Fear

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Gregory J. Quirk

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Abstract

Fear is a conscious emotion but can also be seen as a bodily response to threat. Understanding how the brain assigns emotional significance to sensory stimuli through experimental fear conditioning has advanced our understanding of fear learning. The amygdala serves as a key node in the fear circuit, associating conditioned stimuli (such as tones) with unconditioned stimuli (such as shocks), at specific synapses using NMDA receptors and associated signaling cascades.

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The output neurons of the amygdala project to hypothalamic and brain stem areas that mediate autonomic, hormonal, and behavioral fear responses. Transmission through the amygdala is modulated by inputs from the prefrontal cortex and hippocampus. Fear memories are long lasting and like other forms of memory are consolidated, reconsolidated, or extinguished, depending on reactivation of the memory. Fear circuits in rodents have homologues in the human brain. The human amygdala responds to fearful faces as well as conditioned cues and is modulated by prefrontal and hippocampal circuits. Translation of rodent studies to humans has led to new treatments for anxiety disorders based on modulation of fear extinction and reconsolidation.

Brief History

The scientific study of fear, and emotion in general, dates back to the late nineteenth century, when the psychologist William James suggested that our emotional response to a dangerous stimulus precedes our conscious perception of fear. Hence, when we see a bear, we first start running and then become afraid (not the other way around). The stimulus first triggers the emotional response in the body (e.g., sweating, heart racing), which then feeds back to the brain to trigger the conscious feeling of fear. This view was challenged in the 1920s by Walter Cannon, who argued that the sympathetic "fight or flight" response was essentially the same for all emotions and therefore could not serve as a trigger for specific emotions. These two views were later synthesized by the Schachter–Singer theory in the 1960s, which stated that bodily feedback was interpreted by the brain based on the context (social cues) in which the arousal occurred, to arrive at the appropriate emotion. This dialectic between the role of the brain and body in the generation of emotion continues to this day, but there is general agreement that there are systems in the brain that can appraise the emotional significance of stimuli without conscious awareness. In the 1970s, fear research was advanced by studies of animals' species-specific fear responses, which evolved to help animals detect and avoid danger. The neural circuits of specific fear behaviors such as freezing or avoidance could be determined in animal models and then translated to humans using functional brain imaging.

Nothing in life is to be feared, it is only to be understood.
  – Marie Curie, first female Nobelist (Polish, 1867–1934)

Fear Is a Bodily Response to Threat

When we think of fear, we probably think of common bodily responses in a fearful situation, such as sweaty palms or our heart racing. In fact, fear can be defined as a **response** triggered by our brain when it detects threats: cues predicting danger or bodily harm. Fear responses consist of a set of **behavioral**, **autonomic**, and **hormonal** responses, often called the "flight or fight" response (see Fig. 1, also ▶ Chap. 48, "Autonomic Nervous Systems" by Buijs). Fear reactions to a threatening stimulus might include jumping backward, increasing heart rate, and releasing adrenaline into the bloodstream. Fear responses are thought to help the organism evade or survive an interaction with a predator. Some fear responses are common across species (e.g., changes in heart rate, escape responses), while others differ. For example, humans can show facial expressions of fear, whereas rats stop all bodily movement by freezing. In addition to bodily responses to threats, fear in humans involves conscious feelings. Even though the term fear is used for both processes, the neural mechanisms underlying these processes may be quite different (see review by LeDoux 2014). Regarding research, we know considerably more about bodily responses than conscious feelings of fear.

What triggers fear responses? Some fear-inducing stimuli are thought to be **innate**, i.e., available at birth prior to any experience. While this is difficult to test experimentally, it is widely believed that a small number of threats that were present throughout evolution serve as innate fear stimuli, such as insects, snakes, heights, and loud noises. However, the majority of threats that modern humans fear are **learned** through experience or instruction. For example, thinking about an upcoming final exam might get your heart racing. More serious triggers for fear responses might include events surrounding a violent crime or a natural disaster.
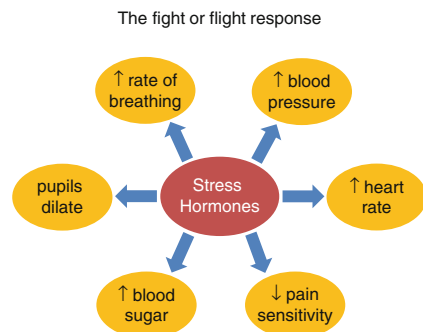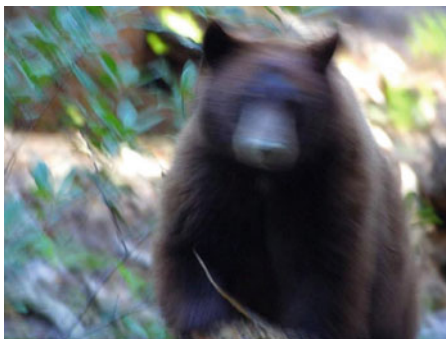
Fig. 1 Danger stimuli (like a charging bear) trigger a complex series of behavioral, autonomic, and hormonal reflexes that help us detect, avoid, and survive an encounter with a predator (Photo from public domain). This is termed the "flight or fight" response, which involves autonomic responses induced by stress hormones

Fear Learning Is Studied with Experimental Fear Conditioning

If you were robbed one day on a street corner, you might tense up or walk faster the next time you visited that corner. This is a common example of a **conditioned fear response**. The ability to show conditioned fear responses helps organisms survive encounters with new threats in the environment and is conserved across species, from flies to humans. In humans, however, excessive conditioned fear responses are thought to underlie anxiety disorders such as **phobias**, **panic disorder**, and **posttraumatic stress disorder** (**PTSD**) (see Fig. 2). For this reason, fear research in the past 20 years has focused on the neural mechanisms of fear conditioning.

Fear conditioning is an example of classical conditioning, as described by the Russian physiologist Ivan Pavlov (1927), in which a neutral sensory stimulus (**conditioned stimulus**, CS) is paired with an aversive **unconditioned stimulus** (US), resulting in a **conditioned response** to the stimulus. In humans, the CS is usually a visual stimulus presented on a video screen, the US is a mild shock to the fingers, and the conditioned response is an increase in sweating on the palm of the hand, also known as the **galvanic skin response** (see Fig. 3). In rodents, the CS-US combination can be a sensory stimulus (tone, light, or odor) that is paired with a footshock. The conditioned fear response is **freezing** or potentiation of startle response to a loud noise. Freezing is a natural fear response in many animals and is easily measured with a stopwatch or video-tracking system. In rodents conditioned freezing is also induced by exposure to a context in which shock previously occurred. Thus, conditioned fear response can be evoked by specific places, as well as specific sensory stimuli.

