2 The Amygdala and the Neural Pathways of Fear

Jacek Dębiec and Joseph LeDoux

Contents

Abstract

Fear and anxiety are evolutionarily developed responses to perceived or anticipated threat. They involve behavioral, autonomic, and endocrine alterations aimed at increasing an organism's chances of survival. Excessive or uncontrolled fear and anxiety may lead to anxiety disorders. Animal and human studies indicate the critical role of the amygdala in adaptive and maladaptive fear. Recent advances elucidating the organization of the neural circuitry and molecular mechanisms of fear provide new insights in normal as well as pathological fear. In this chapter, we review the microcircuitry of the amygdala with a special emphasis on its relevance to fear processing and fear learning. We also discuss recent developments in understanding the basic molecular mechanism of fear. Finally, we address some of the implications of amygdala research for developing novel therapeutic approaches to maladaptive fear and anxiety.

INTRODUCTION

Research on neural mechanisms of fear and anxiety has advanced significantly in recent decades. Animal models have been particularly useful in characterizing the microanatomy as well as the cellular and molecular mechanisms of fear and anxiety. More recently, animal studies have been complemented by a growing body of human research, especially involving functional imaging. Both avenues of investigation point at the key role of the amygdala in processing fear.

Fear is a natural, evolutionarily developed response to environmental threats. It includes autonomic and endocrine changes supporting defensive behaviors, such as fighting, fleeing, or immobility (freezing). Physiological adjustments allow increased blood flow and energy supply to skeletal muscles and the brain. These alterations support actions aimed at increasing the organism's chances of survival. Information about natural threats have been evolutionarily hardwired into animal brains, which appear to selectively respond to relevant environmental factors, such as sights, sounds, or odors of common predators; specific social behaviors of conspecifics; and painful or intense stimuli (e.g., sound of thunder, etc.). These natural factors elicit innate fear. However, an individual has to learn through experience about a variety of other possible threats. While innate pre-programmed fear reactions are inherited, acquired fear responses result from a capacity of an organism to learn and remember cues associated with danger experienced throughout life. Whereas fear is considered to be a response to an actual danger and is typically triggered by specific stimuli, anxiety is a state of preparation for a predicted threat, which can be real or imaginary.

Maladaptive fear and anxiety occur in anxiety disorders. Although anxiety disorders may involve innate mechanisms that unfold during life, such as a tendency for extreme shyness *(1)*, fear learning contributes significantly to many anxiety pathologies *(2–6)*. Thus, defining neural networks as well as cellular and molecular pathways underlying fear learning is crucial for better understanding of pathogenesis of anxiety disorders and for development of new treatment approaches.

One of the most commonly and successfully used experimental models of fear learning is Pavlovian fear conditioning *(7)*. In this procedure, a neutral event (a conditioned stimulus, CS), such as tone, is paired with an aversive event (an unconditioned stimulus, US), such as a mild electric shock (Fig. 1) *(6,8,9)*. Once the CS and the US are paired, the CS acquires an ability to elicit behavioral, autonomic, and endocrine fear responses. These responses are expressed automatically on subsequent exposures to the CS. Fear conditioning has been observed in a variety of species, ranging from insects and worms to birds and mammals.

