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Implications of memory modulation for post-traumatic stress and fear disorders

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Abstract

Post-traumatic stress disorder, panic disorder and phobia manifest in ways that are consistent with an uncontrollable state of fear. Their development involves heredity, previous sensitizing experiences, association of aversive events with previous neutral stimuli, and inability to inhibit or extinguish fear after it is chronic and disabling. We highlight recent progress in fear learning and memory, differential susceptibility to disorders of fear, and how these findings are being applied to the understanding, treatment and possible prevention of fear disorders. Promising advances are being translated from basic science to the clinic, including approaches to distinguish risk versus resilience before trauma exposure, methods to interfere with fear development during memory consolidation after a trauma, and techniques to inhibit fear reconsolidation and to enhance extinction of chronic fear. It is hoped that this new knowledge will translate to more successful, neuroscientifically informed and rationally designed approaches to disorders of fear regulation.

The laboratory study of fear learning and memory continues to yield knowledge that holds promise for the understanding and treatment of post-traumatic stress disorder (PTSD) and other fear-related disorders. Here we discuss how these new and exciting observations are being translated from the basic science fields to the clinic. Furthermore, we point areas where basic research using animal models can be improved to better account for the dysregulation of fear seen in many disorders.

Experiencing an extremely traumatic event, such as combat or violent assault, can lead to PTSD. Estimates are that up to 90% of all people will be exposed to a severe traumatic event during their lifetime[1]. Given the high rates of trauma exposure, the prevalence of PTSD is relatively low, affecting approximately only 5–10% of the general population, with women being twice as likely to develop PTSD as men[2]. However, the rates of lifetime PTSD are closer to 20–30% in highly exposed trauma populations, such as low-income urban populations[1] and repeatedly traumatized soldiers. Recent studies have demonstrated a steep dose-response curve between trauma frequency and PTSD symptom severity, such that the more traumatic events a person experiences, the greater the intensity of PTSD symptoms[3, 4]. PTSD is the fourth most common psychiatric diagnosis[1] and is defined by three primary symptom clusters after an event that elicited fear, helplessness or horror[5]. The first cluster of symptoms includes re-experiencing the traumatic event through intrusive thoughts, nightmares, flashbacks and related phenomena that are often produced by reminders of the

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traumatic event. The second cluster is characterized by avoidance symptoms, including loss of interest in social situations and emotional detachment. The third cluster includes psychophysiological reactivity in response to trauma-related stimuli, including exaggerated startle, hypervigilance, elevated perspiration and shortness of breath.

Several other anxiety disorders are also characterized primarily by a dysregulated fear response. These include simple phobia; social phobia (also called social anxiety disorder), which involves fear and avoidance of social situations; and panic disorder. What is particularly interesting about this collection of disorders is that they all share a similar set of fear or panic symptoms that now have a clearly understood neurological basis (Fig. 1). Anxiety disorders affect around 18% percent of adults in the United States in a given year. Moreover, in 64% of suicide attempts, at least one anxiety disorder is present. Therefore, from a clinical perspective, improving treatment and identifying prevention measures is of critical importance. Furthermore, from a scientific perspective, we would argue that the fear-related anxiety disorders provide among the 'lowest-hanging fruit' for understanding the neural circuitry and pathophysiology of psychiatric disorders. This is because (i) the neural substrates of fear have been well worked out through over 50 years of neurobiological studies, (ii) the basic behavioral mechanisms underlying fear have been studied for over 100 years since the time of Pavlov, (iii) these neural and behavioral mechanisms are remarkably well conserved across mammalian species, including humans, and (iv) in many cases of fear-related disorders, particularly PTSD, the traumatic incident that initiates the dysregulated fear response can be identified. As a result of this last component, not only may we improve our understanding of the biological and psychological processes leading to a transformation from a 'normal' fear reaction to a pathologically dysregulated fear response, but we also may be able in some cases to prevent the development of inappropriate fear responses through early intervention.