The Brain Mechanism of Fear Learning Is Conserved Across Species

The key structure for fear conditioning is the **amygdala**, a subcortical region located in the medial temporal lobe. Damage to the amygdala prevents experimental animals (from lizards to fish to rats) or humans from acquiring conditioned fear responses. Rats without an amygdala do not freeze to a tone that had been paired with a shock, and humans without an amygdala do not show conditioned sweating responses. The connections of the amygdala are well suited to the job of detecting threats in the environment. Sensory cues (such as tones or lights), as well as somatosensory stimuli such as shocks, can access the **lateral nucleus** of the amygdala directly from the periaqueductal gray (midbrain) and somatosensory thalamus, without requiring cortical processing (see Fig. 4). Tone and shock inputs converge onto single lateral nucleus neurons and become associated though **synaptic plasticity**. The lateral nucleus projects to the **basal nucleus**, which in turn projects the **central nucleus**, which is the main output structure of the amygdala. Projections to central nucleus are both direct and indirect through GABAergic intercalated cells, which inhibit output neurons of the central nucleus. Inhibition within the amygdala is extensive, serving to carefully control the expression of fear.

Fig. 2 Traumatic experiences such as the typhoon Haiyan in the Philippines (top) or armed conflict in Ethiopia (bottom) can produce intense fear reactions. In some individuals, this will lead to posttraumatic stress disorder, a prolonged illness related to fear conditioning (Both photos in public domain)

Central nucleus output neurons project to multiple areas that trigger behavioral and autonomic fear responses (see Fig. 5), including the **lateral hypothalamus** (for autonomic reactions), the paraventricular hypothalamus (for stress hormone release), and the **periaqueductal gray** in the midbrain area (for freezing responses). The fact that the amygdala receives direct inputs from the sensory thalamus, and sends direct outputs to fear-producing areas, makes it well positioned to respond rapidly to threats in our environment, even before we are consciously aware of them.
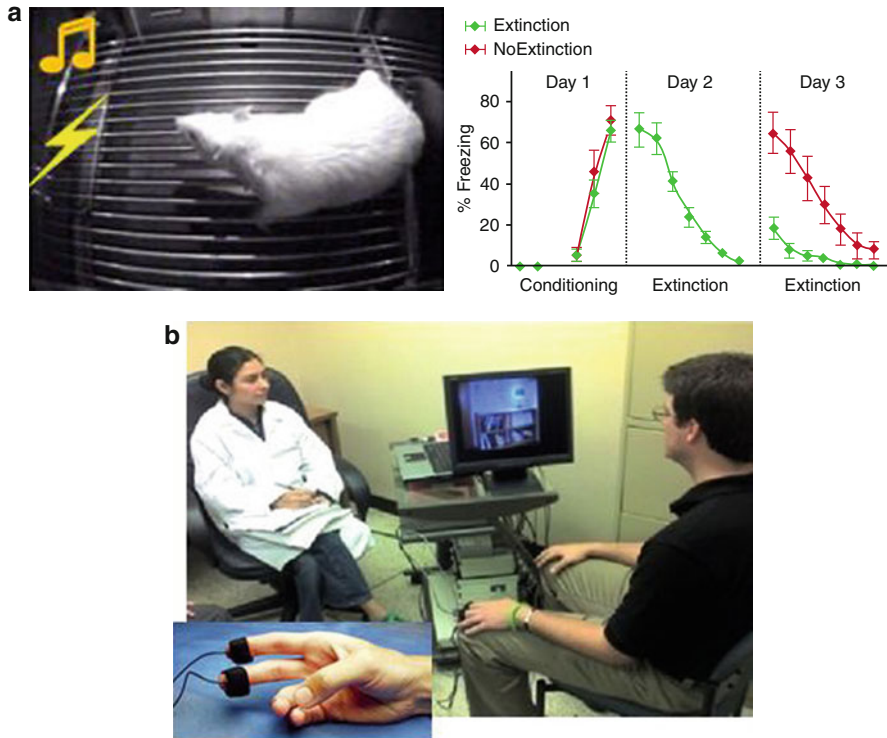
Fig. 3 Fear conditioning in rats and people. *Top*: rats exposed to a tone previously paired with a mild footshock express fear by freezing to the tone. *Bottom*: in human fear conditioning, a visual image on a monitor is paired with a mild shock to the fingers. As subjects learn that the image predicts the shock, the appearance of the image induces a mild sweating on their palms, as measured with the skin conductance response (*SCR*) (Photo of human fear conditioning from University of Puerto Rico)

Further control of the amygdala comes from inputs from the **medial prefrontal cortex** and **hippocampus** (see Fig. 6). The hippocampus processes contextual information, and its projections to basal nucleus allow shocks to be paired with contexts. The medial prefrontal cortex modulates amygdala output in extinction of conditioned fear (discussed below).