Animal studies using fear conditioning demonstrate a unique and powerful character of fear learning. First, fear conditioning occurs very quickly. Usually, a single pairing of the CS with the US is sufficient to establish a memory. Second, once learned, conditioned fear responses persist, often remaining throughout the
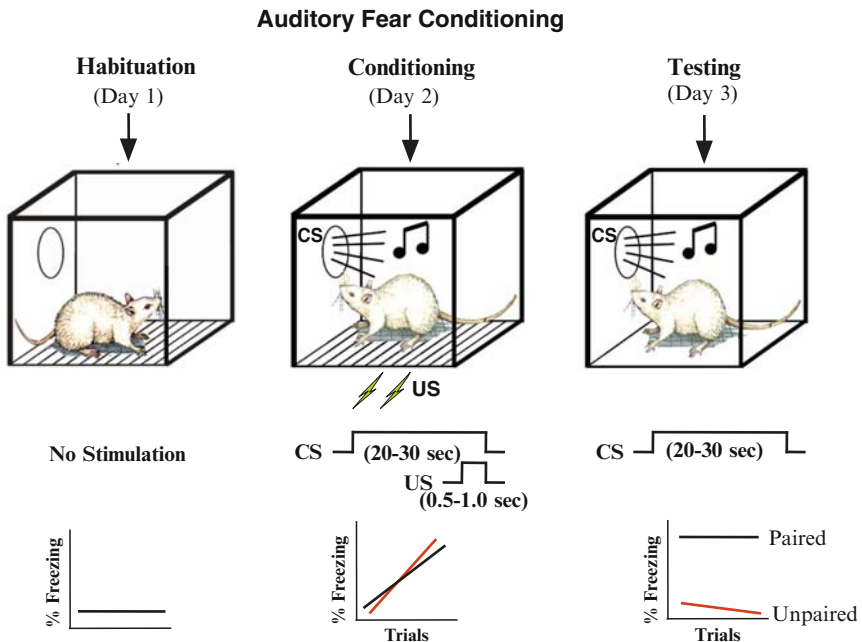
Auditory Fear Conditioning

Fig. 1. Auditory fear conditioning. In auditory fear conditioning, a neutral stimulus (conditioned stimulus, CS), such as tone, is paired with an aversive event (unconditioned stimulus, US), often a mild electric shock to the foot pads. As a consequence, subsequent presentations of the CS trigger fear responses, such as immobility or freezing

life of an organism. Third, defensive responses to stimuli previously associated with aversive events may weaken or extinguish through experiences that show that the CS no longer predicts harm. However, the original conditioning can frequently be recovered either spontaneously or as a result of a new stressful experience months or years after it has been extinguished. Fourth, fear motivates other kinds of behaviors, such as approach and avoidance. Avoidance can be adaptive, but in anxiety disorders avoidance often takes on a maladaptive role, with the patient successfully avoiding fear and anxiety but at the expense of failing to perform routine life roles.

THE INTRA-AMYGDALA MICROCIRCUITRY OF FEAR

The amygdala was named by the nineteenth century German anatomist Karl Burdach for the almond-like (in Greek almond: *amygdale*) shape of one of its subregions *(10)*. Although the amygdala is a complex structure involved in a variety of functions, overwhelming evidence shows the critical role of the amygdala in fear *(6,11–18)*, as well as in fear and anxiety pathologies *(19–22)*. The role of the amygdala in fear is ubiquitous in vertebrate species *(6)*.