An important observation in recent years is that there are several different learning components that distinguish normal fear or trauma exposure and recovery from the pathological responses to trauma exposure associated with lack of recovery and/or worsening of symptoms (Fig. 2). Evidence suggests that exposure to trauma in the past, before the 'index trauma' associated with the PTSD— particularly childhood trauma exposure—is of substantial importance. Furthermore, it appears that some gene pathways (for example, *FKBP5*; ref. 3) interact with childhood trauma, but not adult trauma, to predict adult PTSD. One possible reason for this is that developmental critical periods of amygdala function are glucocorticoid dependent[6], and *FKBP5* regulates glucocorticoid receptor sensitivity. Also, it is known that the level of trauma exposure is of critical import in the later development of post-traumatic symptoms. During the minutes to hours, and possibly days, after trauma exposure, the memory remains in a labile state, called the consolidation period. Some updates on the neurobiology of consolidation are outlined below, and there are exciting areas of inquiry suggesting that new pharmacotherapeutic and psychotherapeutic approaches may be initiated that may inhibit the emotional component of fear memory consolidation, without markedly affecting the explicit memory formation. Such an approach may not cause amnesia *per se* but could prevent the severe emotional reactions that underlie later development of PTSD. Another aspect of memory modulation that will be addressed below is the idea of reconsolidation, in which reactivation of a memory may cause it to re-enter a labile state after it has become permanent. The extent to which reconsolidation occurs with chronic, long-term memories in humans remains under some debate, but, if robust, it is an extremely exciting potential area of modulation. Finally, there are several further cognitive mechanisms that are associated with pathological reactions, such as generalization and sensitization of reminders of fear or trauma. In contrast, the mechanisms of discrimination and extinction of memory serve to counter these processes. In summary, as

outlined below, understanding the different components of fear memory formation and modulation may enable powerful and targeted treatment and intervention approaches.

Although there are several existing pharmacological and psychotherapeutic treatments for fear-related disorders[7, 8], all of these rely on empirically derived approaches. The first-line medication approach for all anxiety disorders includes the antidepressant and anxiolytic classes of selective and nonselective serotonin and other monoamine reuptake inhibitors (for example, fluoxetine, sertraline or venlafaxine). Although our understanding of the monoaminergic regulation of fear circuitry is improving, it is clear that these are not specific in their actions, they can have difficult side effects and they are only effective in some cases. The second-most-common class of agents used to treat these disorders are the benzodiazepines (for example, clonazepam, alprazolam or lorazepam), which act through enhancement of $GABA_A$ activity. Enhancing inhibitory transmission in the amygdala and bed nucleus of the stria terminalis (BNST) has been shown to diminish fear responses, but these agents have all of the same limitations as the monoaminergic anxiolytics, in addition to having abuse and tolerance potential.

A particularly promising area of inquiry arises from the burgeoning understanding of the neurobiological mechanisms of learning and memory. Although there are many ways to model the disorders of fear regulation, among the most robust approaches results from functionally dissecting the differential cognitive, learning and memory components that regulate fear learning, consolidation, modulation, generalization, sensitization, discrimination and extinction. Below we will review some of the differential learning and memory aspects underlying fear processing and illustrate how breakthroughs in these areas are leading to new approaches to the modulation of memory, and thus new treatment and intervention approaches targeting disorders of fear regulation.

The essential neural circuit supporting fear conditioning

The progress made in developing strategies to treat fear-related disorders has been greatly aided by the knowledge gained in the past several decades regarding the brain circuitry involved in Pavlovian fear conditioning and the cellular and molecular mechanisms in this network that support this form of learning. Fear conditioning involves learning an association between a neutral conditioned stimulus, such as a light or tone, and an aversive unconditioned stimulus, typically a foot shock (Fig. 3a). Memory for fear conditioning is inferred by presenting the cue that signaled the shock (Fig. 3b), and several conditioned responses consistent with a state of fear can be assessed. Some commonly measured fear responses in rats and mice include freezing behavior and potentiated startle; in humans, potentiated startle and skin conductance responses are often measured.

At the heart of the brain circuitry mediating fear learning and fear responses is a group of subcortical nuclei referred to collectively as the amygdala (Fig. 1). The lateral nucleus of the amygdala receives multimodal sensory information regarding the conditioned stimulus from thalamic and sensory cortical areas[9, 10]. This converges with input regarding the unconditioned stimulus, believed to arrive from somatosensory thalamic and cortical areas[11, 12] and the periaqueductal gray[13]. This convergence of the conditioned stimulus and unconditioned stimulus, along with other types of data, indicates that the lateral nucleus is a critical site for plasticity underlying fear learning[14]. Because the central nucleus of the amygdala sends projections to several brain areas responsible for generating fear responses[15], it typically has been thought of as an output structure. However, the central nucleus also receives direct thalamic and cortical inputs, and work has shown that preventing the activity of NMDA-type glutamate receptors and preventing the synthesis of protein in the central nucleus blocks the acquisition and consolidation of fear conditioning,

respectively[16, 17]. Recent studies[18, 19] showed that the lateral (CEl) and medial (CEm) divisions of the central nucleus make distinct contributions to fear conditioning, with the CEl being necessary for the acquisition of fear and the CEm responsible for the production of fear responses.