The Amygdala Is a Crucial Node in Fear Circuitry

The amygdala has become the focal point of research investigating the mechanisms of emotional learning. This is due to a number of factors, including the necessity of the amygdala for fear conditioning, its known inputs/outputs, and the increasing body of knowledge about the mechanisms of fear learning in the amygdala. Understanding the synaptic mechanisms in fear conditioning was facilitated with the
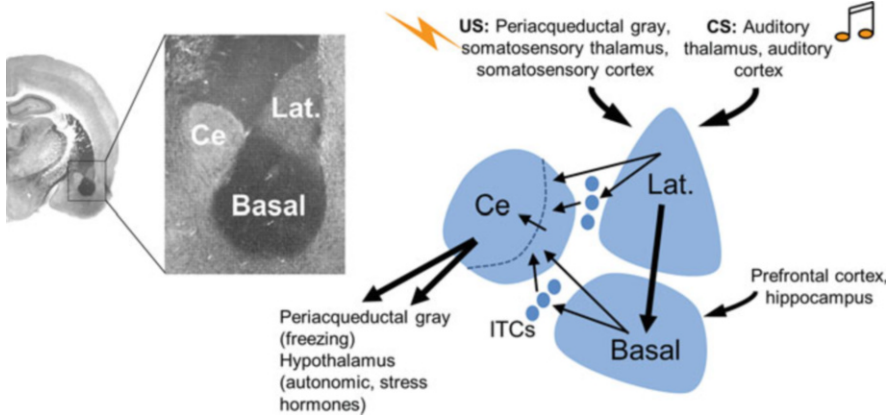
Fig. 4 Connections of the amygdala that support fear conditioning. Shown in rat brain with AChE staining, the amygdala consists of three main subdivisions. Shock (unconditioned stimulus, *US*) and tone (conditioned stimulus, *CS*) converge onto lateral nucleus neurons (*Lat.*), where they become associated via NMDA receptor-mediated synaptic plasticity. The lateral nucleus projects to basal (*Basal*) and central (*Ce*) nuclei, which communicates with lower areas that mediate fear responses. These connections are both direct and indirect through GABAergic intercalated cells (*ITC*), which inhibit Ce via projections to its lateral and medial subdivisions.
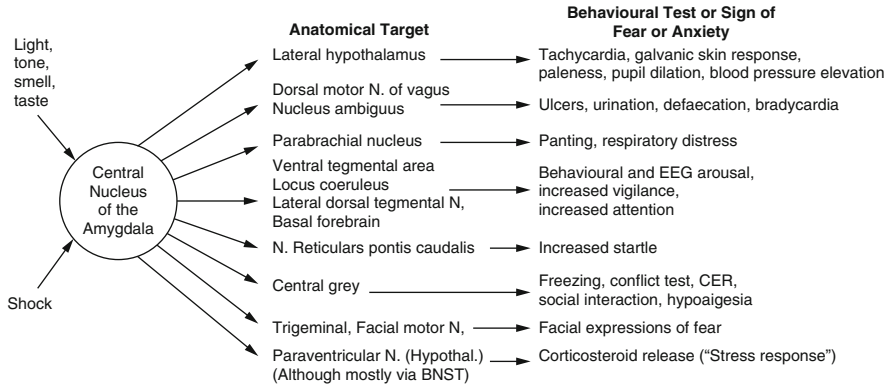
Fig. 5 The central nucleus of the amygdala projects to multiple areas of the hypothalamus and brain stem, each responsible for a different aspect of fear expression. The amygdala, therefore, can modulate all aspects of fear (From Davis chapter in The Amygdala, p. 214, second Ed., 2000, Oxford press)

development of an in vitro slice preparation in which amygdala neurons could be recorded from intracellularly while stimulating axons that originate in the **medial geniculate nucleus**, which transmit tone information to the lateral amygdala. These inputs exhibit **long-term potentiation**, in which high-frequency stimulation causes plasticity of synaptic responses (see ▶ Chap. 85, "Learning and Memory"). During fear conditioning, medial geniculate inputs become potentiated, so that subsequent
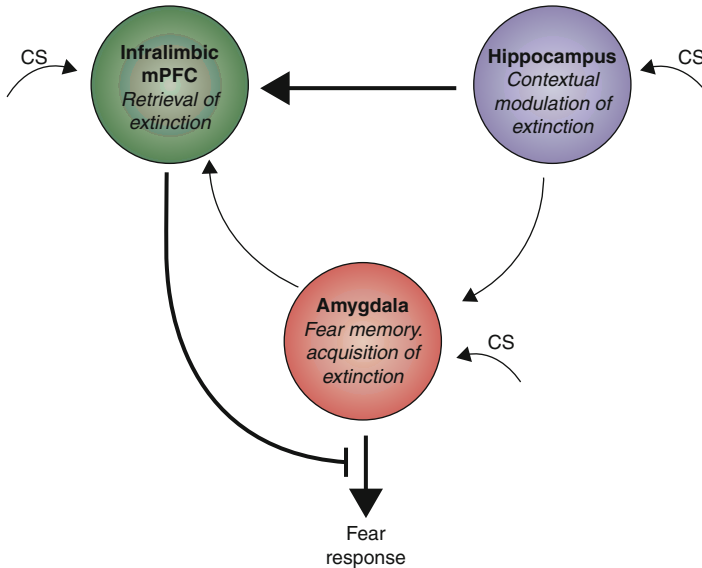
Fig. 6 The output of the amygdala is regulated by the prefrontal cortex (mPFC) and the hippocampus. In extinction of fear, the infralimbic mPFC strengthens inhibitory connections within the basal nucleus and ITCs, thereby facilitating the retrieval of extinction memories. The hippocampus gates the expression of extinction based on contextual information (Adapted from Maren and Quirk (2004) and Milad and Quirk (2012))

presentations of tones can more easily drive amygdala circuits to produce a fear response. Potentiation of amygdala synapses involves insertion of **AMPA-type** glutamate receptors into the dendritic spine, a process that is dependent upon calcium entry through **NMDA-type** glutamate receptors (see Fig. 7). NMDA-mediated calcium triggers a molecular cascade of **protein kinases** that phosphorylate AMPA receptors and other kinases. The short-term effects include translocation of AMPA receptors to the synapse, but longer-term effects involve activation of **transcription factors** leading to **translation** of new proteins. There are additional pathways involving structural changes such as actin polymerization and synaptic adhesion molecules. See Fig. 8 for more full description of synaptic plasticity processes in the lateral amygdala in fear conditioning.

One particularly well-studied transcription factor is cAMP/Ca(2+) response element-binding protein (**CREB**). Overexpressing CREB in lateral amygdala neurons activated by learning strengthens fear memory, while eliminating this same set of neurons eliminates the memory (in genetically engineered transgenic mice, see Fig. 9). In addition, "epigenetic" modifications of genes can alter fear conditioning. These include methylation of histone proteins that regulate gene transcription (see ▶ Chap. 76, "Epigenetic Mechanisms: DNA Methylation and Histone Protein Modification" by Gagnidze and Pfaff). Such epigenetic modifications can be passed on to offspring, raising the intriguing possibility of transgenerational communication of fear memories. Understanding the molecular basis of fear conditioning could lead to
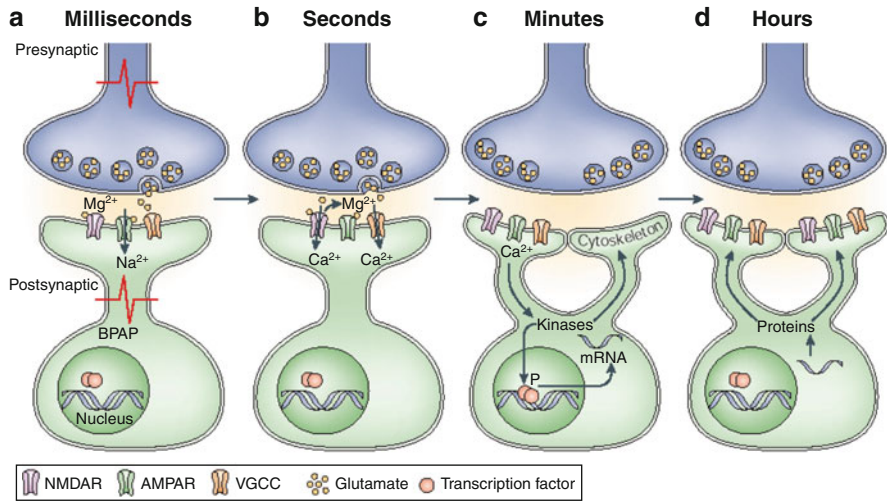
Fig. 7 Synaptic changes that occur in the lateral amygdala in the moments following fear conditioning. Glutamate released from synaptic vesicles binds to AMPA receptors, allowing sodium current to depolarize the dendritic spine. Depolarization unblocks NMDA channels, allowing calcium to enter. Calcium activates protein kinases, which leads to cytoskeleton changes (spine doubling) and also triggering of gene transcription factors (such as CREB) and translation, generating new proteins (e.g., receptors) (From Lamprecht and Ledoux 2004)

