CR), while group CBT with exposure therapy is the best psychosocial intervention (9). For specific phobias, the optimal treatment is CBT and exposure therapy. For all anxiety disorder, anxiolytic agents such as benzodiazepines can be used as a temporary adjunct to aid in minimizing anxiety, in particular when starting a medication therapy. In general, it is important to try to avoid long-term use of benzodiazepines for anxiety disorders, since it may lead to tolerance and increase risk of abuse or dependence, although particularly resistant cases may require longer-term administration.

The past decade has witnessed a rapid growth in our knowledge of the neurobiological basis of anxiety, through our examination of the behavioral components of the fear response. Significant advances in the spatial and temporal resolution of brain imaging techniques have clarified the neuroanatomical pathways responsible for processes relevant to fear and anxiety in humans, such as fear conditioning, acquisition, consolidation and reconsolidation, and extinction (see Table 1 for a glossary of terms). Animal studies, primarily on rodents, have shown that the amygdala, in connection with a complex network including the prefrontal cortex (PFC), thalamus and hippocampus, is integral to multiple aspects of emotional processing, including mediating adaptive and pathological fear responses (10). Neural circuits, defined by brain imaging and the use of pharmacological challenge studies, have yielded clues about receptor and gene expression that may elucidate the potential causes and vulnerabilities to anxiety disorders.

This article will review research relating to the basic mechanisms of the neurobiology of fear and the application of this research to anxiety disorders (in particular specific phobias, SAD, PD and PTSD), and will suggest potential therapeutic strategies for the future. As many of the initial pharmacological findings derived from animal models are now being applied to patients in the anxiety clinic, there is an emergence of a new translational field in psychiatry.

## Classical Fear Conditioning

The original model of classical conditioning was most famously demonstrated by Ivan Pavlov (11). It begins with the observation that certain stimuli, referred to as unconditioned stimuli (US), reliably yield an unconditioned response (UR). When a neutral stimulus is paired with the US it may also yield the same response through condi-

**TABLE 1**
*Terms Used in Conditioning*

| Term | Definition |
|---|---|
| Classical Conditioning | A process by which previously neutral stimuli acquire meaning to the organism. |
| Unconditioned Stimulus (US) | A trigger that produces an auto matic, unlearned response. |
| Unconditioned Response (UR) | A naturally occurring reaction to an US. |
| Conditioned Stimulus (CS) | A neutral trigger that, through classical conditioning, is able to produce a conditioned response. |
| Conditioned Response (CR) | The learned reaction to a CS. |
| Generalization | The ability to respond similarly to stimuli which are qualitatively different but functionally equivalent. |
| Acquisition | The initial stage of learning, where a neutral stimulus (CS) is associated with a meaningful stimulus (US) and obtains the capacity to elicit a similar response (CR). |
| Short-term memory | Memory of a limited amount of material that is held for a short period of time. |
| Long-term memory | Memory with a very high capacity which lasts over a long period of time. |
| Consolidation | The process by which short-term memory is converted into long-term memory. |
| Retrieval | Locating and returning to consciousness information stored in long-term memory. |
| Reconsolidation | A process by which a previously consolidated memory, which has been retrieved and becomes labile, undergoes another consolidation. |
| Extinction | The process by which a CS loses the ability to elicit a CR. |

tioning. Under these conditions the neutral stimulus is referred to as the conditioned stimulus and the response to the CS is the conditioned response (CR). Pavlov's experiment involved a dog that was presented with food (US) and salivated (UR). Then, the tester presented the food while at the same time ringing a bell (a neutral stimulus), and repeated the pairing several times. Finally, the food was taken away and the tester again rang the bell (CS), which produced salivation (CR).

Pavlovian fear conditioning occurs when a neutral stimulus is paired with an aversive stimulus. For instance, in the Little Albert experiments (12), an 11-month-old boy was given a rat (CS) to play with, and showed no fear response. Then, when again presented with the rat and simultaneously a very loud noise (US), Albert began to cry (UR). With repeated pairing of the rat and loud noise, Albert was shown the rat alone (CS) and began crying (CR). Even stimuli similar to a rat (any small, white, furry object) would create a fear response in the boy. Although fear responses serve an evolutionary valuable function in protection from potential dangers, they may also be maladaptive in that any contextual stimulus can become associated with recurrent fear and anxiety (i.e., generalization). In typical fear-conditioning rodent models, a US such as a mild electric footshock is used to elicit a CR, like behavioral freezing or alterations in blood pressure or heart rate.