Learning of environmental contextual cues also occurs during standard fear conditioning. Although contextual fear conditioning also depends on the amygdala[20], it requires the dorsal hippocampus, which is not normally involved in fear conditioning to discrete cues. Lesions of the dorsal hippocampus shortly after fear conditioning were found to block the formation of contextual fear[21], and subsequent work showed that pharmacological disruptions in the hippocampus around the time of learning have similar effects[22]. The neural interactions of the fear circuit external to and within the amygdala are more complex than is being presented here, and we direct the reader to a recent review for a more detailed description[14].

Data from studies of fear conditioning in humans largely mirror findings from rodents with respect to the brain areas engaged during acquisition. People with damage to the amygdala show a disruption in fear learning, as measured by changes in skin conductance responses[23]. Functional brain imaging studies have shown increased amygdala activation during acquisition of fear conditioning[24] and during the production of fear responses[25]. Human brain imaging studies have also demonstrated that the hippocampus and related areas are active during contextual fear learning[26], which parallels findings from rodent research.

Many studies spanning the preclinical to clinical in humans have demonstrated that the brain areas implicated in rodent models are also robustly involved in human fear learning and modulation. Furthermore, these areas appear to be notably dysregulated in fear-related disorders such as panic disorder, specific and social phobia, and PTSD. Perhaps the most replicated and robust finding is the activation of amygdala nuclei in the presence of fearful cues, most notably fearful faces[27](Fig. 4a). Several studies have demonstrated hyperactive amygdala response in people with PTSD and other fear disorders relative to healthy subjects[28]. In addition to the action of the amygdala in directly mediating the fear response reflex, many areas are involved in the inhibition and modulation of amygdala activity, most notably the hippocampus[29–31] and medial prefrontal cortex[32–37]. These areas have also been demonstrated to have abnormal responses to fearful cues and fear inhibition in human functional magnetic resonance imaging studies[38–41](Fig. 4b–f). These data provide face and construct validity for the power of understanding the learning and modulation mechanisms of fear memories in rodent models to provide new therapeutic approaches to amygdala, hippocampal and ventromedial prefrontal cortex (vmPFC) regulation of fear in human disorders.

Blocking fear memory formation to prevent fear disorders

To appreciate how the study of fear conditioning can help develop strategies to treat fear disorders, it is critical to understand the different phases of learning and how they are typically studied in the laboratory. Acquisition of fear conditioning (Fig. 5a) refers to the process by which the organism learns that the conditioned stimulus predicts the unconditioned stimulus. Treatments that block the acquisition of fear conditioning are applied before conditioned-unconditioned stimulus pairings and prevent the development of short-term memory (STM) memory, tested within a few hours, and consequently the formation of long-term memory (LTM), tested many hours or days later. There are several cellular and molecular processes known to underlie the acquisition of fear conditioning. For example, NMDA antagonists applied just before training prevent the acquisition of fear conditioning, resulting in disrupted STM and LTM[42].

The consolidation of fear conditioning refers to the transformation of memory from a labile state immediately after acquisition to a more permanent state with the passage of time. Treatments that disrupt the consolidation of memory are usually applied a few minutes to a few hours after conditioned-unconditioned pairings, leaving STM intact but resulting in disrupted LTM (Fig. 5b). The time window for memory consolidation is defined by the period of time after acquisition during which memory can be disrupted by amnesic treatments. For example, protein synthesis inhibitors applied after acquisition of fear conditioning do not affect STM and are only effective in disrupting LTM if they are delivered within a few hours after conditioned–unconditioned stimulus pairings[43]. The acquisition and consolidation of fear conditioning require many cellular and molecular changes in addition to the two examples given here, a full explanation of which is beyond the scope of this review. We point the reader to some excellent recent reviews that describe these in depth[44, 45].

The point at which a traumatic event occurs represents the first opportunity to use treatments designed to disrupt the acquisition and/or consolidation of the memory. There are several recent studies that suggest that molecular mediators of fear consolidation may be impaired by specific treatments targeting this memory process. Among the most robust are data suggesting that modulation of the endogenous opioid system may inhibit fear consolidation. Rodent studies have suggested that μ-opioid pathway activation opposes fear consolidation and enhances extinction[46, 47]. Moreover, κ-opioid antagonists have similar effects on fear learning[48] and mediate stress effects on attention[49]. Morphine treatment after the experience of traumatic burns may decrease later PTSD symptoms in children[50]. More recent studies in civilians and soldiers suggest that acute morphine administration during the immediate aftermath of traumatic injury may prevent the subsequent development of PTSD[51]. It has not been fully clarified, however, whether opioid treatment is acting at the level of pain control and, by thus decreasing the pain—the unconditioned stimulus—decreasing the initial fear learning. Alternatively, given the animal results, the opioid pathways may be directly acting in amygdala and brainstem areas involved in fear consolidation and thus may have a direct neural mechanism for decreasing the fear memory, independent of pain regulation.