new pharmacotherapies to treat anxiety disorders or protect people at risk for developing anxiety disorders (such as emergency workers).

Regulating the Expression of Fear Memories

So short is love, and so long is forgetting,
– Pablo Neruda (Chilean, 1904–1973)

Like Neruda's love affair, fear memories are thought to be permanently stored in the brain, presumably to protect the organism from possible future encounters with potential threats. Fear memories are not always expressed and are subject to regulation by cortical areas. In addition, fear memories can change with the passage of time or become modified in light of new experiences.

Consolidation and Reconsolidation of Fear

Like other forms of learning, fear memories undergo a period of post-training **consolidation**, which stabilizes the newly formed memory through structural changes in the synapse. Interfering with this process by administering blockers of protein synthesis shortly after training (see above) leads to a permanent loss of the
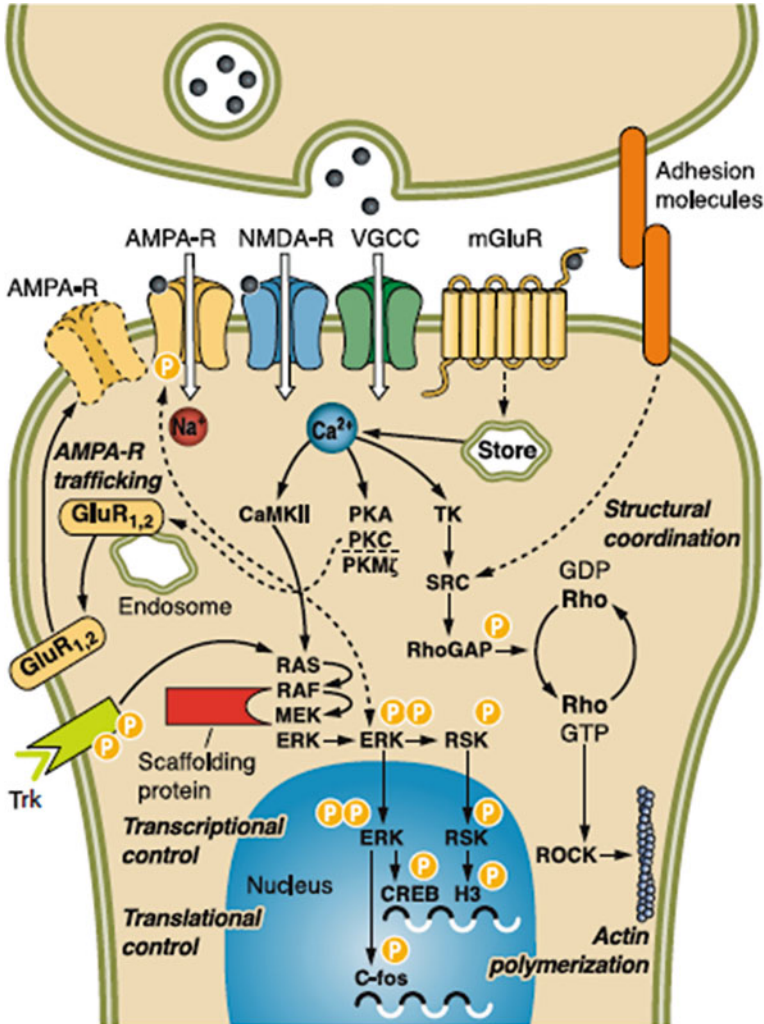
Fig. 8 Molecular cascades of fear memory stabilization in the amygdala. A postsynaptic increase in intracellular Ca2 concentration, mediated through Ca2 influx via NMDA receptors (*NMDA-R*) and voltage-gated Ca2 channels (*VGCCs*) and through release from intracellular stores upon activation of metabotropic glutamate receptors (mGluRs), triggers a large number of signaling steps. Three major, mutually interconnected signaling routes involve Ca2/calmodulin-dependent protein kinases II (CaMKII), the protein kinase (*PK*) family of enzymes, and tyrosine kinase (*TK*) pathways. Signaling cascades can reach the nucleus to induce macromolecular synthesis, and they can control translational processes. Consequently, they can act on cytoskeletal and adhesion molecules to reorganize and stabilize synaptic structures or regulate AMPA receptor (*AMPA-R*) trafficking to the synapse. At intermediate steps, protein kinase signals converge on the mitogen-activated protein kinase (*MAPK*) signal transduction pathways, including the extracellular regulated kinases (*ERK*). RAS, RAF, and MEK kinases transduce intra- and extracellular signals, mediated, for instance, through tyrosine receptor kinases (*Trk*), to the MAPK/ERK pathway. Scaffolding proteins dictate specificity of activation as well as entry in the nucleus. MAPKs translocated into the

memory. Once consolidated, however, fear memories are not static. Research in the last 15 years suggests that recalling a fear memory triggers a new wave of consolidation that is required to "re-store" the fear memory. Termed **reconsolidation**, this process involves many of the same molecular processes involved in the initial consolidation (see Fig. 10). For example, administering the protein synthesis inhibitor anisomycin into the amygdala of previously fear-conditioned rat, shortly after retrieving the memory with a tone, leads to erasure of the fear memory, presumably because reconsolidation of the fear memory was prevented from occurring. The loss of memory following reconsolidation blockade is specific to the memory that was retrieved, and anisomycin has no effect if retrieval was omitted. Reconsolidation has been demonstrated in a variety of species including humans, as well as a variety of types of memory. It is thought that reconsolidation allows for updating of the memory in light of newly learned information. Thus, memory is not static but is continually reformed and updated. There is the exciting possibility that anxiety disorders or addictions might be treated by triggering reactivation in a clinical setting and then blocking reconsolidation in order to erase the fear or addiction memories.