## Neuroanatomy of Anxiety

The area of the brain responsible for the acquisition and expression of fear conditioning is the amygdala (13). Located within the medial temporal lobe, the amygdala is comprised of 13 nuclei, three of which, the basal amygdala (BA), lateral amygdala (LA), and central nuclei, are involved in the pathways of fear response (14). Stimuli received by the sensory thalamus are transmitted to the LA, and then are transferred to the central nucleus (CA) ("short loop" pathway). The BA also serves as a connection between the LA and central nucleus. The "long loop" pathway sends signals to the LA from the sensory cortex, insula, and prefrontal cortex (15, 66; Figure). From there, the information projects to the effector sites in the brain stem and hypothalamus, which produce the autonomic and behavioral manifestations of the acute fear response (16). It has been shown that the LA is the area responsible for memory consolidation and plasticity in fear conditioning (17, 18). Disruption or lesions of the LA or CA can disrupt the acquisition of conditioned fear and long-term contextual fear memory (19–21); there is evidence that lesions of the BA can affect fear responses (22). The molecular mechanism by which fear acquisition occurs in the LA is long-term potentiation (LTP) (23). It is proposed that consolidation of memory occurs during a process in which calcium enters the cell via *N*-

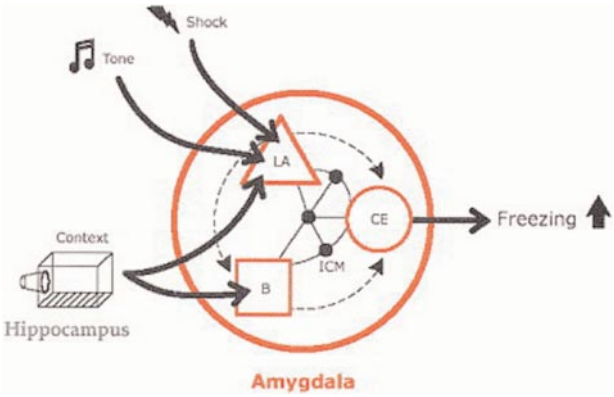


**Figure.** Fear conditioning circuitry.

In auditory fear conditioning, animals learn to fear an innocuous tone. By pairing tone and shock, the tone acquires the capacity to elicit defensive reactions, such as freezing (arrow pointing up). Tone and shock stimuli converge in the lateral amygdala (LA), resulting in associative plasticity in the tone—LA pathway. Subsequent presentations of the tone can now activate LA neurons. The LA then communicates with the central nucleus (CE), which controls the expression of fear by way of connections to specific circuits that mediate freezing behavior. The LA connects with CE directly and by way of connections to other amygdala areas, including the intercalated cell masses (ICM), which gate the output, and the basal nucleus (B), which processes contextual information from the hippocampus.

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methyl-*D*-aspartate (NMDA) receptors and through voltage-gated calcium channels (VGCCs) (24). Blockage of the VGCCs will disrupt short-term memory but not long-term memory, indicating that this pathway requires only NMDA receptors to be active (25–27). Some animal studies have shown that blockage of NMDA receptor by the antagonist D,L-2-amino-5-phosphonovaleric acid (APV, AP5), will block fear acquisition, but not expression (28–30), although more recently studies have shown that both processes are inhibited (31–33). Gene studies have shown high expression of NMDA receptors in the hippocampus as well, indicating the importance of this brain structure in Pavlovian conditioning (34). As in the amygdala, blockage of these receptors will inhibit conditioned fear responses (35, 36).

The application of these preclinical findings to humans is, currently, limited, but potential avenues include the use of NMDA receptor antagonists and calcium channel blockers to impair memory consolidation and thereby treat anxiety symptoms. Memantine, a non-competitive NMDA receptor antagonist, is widely used as a memory-enhancing agent in patients with moderate-to-severe Alzheimer's disease, most likely by improving neuronal plasticity and reducing excitotoxicity in the hippocampus (37). It has also been found to have anxiolytic properties in some animal studies (38, 39), but not in others (40, 41). It has not yet been studied as a primary anxiolytic agent in humans. Interestingly, Zarate and colleagues (42) found in a double-blind, placebo-controlled trial, that memantine was not effective in the treatment of major depressive disorder, suggesting potentially different pathways for mood modulation. Lamotrigine, a glutamate antagonist that acts by blockade of voltage-dependent sodium channels and calcium channels, is indicated for treatment of seizures and bipolar disorder. Mirza and others used a conditioned emotional response (CER) model in rats, with the pairing of houselight (CS) to electric footshock, to determine if the CS would associate with reduced lever pressing to receive food. One of their findings was that a $Na^+$ agonist blocked the anxiolytic effects of lamotrigine, while a $Ca^{2+}$ channel agonist did not, suggesting that the anxiolytic properties may be mediated by blockade of sodium channels (43). Hertzberg and colleagues used lamotrigine in a small double-blind trial of patients with PTSD, and found it to be more efficacious than placebo in reducing the severity of symptoms of PTSD, including re-experience and avoidance (44). VGCC inhibitors provide another potential avenue for treatment of anxiety disorders (see Table 1). For example, pregabalin, an anticonvulsant that binds to the alpha-2-delta protein to block VGCC, has shown promise as a therapeutic agent for generalized anxiety disorder (GAD) (45), and might gain FDA approval by the end of 2007.