Another pathway that has been associated with fear memory consolidation is activation of β-adrenergic receptors in amygdala[52]. As propranolol has been used in humans safely for decades for blockade of cardiovascular sympathetic activity, as well as for inhibiting social anxiety responses, it is a safe medication to use potentially to intervene in fear and trauma memory consolidation. Although preliminary studies were promising[53] and propranolol appears to decrease amygdala activation in humans[54], more recent, larger studies have not found a significant effect of propranolol administration after trauma[55–57].

There have also been exciting recent approaches focused on non-medication-based psychotherapeutic approaches. Specifically, it has previously been shown in animal models that re-exposure to a conditioned cue in the absence of reinforcement can impair the initial consolidation of that fear memory process[58] (but see ref. 59). Translating this to humans, Rothbaum and colleagues recently performed a proof-of-concept trial with 137 traumatized civilians, with full exposure-based psychotherapy in the emergency department in the hours after the trauma[60]. Exposure therapy is thought to rely on extinction mechanisms (see below) and to be well modeled by extinction in rodents. It was found that this early intervention may have a significant protective effect on development of PTSD and depression symptoms assessed 4 and 12 weeks later. Larger, randomized trials are needed, but this suggests the possibility that exposure to appropriate therapy after trauma may lead to more rapid recovery or even prevention of PTSD formation.

There are many questions that have been raised regarding the wisdom and ethics of potential prevention of memory formation in the aftermath of trauma exposure. In particular are issues related to the ethics of induced amnesia and the potential complexity of complete forgetting of an event that may be important to remember for reasons related to future safety or possible legal ramifications. One potential solution to this issue is the recognition of multiple memory systems—that a given traumatic experience is encoded in parallel across declarative, emotional and motor pathways, which all have different underlying neurocircuitry. If the field of neuroscience is able to identify ways to target the overlearning of the emotional component of the memory while leaving the declarative trace intact, it may be possible to convert an overly strong, indelible, overwhelming emotional experience—one that becomes a 'black hole' of memories for many with PTSD—to simply a bad memory, which can then be managed, modulated and overcome in appropriate ways, leading to recovery.

Enhancing fear extinction to treat fear–related disorders

The extinction of fear conditioning refers to the decrease in fear responses during repeated presentations of the conditioned stimulus without unconditioned stimulus reinforcement. Extinction can refer to the within-session decrement in fear responses while animals are receiving presentations of the conditioned stimulus alone during extinction training. It can also refer to the retention of extinction learning when animals are presented with the conditioned stimulus at later time points (Fig. 5c). Extinction is thought to involve new learning rather than erasure or unlearning of the association. Evidence for this assertion comes from the observation that fear responses spontaneously recover with passage of time[61], that fear responses show renewed responding when the conditioned stimulus is presented in a different environmental context from that in which extinction training occurred[62], and that presentation of the unconditioned stimulus alone reinstates fear to a cue that has undergone extinction training[63]. The extinction of fear conditioning relies on some of the same brain circuitry necessary for acquiring fear memories, including the amygdala[64] and hippocampus[29]. There is good evidence that extinction also requires activity of the vmPFC, which is not normally involved in the acquisition of fear conditioning. In rats, the infralimbic portion of the vmPFC appears to be critical for the extinction of fear conditioning. Lesions of this area have been shown to disrupt the retention of extinction[32], and neurons in the infralimbic cortex show increased firing during the recall of extinction memory[33]. Neurons in the infralimbic cortex are thought to decrease fear responses by means of projections to GABAergic intercalated neurons positioned between the lateral or basal and the central nuclei of the amygdala, which inhibit the output of the central nucleus. Studies of extinction learning in humans largely parallel studies rats, demonstrating that the vmPFC[36, 38], amygdala[24] and hippocampus[31] are all engaged during extinction learning or the recall of extinction.

Pharmacological approaches that enhance fear extinction are being evaluated for treatment efficacy in PTSD. The use of D-cycloserine (DCS), a partial NMDA receptor agonist, as a potential treatment for PTSD arose as a result of many preclinical studies implicating NMDA receptor activity in learning and memory processes[65, 66]. DCS was first tried in humans for anxiety disorders in combination with virtual reality exposure (VRE) therapy for the fear of heights[67]. After treatment, those patients that received DCS in combination with VRE showed greater improvement than those who received placebo and VRE. Since that study, DCS has been shown to be an effective therapeutic compound for increasing the rate of recovery with exposure-based psychotherapy several fear- and anxiety-related disorders, including panic disorder[68], social anxiety disorder[69], obsessive-compulsive disorder[70] and PTSD[71]. Although there have been some negative trials, most of these can be explained retrospectively as the mechanism of DCS is further understood, and two recent meta-

analyses support the conclusion that it is an effective augmentation strategy to enhance the rate of emotional learning underlying exposure-based psychotherapy[72, 73]. Other methods of augmenting NMDA receptor activity in conjunction with extinction are also now being explored.