The amygdala is located bilaterally deep inside the temporal lobe. It consists of several distinct groups of cells organized in nuclei *(23)* (Fig. 2). The regions
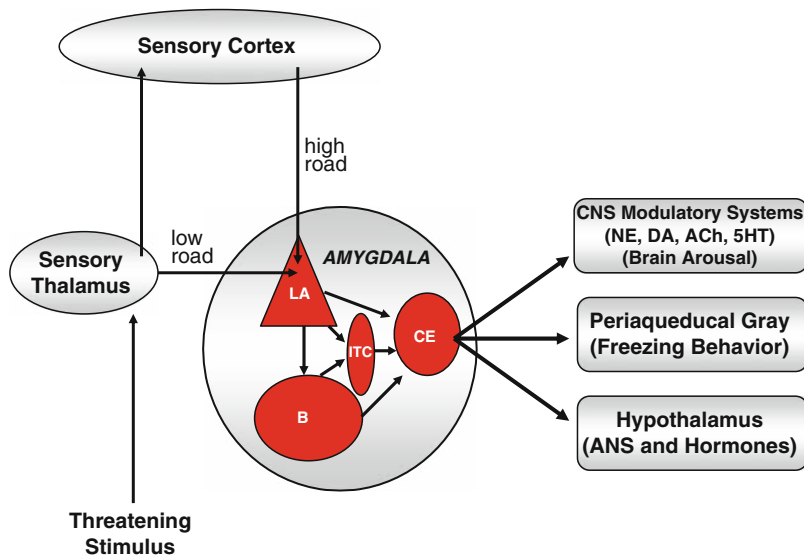
Fig. 2. Amygdala inputs, internal connections, and outputs. The amygdala consists of a group of nuclei. The nuclei most relevant to fear conditioning are the lateral (LA), basal (B), and central (CE) nuclei of the amygdala, as well as the subgroup of neurons known as intercalated cells (ITCs). The LA is the main sensory input area. It receives inputs from the thalamus and the cortex; thus, it is responsible for linking the CS with the US. The basal nucleus receives projections from the hippocampus and enthorhinal and polymodal associative cortices, areas that may convey information about the environmental context in which the fearful event is occurring. The CE is the common output area controlling expression of behavioral, autonomic, and endocrine fear responses. The LA is connected with the CE in direct and indirect (via the basal nucleus and the ITCs) ways. The ITCs have inhibitory control over the CE. Major identified neuromodulators involved in fear regulation include NE norepinephrine, DA dopamine, *ACh* acetylcholine, *5HT* 5-hydroxytryptophan (serotonin)

most relevant to fear conditioning are the lateral (LA), basal (B), and central (CE) nuclei, as well as a distinct subgroup of neurons known as the massa intercalata or intercalated cells (ITCs) *(6,18,23–26)*

The LA is considered to be a sensory gateway of the amygdala. It receives inputs from all sensory modalities, including visual, auditory, tactile, olfactory, and gustatory, as well as from fibers transmitting pain *(11)*. Although other amygdala nuclei also receive some sensory afferents, the LA is the main region where the sensory pathways converge. Studies using fear conditioning demonstrate that the LA is responsible for linking information about the neutral cue (CS) with that of the noxious stimulus (US). One of the most thoroughly investigated variants of fear conditioning is auditory fear conditioning, whereas a CS consists of a single tone. Fear conditioning studies reveal that auditory information reaches the LA through two distinct sensory inputs: thalamic and cortical *(6,11)*. The thalamic pathway conveys a rapid but imprecise auditory signal from extralemniscal areas, whereas the cortical pathway delivers a refined representation
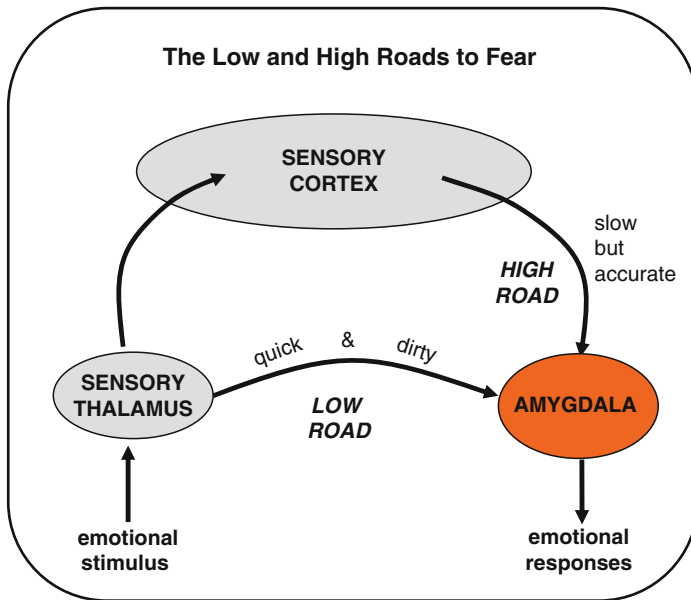
The Low and High Roads to Fear