Extinction of Fear

Once an organism has learned that a stimulus predicts danger, repeated presentations of the stimulus in the absence of danger causes conditioned fear responses to **extinguish** (see Fig. 3a). Since the time of Pavlov, it has been known that extinction does not eliminate the CS-US association but inhibits the expression of the memory. Following extinction, fear responses can return with a change in context, a reminder shock, or simply the passage of time. Expression of amygdala-based fear memories is tightly regulated by inputs from the **infralimbic prefrontal cortex**, which project to inhibitory interneurons within the amygdala basolateral and central nuclei. The infralimbic cortex is activated in both rodents and humans during retrieval of extinction memory, as well as during acts of "courage" (see Figs. 6 and 11). Extinction of fear can be considered a form of "safety memory" that is learned and consolidated in a similar manner to fear conditioning, requiring NMDA receptors, protein kinases, and protein synthesis. Unlike fear memory, extinction memory is only expressed in the context in which extinction was learned, in other words "the tone is now safe in this place only." Context specificity of extinction is conferred by **hippocampal inputs** to both the prefrontal cortex and amygdala. Advances in the neuroscience of extinction are relevant for cognitive behavioral therapies (CBT) of certain anxiety disorders, which employ extinction techniques (see below).

Fig. 8 (continued) nucleus phosphorylate transcription factors, such as cAMP response element-binding protein (*CREB*). Actin rearrangement is under the control of Rho GTPases, whose activation from a GDP- to a GTP-bound form is controlled via Ca2 or kinase pathways, including tyrosine kinases (*TK*) and SRC kinases. Rho GTPases control activity of Rho-associated kinases (*ROCK*), a key molecule for regulation of the cytoskeleton (Adapted from Pape and Pare 2010)
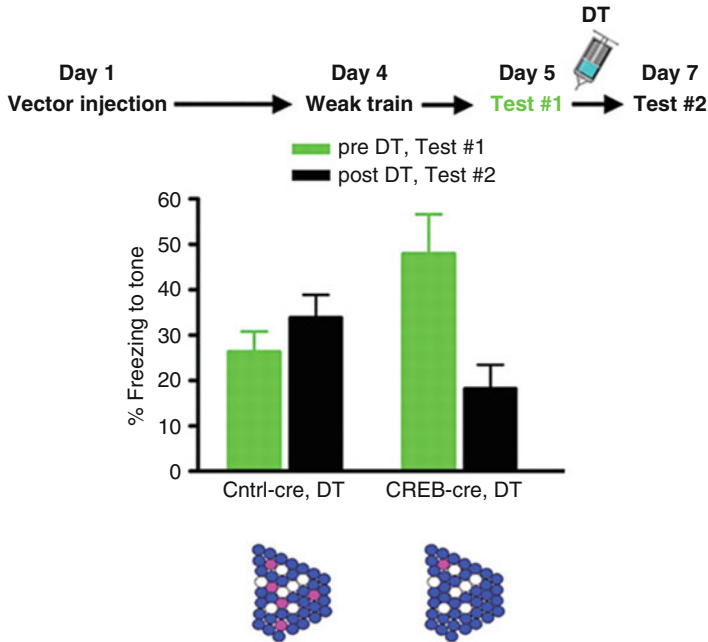
Fig. 9 Overexpressing the transcription factor CREB in lateral amygdala neurons enhances fear memory induced by weak training; subsequent ablation of these neurons reverses this enhancement. *Lower*: purple circles indicate CREB enhanced in neurons, which strengthened freezing (compare *green bars*). Deleting this same set of neurons (*white circles on right*) with diphtheria toxin (*DT*) eliminated the memory permanently (Adapted from Han et al. 2009)

Active Avoidance

Fear-conditioned responses can be thought of as a passive or automatic response to danger, such as freezing or changes in blood pressure. However, individuals can also respond actively by avoiding direct encounters with threats or by engaging in behaviors that decrease the likelihood of danger. These behaviors have been termed **active avoidance**, because, unlike passive fear conditioning, they involve a decision to engage in a specific behavior. Active avoidance learning is thought to occur in two stages: (1) a Pavlovian phase in which the CS (such as a tone) is associated with the US (such as a shock) and (2) an instrumental phase in which a specific behavior is associated with elimination of the CS and US. For example, in the shuttle avoidance task, a rat learns that it can move to an adjacent chamber when the tone occurs, thereby preventing the occurrence of a shock. As avoidance is learned, freezing to the tone dissipates because the rat learns that it can control the situation. For this reason, avoidance learning is adaptive and is an emerging focus of fear research. In expression of active avoidance, the amygdala communicates tone-shock associations to **prefrontal cortex** and **ventral striatum**, areas which mediate the behaviors of avoidance. The **infralimbic PFC** is responsible for inhibiting freezing during

Consolidation model:

Short-term memory (STM)

• Lasts for seconds to hours

• 'Labile' (sensitive to disruption)

• Does not require new
  RNA or protein synthesis

Long-term memory (LTM)

• Lasts for days to weeks

• Consolidated (insensitive
  to disruption)

• Does require new RNA
  or protein synthesis

**Re-consolidation
model:**

Active state (AS)

• Lasts for seconds to hours

• 'Labile' (sensitive to disruption)

(Does not require new
  RNA or protein synthesis)

Inactive state (IS)

• Lasts for days to weeks

• Inactive (insensitive
  to disruption)

(Does require new RNA
  or protein synthesis)

Fig. 10 (**a**) Traditional consolidation theory states that a single consolidation process occurs shortly after training to form a permanent memory. (**b**) In the reconsolidation model, reactivating a memory shifts it from an inactive state to an active state that is updated and restored in a protein synthesis-dependent process. Thus, memory maintenance is a dynamic process rather than static one (Adapted from Nader 2003)

avoidance training, as well as extinguishing avoidance behaviors when danger is no longer present.

