Learning, extinguishing, and renewing fear responses

Imperfect Memory

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Memories of fear are essentially records of the causative relationship between specific stimuli that induce emotions. Is eliminating memories of learned fear the only effective method of treating anxiety?

An individual's understanding of potential threats lying in wait for her/him is essential for survival. Danger is usually signaled by specific information, allowing the individual to prepare for it by selecting an appropriate defense response: avoiding the threat, taking flight from it, or fighting the antagonist if it is too late to escape. The physiological state leading to selecting one of these responses - learned fear - sometimes takes on a pathological form, which may lead to anxiety disorders such as phobias, panic attacks, and post-traumatic stress disorder (PTSD). Anxiety disorders affect approximately 10% of people at various stages of their lives, and constitute a major clinical problem. It is not clear what defines individual tendencies to developing pathological fear, since there is significant variation in the human population in this area. For example, having experienced a traumatic event (such as a natural disaster, war, rape) carries a risk of developing PTSD in approx. 15% of people. Although currently available therapies for anxiety disorders help many patients, there is a high risk of fear relapse. In order to create effective, personalized therapies it is necessary to learn about the brain mechanisms that underlie both learning (acquiring) and unlearning (extinguishing) fear responses.

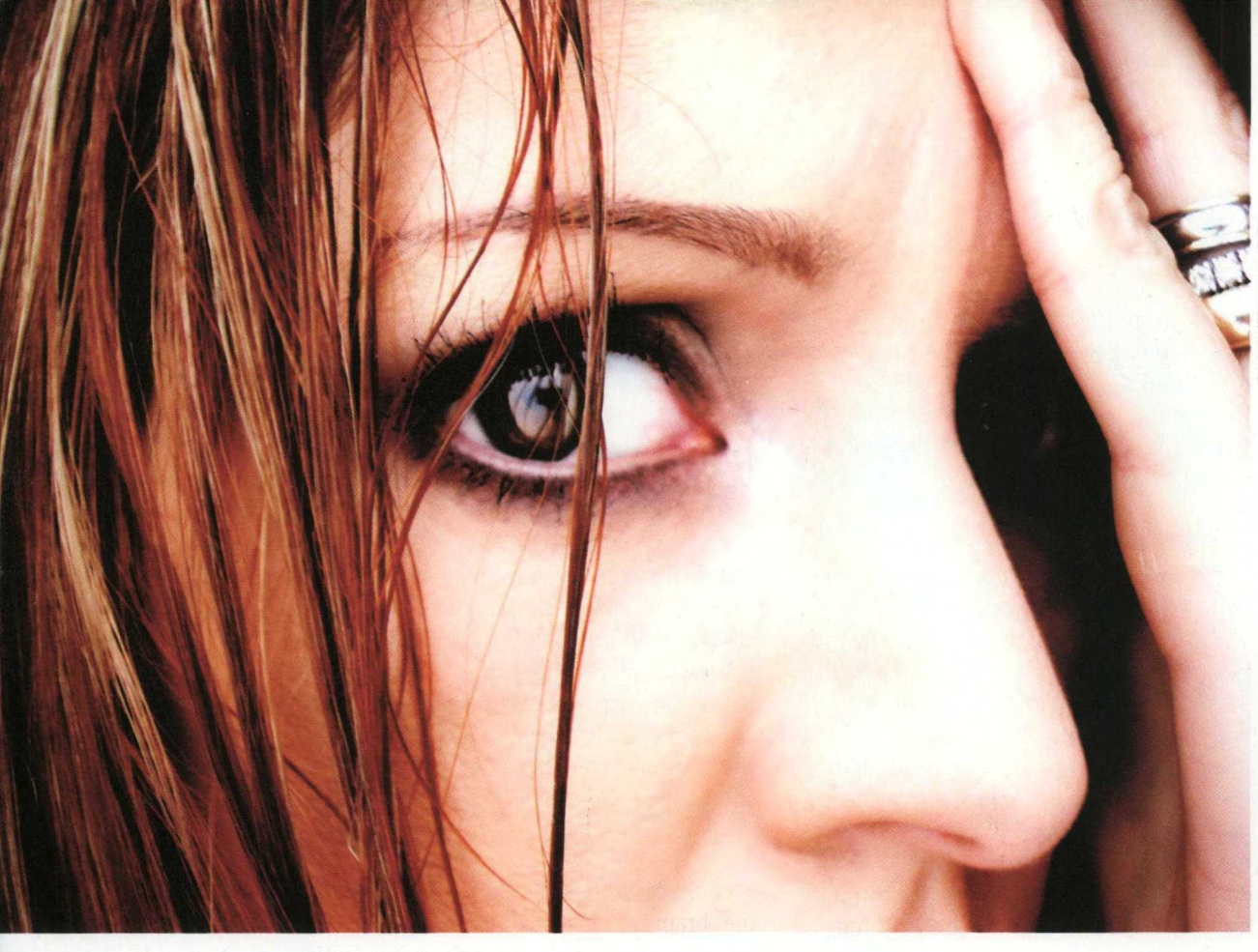
Kai Kusik-Greenbaum, www.sxc.hu

The brain structure(s) responsible for learning and expressing fear is the amygdala. In the conditioning and expression of fear, an important role is played by the lateral, basolateral, central, and intercalated nuclei of the amygdala

Learning fear

Memories of fear are essentially a relatively precise record of the causative relationship between specific stimuli that induce emotions. Fear responses are frequently triggered by a similarity between just some elements of a threatening situation that occurred in the past and the current one - this may trigger a fear response even if the context is quite different from the original situation. Fear may also be triggered not just by real stimuli but by the patient simply imagining such stimuli. Memories of fear are enduring, easy to recall, and difficult to eliminate.