SENSORY CORTEX

HIGH ROAD — slow but accurate

quick & dirty

SENSORY THALAMUS

LOW ROAD

AMYGDALA

emotional stimulus

emotional responses

Fig. 3. Two roads to fear. Sensory information reaches the LA (lateral nucleus) through two independent sensory inputs: The "low road" or thalamic pathway provides the amygdala with a rapid but imprecise signal, while the "high road" delivers a more complex and detailed representation derived from cortical association areas responsible in humans for conscious processing. The two-road model of signal transmission illustrates how fear responses can be initiated (by the direct low road) before we are aware of the eliciting stimulus

from associative cortices, which in humans are responsible for conscious processing. This last pathway, however, includes additional synaptic connections, which results in longer transmission. The "two-roads" model of signal transmission is used to illustrate how fear responses can be triggered (by thalamic road) before we are aware of the initiating stimulus (Fig. 3) *(6)*.

While the lateral nucleus is believed to be the main sensory gateway, the central nucleus is considered to be the major output region *(27–29)*. The CE projects to brain stem regions and through these projections controls expression of fear responses, including some behavioral responses, such as freezing, as well as autonomic and endocrine reactions. In addition, the CE is responsible for activating amine modulatory systems, such as adrenergic, serotonergic, dopaminergic, and cholinergic systems *(11,18,23)* (Fig. 2).

The major input and output amygdala regions, the lateral and the central nuclei, respectively, are connected through direct and indirect routes *(23,30)*. The indirect routes are believed to be major communication channels between the both nuclei and involve connections from LA to the basal nucleus and the ITCs, both of which project to CE. The basal nucleus also receives inputs from the hippocampus and entorhinal and polymodal associative cortices and delivers

information about the environmental context in which the threat is occurring *(23,24)*. In addition to fibers descending to the CE, the basal nucleus also projects to striatal areas. These outputs are believed to control instrumental behaviors *(23,31,32)*. The ITC network extends from the rostral amygdala to the anterior commissure *(33)* and consists of clusters of γ-aminobutyric acid (GABA) or GABA-ergic neurons. These neurons control the flow of activity from the LA and basal nucleus to the CE by way of forward inhibition *(34)*.

SYNAPTIC PLASTICITY AND ITS MOLECULES

Fear conditioning results in alterations in the strength of synaptic signaling in the amygdala (Fig. 4). Although synaptic plasticity occurs in other amygdala regions receiving some sensory inputs, such as the CE *(35)* and basal nucleus
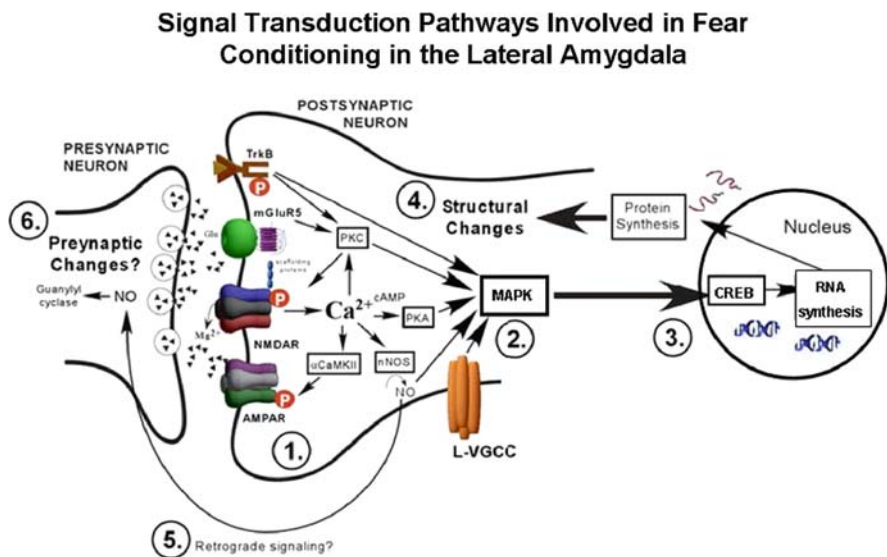