More recent work has identified brain-derived neurotrophic factor (BDNF) as a molecular target for facilitating extinction learning and a potential treatment for fear disorders[74]. Studies have shown that blocking the activity of BDNF in the amygdala[75] or hippocampus[30] disrupts the retention of extinction. Other studies indicate that memory for extinction can be facilitated by infusion of recombinant BDNF in the infralimbic cortex or dorsal hippocampus[35] or by systemic injection of an agonist for its receptor TrkB[76]. Further very interesting work involves the Val66Met variant of BDNF in humans. Carriers of the methionine-encoding allele release less BDNF peptide[77]. Recently humans with this allele have been shown to have been found to have diminished extinction of conditioned fear[78], which may serve as a partial explanation for the increased prevalence of anxiety-related disorders in people with this genotype[79]. Most intriguingly, in the same study[78], it was shown in 'humanized' mouse models using knock-ins of each of the human alleles to the mouse *Bdnf* gene locus that these alleles lead to phenotypes in mice similar to those in human: decreased extinction of fear in the methionine allele carriers relative to that in the valine allele carriers. Some meta-analyses have failed to find increased incidence of anxiety disorders in methionine allele carriers[80]; however, this might be the result of low samples sizes. Together these data extend our understanding and appreciation of the role of BDNF in extinction and recovery from fear and fear-related disorders. They also provide further evidence for the face validity of the usefulness of the extinction-of-fear model in mice for extinction of fear in humans.

Disrupting traumatic memories after retrieval

Recently there has been renewed interest in the notion that LTM becomes susceptible to disruption after a consolidated memory is retrieved. In fear conditioning studies, memory is retrieved by presenting the animal with a single presentation of the conditioned stimulus used to signal shock during acquisition (Fig. 5d). The seminal finding was that when a protein synthesis inhibitor is given after retrieval, LTM is impaired on subsequent tests[81]. This result generated wide interest, and this phenomenon, termed reconsolidation, has now been observed in organisms ranging from invertebrates to humans[82]. Somewhat less is known about memory reconsolidation than about initial consolidation, but the available evidence suggests that the molecular and cellular mechanisms supporting reconsolidation are similar to those necessary for consolidation, although they do not overlap completely[83].

The observation that fear memories can be disrupted by combining retrieval of memory with drug treatment opens up the possibility of using this strategy to treat fear-related disorders. Theoretically, patients could be brought into a clinical setting, presented with a stimulus that retrieves the fearful memory and given a drug, and the fear memory would be weakened. Recent laboratory studies have used this basic approach to determine whether fear memories can be disrupted by combining retrieval with a memory-impairing drug. In one study[84], human subjects were fear conditioned, given a retrieval trial the next day in conjunction with oral administration of the β-adrenergic blocker propranolol, and tested the day after. The results showed that those given the drug while the memory was reactivated showed significantly less fear-potentiated startle during testing the next day than those given placebo. At least one study[85] has shown that a similar approach can be taken to disrupt traumatic memories in humans. In this study, PTSD patients were asked to describe a traumatic experience and were given a single dose of propranolol or a placebo. Patients

given propranolol showed reduced physiological signs of fear when they were asked to once again describe the traumatic experience a week later.

Although there are some differences, there is also evidence that disruption of reconsolidation and extinction may share some interesting properties[86]. Of note, *in vivo* and *ex vivo* physiological studies have suggested that fear learning leads to LTP-like potentiation of synapses with fear learning. Extinction of fear then appears to be associated with depotentiation and LTD-like mechanisms in some models[87, 88]. Thus, diminished representation of synaptic strength may be achieved, in part, both through strengthened extinction and through inhibited reconsolidation.