## Consolidation and Reconsolidation

The conversion of labile, short-term memory into long-term memory is called consolidation, in a process dependent on protein synthesis (46, 47). While originally thought to occur once, the process in which transient information is permanently stored may require new protein synthesis after retrieval (48, 49). The memory trace, upon retrieval, is unstable and is required to undergo reconsolidation before it can be restored (50). Typically, memories are not stored individually, but instead as associated complexes, in which all related components are stored together (51). Recently, Debiec and colleagues (52) used a second-order fear conditioning (SOFC) paradigm, meaning that one CS was linked to another CS to cause an US (53), to test whether a blockade of protein synthesis would disrupt one memory, or the entire associative net-

work. They showed that only directly reactivated memories become labile, but that indirectly reactivated memories within the association complex are not affected (54). These findings may play a role in understanding how stressful events can be unlearned, without causing amnesia for memories temporally associated with the conditioned fear stimulus.

Reconsolidation offers a model for anxiety as a fear response in the absence of a US. It occurs via repeated activation of a memory, which enhances its retention (55). It is well established that emotionally laden stimuli, when compared to neutral stimuli, are more likely to be recalled, and are likely to cause amnesia for words preceding it (56).

Reconsolidation requires involvement of NMDA receptors and beta-adrenergic receptors, with induction by the cyclic adenosine monophosphate response element binding protein (CREB) (54). Propranolol, a central-acting, beta-adrenergic receptor antagonist, has been consistently shown to block recognition and recall of emotionally laden words and memories (57–61), while preserving neutral words. The drug also acts to restore the amnesia caused by the emotional stimulus. Furthermore, propranolol acts to block reconsolidation only and does not interfere with integration of new memories (62). These findings have led researchers to test beta blockers in humans with traumatic experiences, in one case investigating the effects on recall of distressing memories (63). Pitman and colleagues conducted the only randomized controlled trial of propranolol in acute trauma victims, who were administered the medication or placebo within 6 hours of exposure to trauma and continued for 10 days (64). Although they found less severe symptoms of PTSD, as measured on the Clinician-Administered PTSD Scale (CAPS), in those receiving propranolol vs. placebo at 1 and 3 months (with three months being the point where PTSD can first be diagnosed), the results were not statistically significant. With improved study design and larger sample size, further studies are underway to test the efficacy of beta-adrenergic receptors in the prevention of PTSD.

## Extinction

In Pavlov's experiment of classical conditioning, the dog ceased to salivate when the bell was rung (CS) but no food was presented (US) (11). This phenomenon is known as extinction. It does not involve, as the name implies, erasure of old information, but rather it is caused by the integration of new memory (65). The amygdala plays a key role in fear extinction, as do the medial prefrontal cortex (mPFC) and hippocampus. The LA is responsible for decreased firing with continued presentation of the CS, while the mPFC inhibits firing of amygdala neurons, under the modulation of the hippocampus (66). It is the mPFC that is thought to regulate extinction of long-term memory (67). This has been supported by studies showing blocking of extinction after lesion of the mPFC (68), and by blockade of protein synthesis in the mPFC (69). Exposure to chronic stress can also affect the mPFC's ability to modulate extinction, via retraction of dendrites (70, 71). Miracle and colleagues showed that rats exposed to restraint stress showed reduction in extinction 24 hours after initial extinction (72).

Much like in fear acquisition, an important component of extinction is activation of glutamatergic NMDA receptors in the amygdala. It has been shown that NMDA receptor antagonists, like AP5, can cause blockade of extinction, as measured by startle response (73). Conversely, partial NMDA agonists, such as *D*-cycloserine (DCS), have been shown to facilitate extinction. Walker and others used systemic administration, and direct amygdalar infusion, of DCS into rats, and found a decrease in fear-potentiated startle to CS compared to control animals (74). Ledgerwood's group confirmed these findings, and also determined that DCS not only aided in extinction of the original CS, but also reduced but didn't extinguish fear response to a CS paired with another CS, (75). This suggests that DCS may have an effect on extinction of generalized fearful stimuli, such as all furry objects, which caused crying in Little Albert (see above).