Fig. 4. Signal transduction pathways involved in fear conditioning in the lateral amygdala. Consolidation of fear conditioning is initiated by the activation of receptors at the postsynaptic neuron (1). This in turn triggers cascades of intracellular events that regulate the activity of mitogen-activated protein kinase (MAPK) (2). MAPK controls transcription factors, such as CREB (cyclic adenosine monophosphate response element-binding) proteins, which regulate transcription of certain genes (3). Gene activation leads to new RNA (ribonucleic acid) and new protein synthesis and thus structural changes in the postsynaptic neuron (4). Plausible mechanisms of retrograde signaling (5) from the postsynaptic neuron induce changes in the presynaptic neuron (6). cAMP cyclic adenosine monophosphate, NO nitric oxide, PKA protein kinase A, TrkB neurotrophic tyrosine kinase receptor 2, mGluR5 metabotropic glutamate 5 receptor, NMDR N-methyl D-aspartate receptor, AMPAR alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, PKC protein kinase C, CaMKII calcium/calmodulin-dependent protein kinase II, NOS nitric oxide system. L-VGCC L-type voltage-gated calcium channel

(36), the main site of synaptic changes underlying learning and memory is the LA *(13,24,25,37–41)*. The LA is a site where the CS and the US pathways converge. Most of the inputs projecting onto the amygdala are excitatory and release glutamate binding to NMDA (*N*-methyl D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors localized on principal neurons. These neurons in turn transmit the information to other amygdala regions.

The cellular hypothesis of fear conditioning posits that relatively weak CS inputs become strengthened by the cooccurrence of the US, which is capable of eliciting robust responses in the LA. The activation of postsynaptic NMDA receptors on principal neurons by the CS signaling pathways in the context of the strong depolarization by the US inputs triggers calcium influx *(42)* (Fig. 4). This initiates cascades of intracellular processes involving second messengers and protein kinases, which lead to activation of transcription factors, gene expression, new protein synthesis, and synaptic alterations *(24,37,39–41)* Newly synthesized proteins strengthen synaptic connections. For example, it has been demonstrated that fear conditioning stimulates trafficking of AMPA receptors to synapses in LA *(43)*. The insertion of new glutamatergic receptors increases the postsynaptic response elicited by presynaptic inputs.

Synaptic plasticity and learning in the amygdala are regulated by a variety of modulatory systems. Identified neuromodulators include the catecholamines noradrenaline *(44–46)* and dopamine *(47,48)* as well as glucocorticoids *(49,50)*, serotonin *(51)*, nitric oxide *(52)*, BDNF (brain-derived neurotrophic factor) *(53)*, endocannabinoids *(54)*, neuropeptide Y *(55,56)*, and others. These neuromodulators may facilitate changes on principal neurons or inhibitory GABA-ergic interneurons or both.

FEAR MEMORIES: THE QUESTION OF PERSISTENCE

Synaptic changes triggered by experience lead to the consolidation of the new learning. However, before consolidation is completed, interference with any of the stages of underlying intracellular events, from activation of the receptors to new protein synthesis, impairs the memory. According to the standard view of memory consolidation *(57)*, once synaptic alterations are stabilized, memories become immune to interference.

The standard memory consolidation model has been successfully used in clinical studies. For example, it is well established that noradrenergic signaling enhances learning, especially emotional learning *(57)*, and two pilot studies have demonstrated that administration of the β-adrenergic receptor antagonist propranolol shortly after trauma decreases the risk of post-traumatic stress disorder (PTSD) *(58,59)*

The traditional view of consolidation, that once memories are consolidated they persist in an unaltered state *(57)*, was first challenged by studies in the 1960s showing that reactivation of a consolidated memory through retrieval renders this memory susceptible to amnesic treatments *(60–62)*. Recent studies