Stress and Fear

Fear reactions are inherently stressful but are usually short-lived. The release of stress hormones such as **cortisol** and **noradrenaline** augments the body's physical response to danger. Moreover, acting through the amygdala, these hormones strengthen the consolidation of declarative (non-fear) memories of events surrounding the threatening episode. This is why everyone remembers where they were when,

Fig. 11 Fears can be overcome via extinction or conscious will. Madres del los Deseparacidos (Mothers of the Disappeared) in Honduras demonstrating against political repression in 1993 (Photo by G.J. Quirk) (*left*). fMRI activity showing brains of snake phobics who showed courage by approaching the snake (*right*). Approach movements were correlated with activity in the medial prefrontal cortex, an area implicated in extinction of fear (Adapted from Nili et al. 2010)

for example, airplanes struck the World Trade Center (or a national tragedy in your country). Chronic stressors however alter fear circuits in a way that predisposes animals toward high levels of fear (see ▶ Chap. 77, "Stress Research: Past, Present, and Future" by Kloet and Joels). Repeated daily exposure of rats to stressors such as restraint or loud noise increases **dendritic branching** and **spine number** in basolateral amygdala neurons, which increases subsequent fear conditioning (see Fig. 12). Furthermore, chronic stress reduces dendritic branching and spine number in the infralimbic prefrontal cortex and hippocampus, thereby impairing extinction and contextual modulation of fear, respectively. This leads to a viscous cycle of stress-induced dysregulation of fear responses. Some dendritic changes are reversed after stress ceases, but others are not. Researchers are examining ways to protect fear structures against stress's effects.

## Human Fear Circuits Resemble Those in Rodents

Because fear is evolutionarily conserved, it is not surprising that fear circuits in humans closely resemble the circuits studied in rodents. Naturally occurring lesions of the amygdala (due to a rare genetic disorder known as Urbach–Wiethe
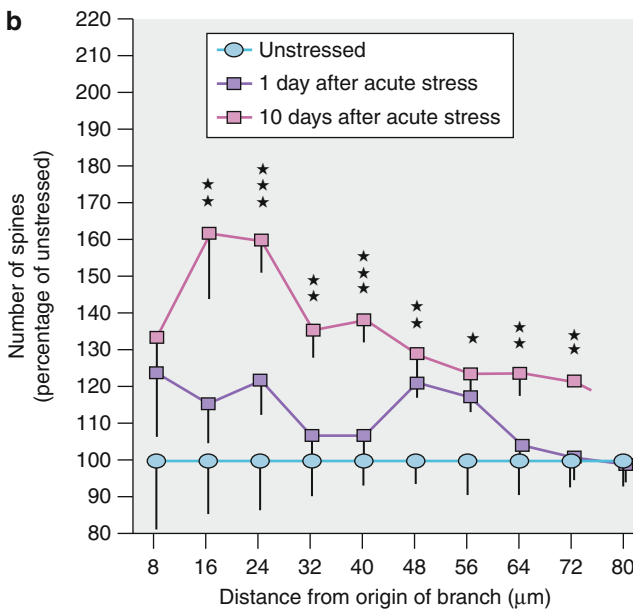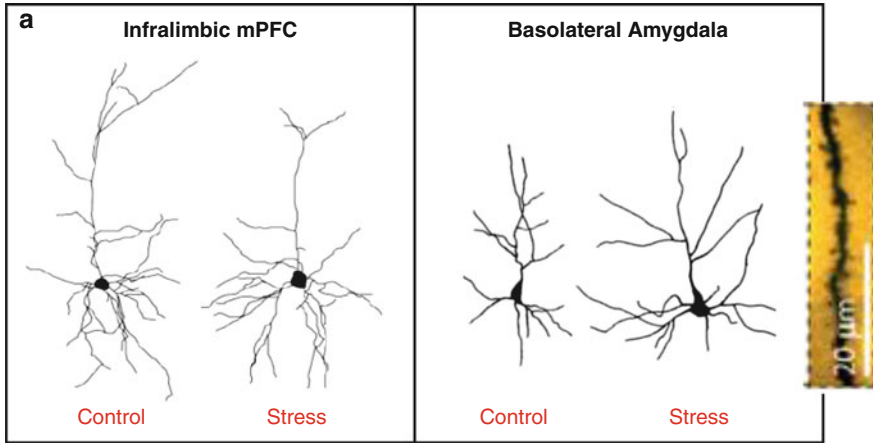
Fig. 12 Stress impacts dendrites differently in fear versus extinction circuits. (**a**) Chronic restraint stress in rats reduces the dendritic branching in the medial prefrontal cortex (*mPFC*) and hippocampus but has the opposite effect in the basolateral amygdala. (**b**) Acute stress also increases the number of dendritic spines (inset) in the basolateral amygdala. Thus, through these effects, chronic stress increases fear expression while at the same time impairing fear regulation (Adapted from Roozendahl et al. 2009)

disease) prevent fear conditioning in the laboratory, as evidenced by a failure to show elevated skin conductance response to the CS (see Fig. 13). Despite this, however, subjects with this disease are unimpaired in their ability to verbally state the CS-US association, an example of declarative memory. Whereas fear
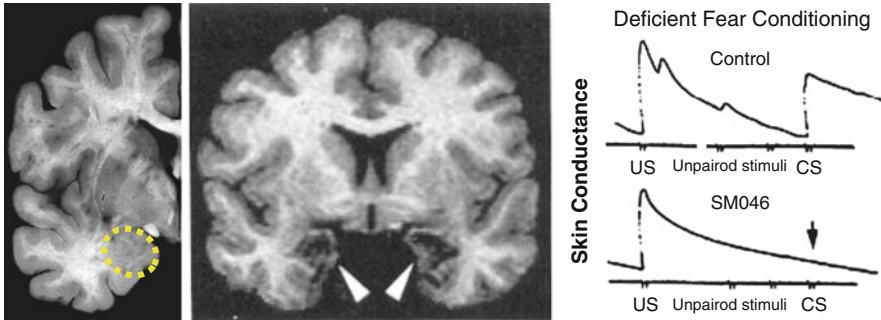
Fig. 13 The human amygdala is located in the most medial part of the temporal lobe (*yellow circle above*). Patient SM had a rare condition causing calcification of the amygdala bilaterally from an early age. During fear conditioning, she showed normal skin conductance increases to shock US but did not show skin responses to the conditioned stimulus (*CS*). She was, however, able to verbally state the CS-US association, indicating normal declarative memory (Adapted from Bechara et al. 1995)

conditioning is dependent on the amygdala, declarative memory depends on the hippocampus.

Functional magnetic resonance imaging (fMRI) has allowed researchers to measure human brain activity in a noninvasive manner. Similar to rodent findings, acquisition of fear conditioning activates the human amygdala, and extinction activates the prefrontal cortex and hippocampus. Faces are a particularly potent stimulus for activating the amygdala, because they communicate socially important cues. As might be expected from its role in danger detection, the amygdala responds particularly well to **fearful faces**. A fearful face need not be consciously perceived in order to activate the amygdala. Flashing a fearful face very briefly (e.g., for 20 ms) followed immediately by a neutral face for a longer time (e.g., 200 ms) results in most subjects reporting seeing only the neutral face. Fearful faces presented subliminally with this **backward masking** technique activate the amygdala as strongly as those presented overtly (see Fig. 14) and even elevate skin conductance. Thus, the amygdala activates fear outputs even before the subject is consciously aware of the stimulus.