Although this strategy is promising, laboratory studies of reconsolidation indicate that there may be limitations to using a reconsolidation-disruption approach as a way to treat fear-related disorders. Several studies have indicated that retrieval does not always trigger reconsolidation, including the observation that both older and stronger memories are less susceptible to disruption after retrieval[89, 90]. If this pattern of data extends to humans with fear-related disorders, it may prove difficult to disrupt traumatic memories after retrieval because these memories are most certainly strong and in many cases have persisted for some time. In fact, many PTSD patients may take years to seek treatment, and chronic PTSD is often the most difficult to treat. Another consideration is that memory retrieval happens outside of the clinical context, often in the form of re-experiencing of the traumatic event. Replaying the traumatic event over and over again can sensitize patients with fear-related disorders and lead to worsening of the disorder. As in sensitization in humans with fear-related disorders, animal studies have also shown that repeated retrieval can strengthen fear memory and make it impervious to disruption with treatments that normally disrupt memory reconsolidation[91]. Thus, even if a drug is given each time a patient re-experiences a traumatic event, it may not be sensitive to disruption.

Future directions

Further areas of interest that are less well developed include studies of generalization versus discrimination, avoidance behavior and combined extinction-reconsolidation processes. The use of more sophisticated behavioral techniques in the laboratory to understand how fear generalizes to stimuli not originally associated with the traumatic event, which is a hallmark of PTSD and panic disorder, may provide powerful insight. An approach to studying generalization is to use differential fear conditioning whereby, in addition to a cue that signals shock, there is also a cue that is not followed by shock. Studies have shown that in rats[92] some animals show good discrimination, whereas others generalize fear to the safe cue, similarly to what is seen in patients with fear-related disorders. Another approach is to use conditioned inhibition training to identify animals that do not inhibit fear in the presence of a safety signal[93]. Both of these strategies can address a potential limitation of animal studies: that the variability of responses is often not factored into the analyses, even though in people who experience a traumatic event there is great variability in responses, with some developing a pathological disorder and others being resilient[94]. In a similar vein, early life stress and previous trauma experience factor into the development PTSD (Fig. 2), yet there are relatively few laboratory studies determining the effects of previous trauma and early life stress on fear learning and fear extinction. More refined protocols are needed to model this important aspect of susceptibility to developing PTSD.

Another line of research that could potentially be relevant for the treatment of fear-related disorders is based on recent behavioral studies[95–97] demonstrating that, if extinction training occurs shortly after a single retrieval trial, fear memories are diminished and show no evidence of recovery. Although this finding is not always consistent[98], the ability to

diminish fear memories in this manner opens another potential avenue by which traumatic memories can be targeted in patients with fear-related disorders.

Conclusions

Our goal is to describe how knowledge of basic learning and memory processes has translated into potential treatments for PTSD and other fear-related disorders. We wish to point to recent areas that have potential to drive clinical treatments in the future. If animal models are modified to better account for fear dysregulation in these disorders, we may improve the impact of preclinical research on prevention and treatment. Recent advances in molecular and cellular approaches to cognitive function are rapidly advancing our understanding of fear-related disorders. Progress in this area is exciting, not only in its potential to affect and improve treatment but also in the hope that it provides to biological psychiatry in general. Success in this arena suggests that if the neural circuitry underlying functional pathophysiology can be defined, then powerful behavioral neuroscience approaches can be effectively translated to the clinic, even in debilitating and previously mysterious psychiatric disorders.

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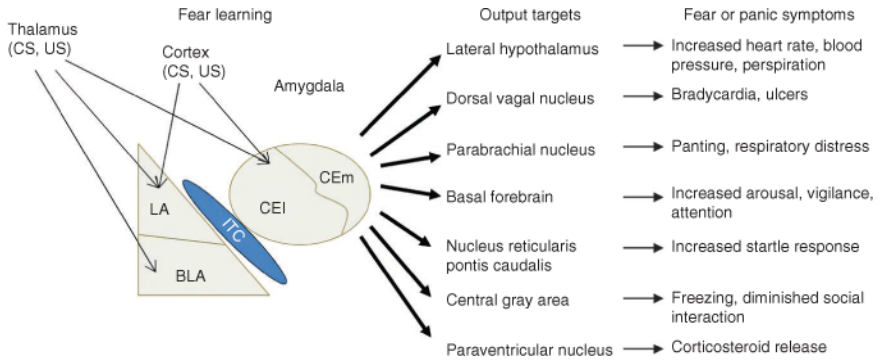

Figure 1.

Schematic depicting the amygdala, the brain site most critical for fear learning. Information regarding the conditioned stimulus (CS) and unconditioned stimulus (US) is transmitted to the amygdala by way of sensory areas in the thalamus and cortex. Within the amygdala, the critical plasticity underlying the acquisition of fear conditioning is thought to occur in the lateral amygdala and the lateral portion of the central nucleus (CEl). The medial division of the central nucleus of the amygdala (CEm) projects to various brain areas that produce fear and panic symptoms seen in people with fear-related disorders. LA, lateral nucleus; BLA, basolateral nucleus; ITC, intercalated cells (see also ref. 99).