Reconsolidation Processes Enable Modification of the Memory

Destabilization of Memory

(Re-)Consolidated   Memory
Memory Trace   Reconsolidation
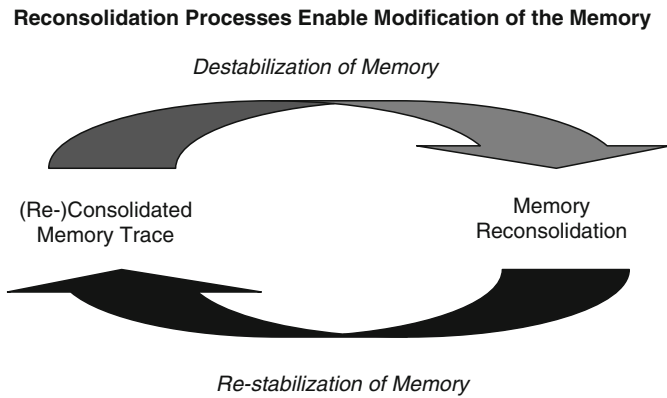
Re-stabilization of Memory

Fig. 5. Reconsolidation processes enable modification of the memory. Reactivation of the consolidated memory renders it labile and susceptible to interferences. This enables the modification of the existing memory trace by the circumstances accompanying the memory retrieval

ultimately challenged the consolidation theory, providing compelling evidence that memory reactivation triggers another round of synaptic plasticity, a phenomenon known as *memory reconsolidation* (Fig. 5) *(62–71)*. It has been demonstrated that reconsolidation of auditory fear conditioning in the LA involves NMDA receptor activation *(66,72)*, protein kinases *(73–75)*, expression of immediate early gene *Zif268 (76)*, and new protein synthesis *(63,77,78)* and is modulated by noradrenergic signaling *(45)*.

One of the implications of reconsolidation research is that even well-consolidated memories may be altered. In particular, a reconsolidation model may be helpful in developing new treatments of fear pathologies, such as PTSD or specific phobias *(62,65,69,70,79–81)*. Blocking reconsolidation may be helpful in attenuating learned fear responses and thus reducing the debilitating impact of traumatic experiences.

EXTINCTION OF FEAR: THE POWER OF CORRECTIVE EXPERIENCE

Learned fear responses may be attenuated by repeated exposure to the fear-arousing stimulus in a safe or neutral context *(82,83)*. This phenomenon, referred to as fear extinction, forms a theoretical basis of exposure therapies *(84–86)*. Extinction is a form of learning in which an organism learns that cues previously associated with a fearful event no longer predict danger. Extinction learning involves an interacting circuiting that includes the amygdala, medial prefrontal cortex, and the hippocampus *(87–96)*. Studies in humans have found involvement of the amygdala and prefrontal cortex in extinction *(97)*.

As a form of learning, extinction shares with fear conditioning similar molecular mechanisms. Specifically, glutamatergic signaling is required to initiate synaptic plasticity processes. Animal studies have demonstrated that enhancing glutamatergic stimulation by using the NMDA receptor agonist d-cycloserine facilitates extinction learning via the amygdala *(98)*. This was further applied in human studies showing that exposure therapy in conjunction with d-cycloserine facilitates fear extinction *(99–101)*.

ACTIVELY COPING WITH FEAR

Successfully extinguished fears often spontaneously recover or may be reinstated by a new traumatic event. Extinction learning is based on a passive exposure to fear-related stimuli. In contrast, a new study in rodents showed that active coping with fear may produce enduring reduction of fear. This new learning paradigm is referred to as *escape from fear* (102,103). In escape-from-fear learning, an organism learns to perform active behaviors that eliminate a fearful stimulus and thus reduce fear. The circuitry underlying escape-from-fear learning involves a circuit switch in the amygdala that, instead of transmitting signaling from the LA to the CE, directs information to the basal nucleus, which through its projections to the striatum and cortex controls actions *(14)*. A recent study in humans using an active coping task found evidence for the involvement of not only the same emotion regulation circuit as extinction—the amygdala and medial prefrontal cortex—but also the striatum (Schiller D, Cain CK, Kuhlman K, LeDoux JE, Phelps EA, unpublished data). One implication of these findings is that therapies actively engaging patients may produce more enduring effects *(104–106)*.