Regulation of fear expression in humans is thought to involve prefrontal circuits similar to those in rodents. Activity within the dorsal anterior cingulate cortex (dACC) is positively correlated with fear conditioning, and dACC sends projections to the basolateral amygdala (similar to the prelimbic cortex in the rodent) (see Fig. 15a). Activity within the ventromedial prefrontal cortex (vmPFC) is positively correlated with extinction of conditioned fear (similar to infralimbic cortex in the rodent), and vmPFC projects to islands of inhibitory neurons within the amygdala, which inhibit amygdala output. The hippocampus also projects directly to the amygdala and prefrontal cortex. Thus, the human amygdala is regulated by cortical "gas and brake" inputs that can determine the appropriate time and place to exhibit conditioned fears.
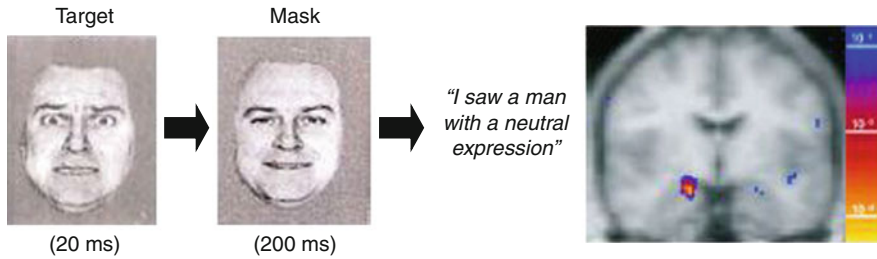
Fig. 14 The amygdala is activated by fearful faces. A fearful target face is flashed for a brief period (20 ms) followed immediately by a neutral mask face for 200 ms, in a procedure called backward masking. The mask interrupts processing of the target so that most subjects report seeing only the mask. Despite this, targets cause robust activation of the amygdala unilaterally. Thus, conscious awareness of danger is not a requirement for amygdala activation (Adapted from Whalen et al. 1998)

Clinical Applications of Fear Conditioning

Anxiety disorders are relatively common, affecting an estimated 18 % of adults in the USA in any given year. According to the current diagnostic manual for psychiatry in the USA (DSM-5), anxiety disorders include **specific phobia**, **panic disorder**, and **social anxiety disorder. Posttraumatic stress disorder** (PTSD) and **obsessive-compulsive disorder** (OCD) are now classified as distinct from the anxiety disorders but still involve high levels of anxiety and fear. PTSD, specific phobia, and panic disorder are thought to involve some degree of conditioning to cues that serve as triggers of anxiety. This is particularly true for PTSD which necessarily involves experiencing or witnessing a traumatic and potentially life-threatening event. However, only a minority of trauma-exposed individuals will develop PTSD. Thus, alterations in fear circuits may contribute to the development of disorders such as PTSD. In support of this, people with PTSD show elevated activity in the amygdala. Compared to trauma-exposed individuals without PTSD, individuals with PTSD were impaired in extinction of conditioned fear. Moreover, they showed reduced activity in the ventral medial prefrontal cortex and increased activity in the dACC, structures that regulate amygdala activity (see Fig. 15b).

While fear conditioning may contribute to the cause of anxiety disorders, extinction of fear may contribute to the cure of anxiety disorders. A standard **cognitive behavioral therapy** for most anxiety disorders is **prolonged exposure** (**PE**), in which the patient is repeatedly exposed to the cues that trigger their fear or anxiety. Performed in the controlled setting of the therapist's office over a period of 10–15 weeks, repeated exposure helps the patient **extinguish** fear responses and form new safe associations with the cues. Different methods of exposure can be used depending on the trigger for anxiety. For snake phobics, this may involve exposing the patient to a live snake. For war-related PTSD, this may involve verbally describing an incident or reading a script of the scene generated by the patient.
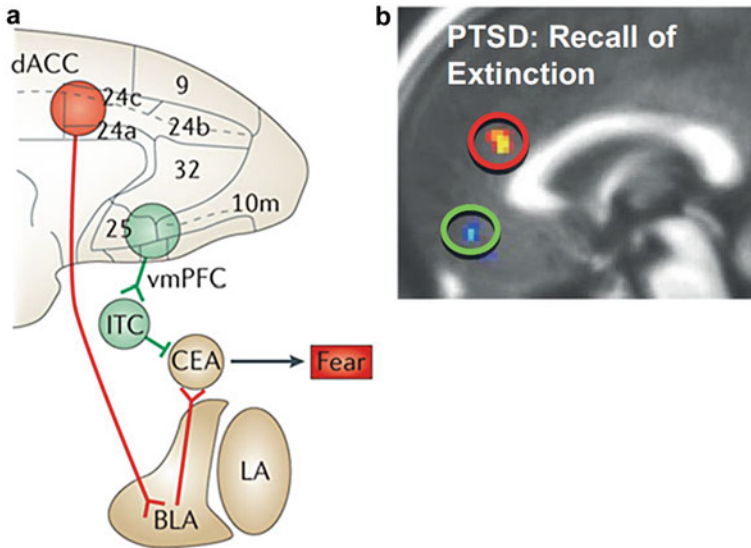
Fig. 15 Human homologues of rodent areas controlling expression of fear. (**a**) The dorsal anterior cingulate (*dACC*) cortex activates fear via projections to the basolateral amygdala (*BLA*), similar to the rodent prelimbic mPFC. The ventromedial prefrontal cortex (*vmPFC*) inhibits fear via projections to the intercalated (*ITC*) cells which inhibit central nucleus (*CEA*) outputs, similar to the rodent infralimbic cortex (Adapted from Pitman et al. 2012). (**b**) Subjects with PTSD are impaired in extinction of fear and show excessive activity in dACC and reduced activity in vmPFC (Adapted from Milad and Quirk 2012)

More recently, virtual reality has been used for exposure, which can be designed specifically around the patient's traumatic experience (see Fig. 16). An important objective of the neuroscience of fear is to provide new tools to facilitate exposure therapy. One such tool is D-**cycloserine**, an NMDA receptor partial agonist. When taken orally prior to an exposure session, it strengthens and accelerates extinction learning (an NMDA-dependent process, see above), thereby increasing the therapeutic effects. D-cycloserine has already shown promise for treatment of phobias, GAD, OCD, and social anxiety disorder. Research is underway to identify additional drugs or methods that can facilitate exposure-based therapies, such as hormones, growth factors, stimulation of the vagus nerve, and transcranial magnetic stimulation.