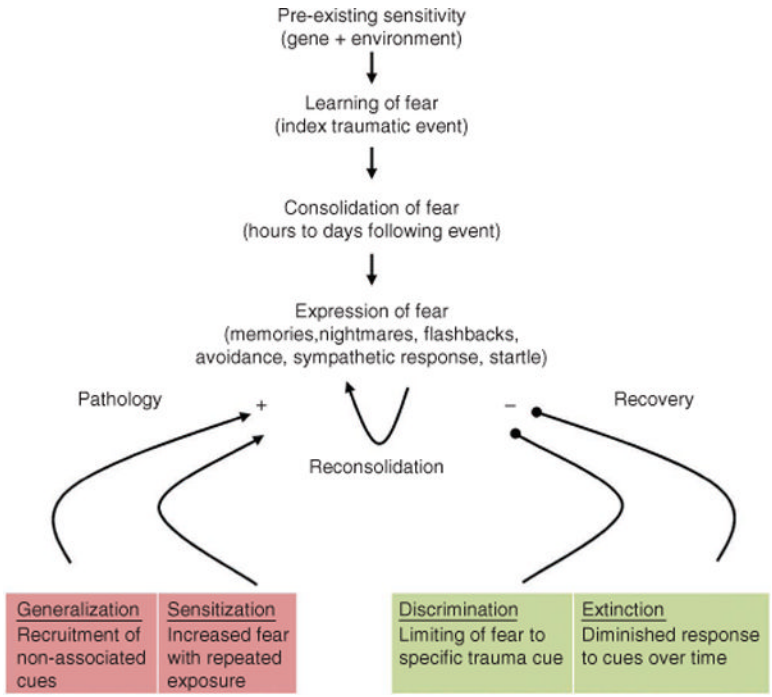

Figure 2.

A model for the development of fear-related disorders. Certain individuals are predisposed to the development of fear-related disorders on the basis of early life experience and genetic background, among other risk factors. When a traumatic event occurs, people learn to fear the cues that are associated with the traumatic event, and this memory consolidates over the course of the subsequent hours and days. The expression of fear comes in several different forms, including flashbacks of the traumatic event, nightmares, avoidance of situations that trigger memory for the traumatic event and altered sympathetic responses such as increased startle. The expression of the fear triggered by memory for the traumatic event may serve to sensitize those who develop psychopathology, resulting in increased fear. Additionally, fear may generalize to cues not associated with the traumatic event in those people who go on to develop a fear-related disorder. In contrast, with resilience, fear responses to cues related to the traumatic event extinguish over time, and discrimination occurs between cues that are associated with the traumatic event and those that are not.

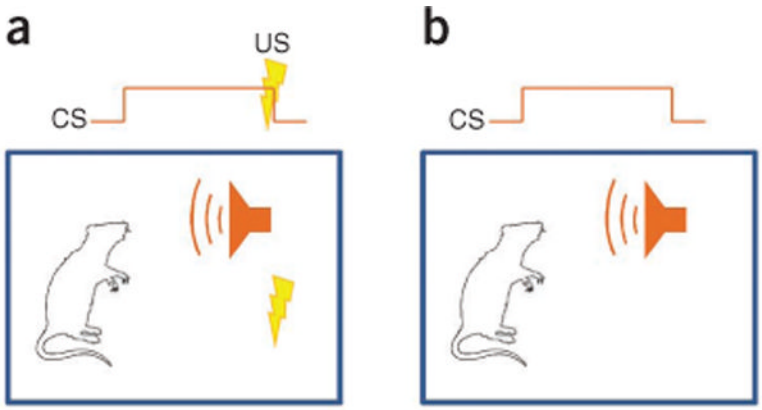

Figure 3.

Basic fear conditioning and testing procedures. (**a**) Fear conditioning involves training an animal to fear a neutral conditioned stimulus (CS) such as an auditory cue by having it signal an aversive unconditioned stimulus (US) such as an electrical shock. (**b**) Memory for fear conditioning is tested by presenting the conditioned stimulus alone and measuring fear responses.