FROM ANIMAL TO HUMAN AMYGDALA

Recent studies using brain-imaging techniques have supported earlier animal research depicting the amygdala as a key structure involved in fear and anxiety (Fig. 6). The amygdala has been implied in adaptive fear *(97,107,108)* as well as in pathological fear and anxiety *(21,109–112)*. In particular, the amygdala has been implied in PTSD *(109–111)* and phobias *(112,113)*.

In addition, pharmacological approaches developed using animal models offer promising results in treating human fear and anxiety pathologies *(58,59,81, 99,101)*.

CONCLUSIONS

Recent studies significantly advanced our knowledge about the organization of neural circuits and cellular and molecular mechanisms underlying fear and fear learning. This has been accomplished in major part thanks to the use of animal models, which allow insights into the microcircuitry and molecular mechanism of fear. Animal research forms a foundation for further human studies and provides clues about possible future therapeutic approaches.
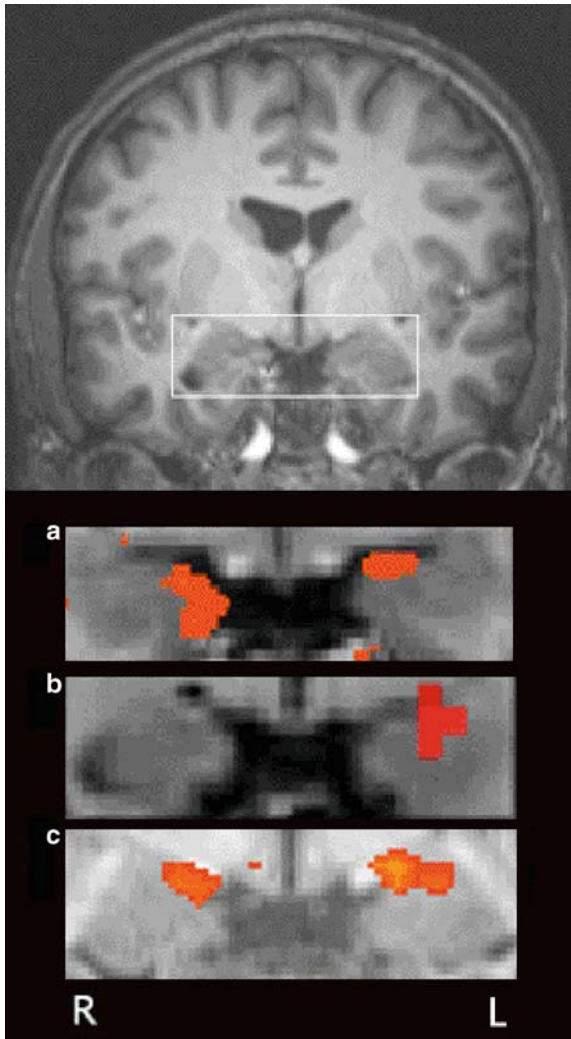
Fig. 6. Functional magnetic resonance imaging (fMRI) of fear learning in the human brain. *Top*: Structural magnetic resonance image (MRI) of the human brain (the box delineates an area containing the amygdala). **a** Conditioned fear: fMRI showing amygdala activation by the conditioned stimulus (CS) following pairing with the unconditioned stimulus (US). **b** Instructed fear: fMRI showing amygdala activation by a CS that was not directly paired with the US but instead the subjects were instructed about the US. **c** Observational fear learning: fMRI showing amygdala activation by a CS after the subjects observed someone else undergoing fear conditioning in which this CS was paired with a US. (Images provided by Elizabeth Phelps)

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