Rather than facilitate extinction, another approach to the treatment of anxiety disorders is to interfere with reconsolidation (see above). Similar to anisomycin in rodents, the noradrenergic receptor antagonist **propranolol** can interrupt reconsolidation in humans. Subjects who underwent propranolol-induced reconsolidation blockade lost their conditioned fear but not their declarative memory of the CS-US association. This suggests that future treatments aimed at reducing traumatic memories might leave autobiographical and event-related memories intact – a desirable outcome. Another emerging approach combines reconsolidation with
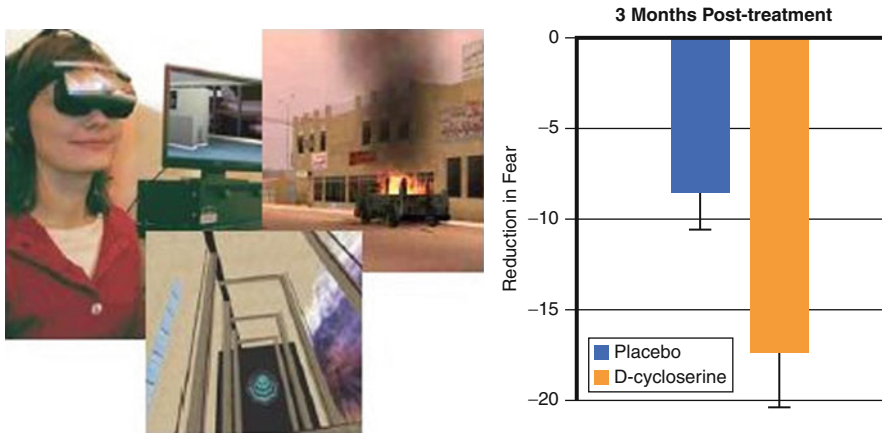
Fig. 16 Advances in cognitive behavioral therapy for anxiety disorders. Based on the principles of fear extinction, exposure therapies are employing virtual reality to depict battle scenes for PTSD or heights for acrophobia. Administering the NMDA receptor partial agonist D-cycloserine to height phobics during virtual reality increased the clinical gains up to 3 months later, presumably because this drug facilitates NMDA-mediated extinction learning (Adapted from Ressler et al. 2004 and Virtually Better (www.virtuallybetter.com)

extinction, by administering extinction training shortly after memory reactivation (when the memory is labile). The intention is to update the fear memory as safe. While this method is effective for erasing fear in animals and humans with experimental fear conditioning, it remains to be tested on people with anxiety disorders.

Another emerging trend is to identify **biomarkers** that can predict a person's susceptibility to develop an anxiety disorder. This is important given that only 15 % of trauma victims go on to develop PTSD. Examples of biomarkers related to anxiety disorders include detection of specific genes, behaviors (conditioned fear responses), bodily responses (salivary cortisol), and cerebral activity patterns (measured with fMRI or PET scans) that predict the development of such emotional disorders. Similarly, biomarkers might be able to predict the extent to which an individual will respond to a given pharmacological or cognitive therapy. For example, cognitive therapy for PTSD is less effective in individuals expressing the short allele of the serotonin transporter. The hope of biomarkers is that they will reduce the number of individuals who develop anxiety disorders and help to personalize therapy for those who do.

Outlook

Our understanding of fear has advanced rapidly in the past 20 years with a focus on the amygdala and related structures in fear conditioning. The next phase of research will dissect the amygdala circuits further using tools such as optogenetics (using light to activate specific subpopulations of neurons), combined with transgenic

manipulations. Increased attention will be given to inhibitory circuits within the central nucleus as a gate for expression-fear conditioning. The interaction of the amygdala with related structures in the prefrontal cortex, hippocampus, and midbrain will be further explored. Behavioral paradigms will move from Pavlovian fear conditioning to include avoidance paradigms, in which the animals must make decisions to avoid danger. Emerging areas include changes in fear conditioning and extinction across the life span and how fear information is socially transmitted between animals. The translation of rodent findings in fear to humans will accelerate. New biomarkers will be found that are capable of identifying people at high risk for anxiety disorders, so they can receive prophylactic treatments. Therapeutic approaches with reconsolidation and extinction will be combined with functional brain imaging to suggest new ways to "edit" fear memories.

References

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR (1995) Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 269(5227):1115–1118

Davis M (2000) The role of the amygdala in conditioned and unconditioned fear and anxiety. The Amygdala. J. P. Aggleton. Oxford, Oxford University Press: 213–288

Han JH, Kushner SA, Yiu AP, Hsiang HL, Buch T, Waisman A, Bontempi B, Neve RL, Frankland PW, Josselyn SA (2009) Selective erasure of a fear memory. Science 323:1492–1496

Lamprecht R, LeDoux J (2004) Structural plasticity and memory. Nat Rev Neurosci 5(1):45–54

LeDoux JE (2014) Coming to terms with fear. Proc Natl Acad Sci U S A 111:2871–2878

Maren S, Quirk GJ (2004) Neuronal signalling of fear memory. Nat Rev Neurosci 5:844–852

Milad MR, Quirk GJ (2012) Fear extinction as a model for translational neuroscience. Ann Rev Psychol 63:129–151

Nader K (2003) Memory traces unbound. Trends Neurosci 26(2):65–72

Nili U, Goldberg H, Weizman A, Dudai Y (2010) Fear thou not: activity of frontal and temporal circuits in moments of real-life courage. Neuron 66(6):949–962

Pape HC, Pare D (2010) Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear. Physiol Rev 90:419–463

Pavlov I (1927) Conditioned Reflexes. London, Oxford University Press

Pitman RK, Rasmusson AM, Koenen KC, Shin LM, Orr SP, Gilbertson MW, Milad MR, Liberzon I (2012) Biological studies of post-traumatic stress disorder. Nat Rev Neurosci 11:769–787

Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, Hodges L, Davis M (2004) Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch Gen Psychiatry 61(11):1136–1144

Roozendaal B, McEwen BS, Chattarji S (2009) Stress, memory and the amygdala. Nat Rev Neurosci 10(6):423–433

Whalen PJ, Rauch SL, Etcoff NL, McInerney SC, Lee MB, Jenike MA (1998) Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. J Neurosci 18(1):411–418