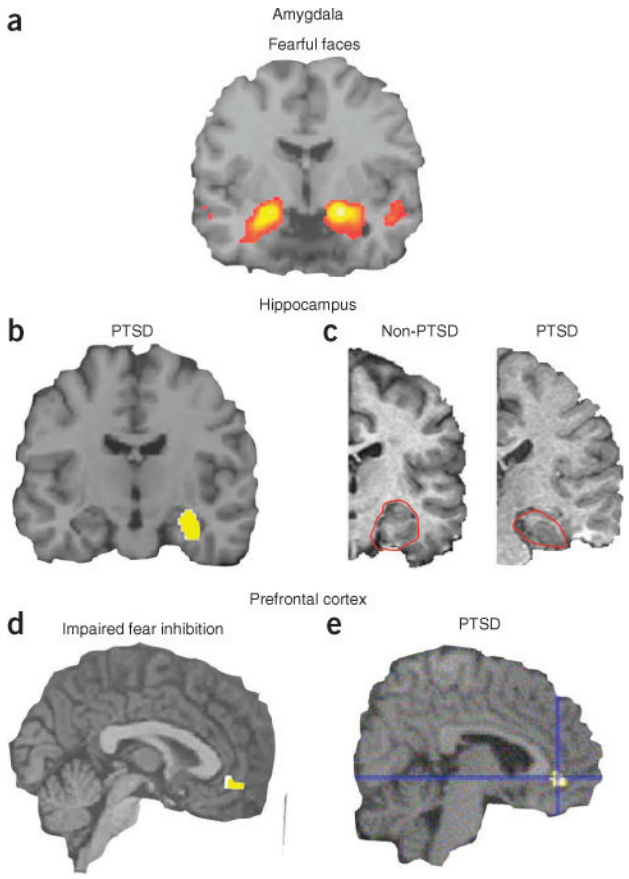

Figure 4.

Human neural circuitry involved in fear-related disorders and PTSD. (**a**) Viewing of fearful or angry faces (compared to shapes) robustly activates human amygdala across protocols and cohorts (reproduced with permission from ref. 27). Often this amygdala activation is increased in fear-related disorders. (**b**) Right hippocampal activity is lower in youths with post-traumatic stress symptoms than in healthy controls (reproduced with permission from ref. 38). (**c**) Reduced hippocampal volume in a patient with PTSD (right) compared to that in a subject without PTSD (left). Hippocampus outlined in red (adapted with permission from ref. 39). (**d**) Reduced neural activation of vmPFC during an inhibition task is associated with impaired fear inhibition (reproduced with permission from ref. 41). (**e**) Subjects with PTSD show lower regional cerebral blood flow activity in the rostral anterior cingulate during exposure to traumatic or stressful script-driven imagery (reproduced with permission from ref. 40).

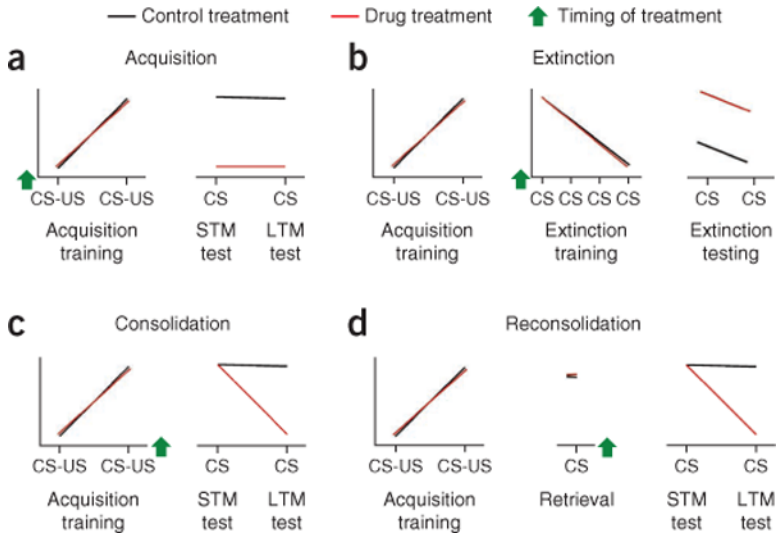

Figure 5.

Different components of fear learning and modulation as they are studied in the laboratory. (**a**) Acquisition training involves pairings of a conditioned stimulus (CS) with an aversive unconditioned stimulus (US). A treatment is said to prevent acquisition of fear if it is applied before training and blocks both STM and LTM from forming. (**b**) Fear memories can also undergo extinction by repeated presentation of the CS without the US during extinction training. Treatments that block the formation of extinction memory are typically given before extinction training and result in more fear during extinction testing in comparison to control treatments. (c) The consolidation of fear memory refers to time-dependent stabilization of memory after acquisition. Treatments that block memory consolidation are usually given shortly after training and result in disrupted LTM but intact STM. (**d**) When a memory is retrieved it may undergo reconsolidation, which results in a period of time during which the memory is labile. Reconsolidation of memory is considered to be disrupted when a drug is applied shortly after retrieval and leaves STM intact yet disrupts LTM. Green arrows indicates the timing of a given treatment or manipulation for each of the different learning phases; *x* axes represent time; *y* axes, fear behavior.