Investigation of the use of DCS in humans with anxiety disorders is already underway. Since DCS acts only to enhance extinction to fear responses, and is not a direct anxiolytic, it is used with exposure therapy or CBT to show an effect. This was evidenced by one small study that used DCS in PTSD patients with limited effect, but did not employ concomitant psychotherapy (76). Ressler and colleagues used 2 single-dose administrations of DCS 2–4 hours prior to exposure therapy in patients with phobic avoidance of heights, and found marked reductions in fear and avoidance symptoms that persisted for 3 months after treatment (77). A recent trial used DCS to augment group exposure therapy in patients with social anxiety disorder, and found rapid improvement in symptoms in patients compared to controls, who received exposure therapy and pill placebo (78). In summary, DCS has shown promise an adjunct treatment for patients with anxiety disorder by enhancing the learning associated with the treatment.

The inability of a person to extinguish a maladaptive fear response to a CS, due to a disruption

in the process of extinction, can result in persistent anxiety. Two pathways for the treatment of anxiety presented so far are the disruption of consolidation of emotional or traumatic memories (see above), and facilitation of the extinguishing of aversive stimuli. The second area is under intense investigation. In addition to using DCS, there are other potential agents being used in animal studies to aid in enhancing extinction. These include yohimbine, an alpha-2-adrenoreceptor antagonist (79), L-type VGCC agonists (27, 80), cannabinoid receptor 1 agonists (81, 82), and mu-opioid receptor blockers (Table 2; 83, 84). Investigation of the applicability of these mechanisms to humans is warranted.

## Conclusion

Using Pavlovian conditioning as a model, the pathophysiology of the fear response has been clarified over the past several years. Many animal studies have shown how these learning paradigms can be applied to humans, and how they can be used to understand the causes of anxiety. Imaging studies, using functional magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning, have helped trace and pinpoint the areas of the brain responsible for induction, maintenance, and unlearning of fear. Although the amygdala and prefrontal cortex are the primary sites of fear acquisition and extinction, other areas are being shown to play important roles as well. In addition, there are neurochemical pathways, not well understood, that may be proven to play a role in anxiety disorders.

The DSM-IV currently categorizes the anxiety disorders by clinical signs and symptoms. The Committee of the DSM-V Prelude Project, is considering re-classifying the anxiety disorders by several hypothetical approaches, including by etiology (vulnerability genes and gene/environment interactions) or by pathophysiology (neural pathways that give rise to certain symptoms) (85). This may be sensible, given the high comorbidity between mood and anxiety disorders. Using deficits in neural cir-

**TABLE 2**
*Experimental Therapeutics for Anxiety Disorders*

**Therapeutic Aim:** Acceleration of extinction of pathological fear responses
**Clinical Application:** Adjunct to cognitive behavioral therapy for specific phobias, social anxiety, and/or PTSD

| Preclinical Rationale | Neurobiological Mechanism | Drug Target | Prototypic Drug | References |
|---|---|---|---|---|
| pharmacologic or genetic disruption of eCB neurotransmission in rodents decreases fear extinction but not memory acquisition | eCBs depress inhibitory networks involved in aversive learning | CB1 (eCB) receptor | AM404, an inhibitor of eCB break-down and reuptake | 81, 82 |
| yohimbine facilitates extinction of cue and contextual fear in mice | NE enhances the learning of fear extinction | $\alpha_2$-adrenergic receptor | yohimbine | 79 |
| D-cycloserine infusion into amygdala strengthens extinction of fear-potentiated startle in rats | long-term retention of extinction requires activation of NMDA glutamate receptors in amygdala | glycine modulatory site of NMDA receptor | D-cycloserine | 77, 78 |
| in the vlPAG of rats, blockade of μ opioid receptors retards fear extinction, while inhibition of enkephalin degradation enhances it | activation of vlPAG μ opioid receptors contributes to extinction of conditioned fear | μ opioid receptors in vlPAG | RB101(S), inhibitor of enkephalin-catabolizing enzymes | 83, 84 |
| the LVGCC inhibitors nifedipine and nimodipine impair fear extinction in mice but not acquisition or expression of conditioned fear | LVGCCs are essential for fear extinction | LVGCC | L-type calcium channel agonists | 27, 80 |

PTSD = post-traumatic stress disorder, eCB = endocannabinoid; KO = knockout; LTP = long-term potentiation; LVGCC = L-type voltage gated calcium channel; Nac = nucleus accumbens; NE = norepinephrine; vlPAG = ventrolateral quadrant of periaqueductal gray; NMDA = *N*=methyl-D-aspartate.

cuits as a means of categorization, certain disorders marked by amygdala-centric fear pathways (such as PD, PTSD, phobias) will be grouped together, while GAD may be re-classified as a mood disorder.

While unable to cover all topics related to the neurobiology of fear and anxiety, our report reviewed the pertinent findings in the area of fear conditioning, including acquisition, reconsolidation, and extinction. Finally, through investigation of these pathways and neuropeptide systems, novel therapeutic interventions can be found for a wide range of anxiety disorders, such as generalized anxiety, panic, phobias, and PTSD.

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