Studies into the basis for fear responses in the brain are mainly carried out in rats and mice. Under laboratory conditions, learning fear involves creating an association between an initially neutral stimulus, such as a sound (conditioned stimulus), and an aversive stimulus of a major biological significance to which the animal naturally responds with fear, such as the delivery of a mild electric shock to the animal's paws (unconditioned stimulus). As a result of the newly formed association, the animal starts presenting a fear response to the conditioned stimulus even when it is not accompanied by the unconditioned stimulus. The fear response results in the formation



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Memories of fear are enduring and difficult to eliminate. A similarity to just some elements of a dangerous situation may be sufficient to trigger a fear response

of several vegetative symptoms, although usually what one observes in practice is just the freezing response - a natural defense mechanism in rodents manifesting itself as a period of watchful immobility, allowing the animal to hide from predators.

Controlled fear

In-depth research into the brain mechanisms involved in acquiring, consolidating, and expressing fear responses has been going on for the last 20 years. The principal element of the neuronal network responsible for learning fear and expressing responses to it is the amygdala. It is a small structure located deep within the medial temporal lobe of the brain, comprising several nuclei (groups of neurons of similar morphology and function) with distinct functional traits. It is known that the following nuclei play a role in conditioning and expressing fear responses: lateral (LA), basolateral (BL), central (CE, which includes the lateral - CEl - and the medial - CEm subdivisions), and intercalated groups of cells (ITC). Information reaches the amygdala via the LA, which transmits it further: either directly to the CEl and onto CEm, or indirectly via the BL and ITC to the CEm. In turn, the CEm transmits information by projections to various structures in the brainstem that control vegetative, secretory, and behavioral components of the fear response, such as increased heart rate and blood pressure, secretion of stress hormones, and the freezing response. Data indicates that associations between the conditioned and unconditioned stimuli are formed within the LA. The CE also plays an important role in expressing memories of fear. Recent studies show that the aversive stimulus removes the inhibition of the CEm by the CEl, and the activation of the CEm results in an expression of the fear response. It is also known that projections from the BL to the CE are essential for the expression of the fear response. Permanent changes to the intensity of connections between inhibitory neurons involved in learning (plastic changes), such as those within the ITC, are also believed to be important. The amygdala is also the location for storing memories of fear: removing a part of the LA and BL a year after conditioning a fear response in rats results in a complete elimination of the expression of the fear response to the specific stimulus previously responsible for triggering fear. The functioning of the amygdala is influenced by information from many other brain structures - the hippocampus, various parts of the cerebral cortex (e.g. the prefrontal cortex and the cingulate cortex), the thalamus, and the brainstem. Although many relationships in this complex neural network remain to be understood, there is a good amount of information on the role

played in controlling the fear response by its most important structure - the amygdala. This brings hope for developing specific therapeutic interventions aiming to effectively erase memories responsible for triggering pathological fear.

Unlearning fear

Anxiety disorders are mainly treated with cognitive behavioral therapy (CBT), which includes prolonged, controlled exposure to the stimulus that triggers fear. This allows the patients to get used to the subject of their fear, and reduces their response to it. Current therapeutical methods make increasing use of virtual reality approaches, which allows the patient to get closer and for longer periods to the objects or situations that trigger a fear response. This is effective in reducing fear triggered by spiders or elevator rides. However, fear that has been effectively mastered in one context (for example in a psychotherapist's consulting room) may suddenly reappear in a different context (for example out on the street) or return spontaneously over time. The phenomena of fear renewal and spontaneous recovery of fear indicate two important features of unlearning fear responses. First, fear extinction is an active learning process and involves modifying an existing memory trace rather than erasing it. Second, in contrast to learning fear, extinguishing fear responses strongly depends on the context, which means that fear is effectively suppressed only under conditions similar to those during the therapy sessions. These properties of fear extinction significantly hinder attempts to devise effective therapies to treat anxiety disorders.

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Dreamstime, użyczenie Anna Pietruszka-Dróżdż

In laboratory studies the basic model for CBT used in the treatment of anxiety disorders is fear extinction. The process involves repeated presentations of the conditioned stimulus not accompanied by the unconditioned stimulus. This way the conditioned fear response may be reduced or even eliminated. In this model, changing the experimental context (in practice the appearance of the experimental cage) leads to the renewal of the previously extinguished fear response. Using a suitable time delay between fear extinction and testing the response to the stimulus which previously caused fear also allows researchers to model the spontaneous recovery of the fear response.

Suppressing fear

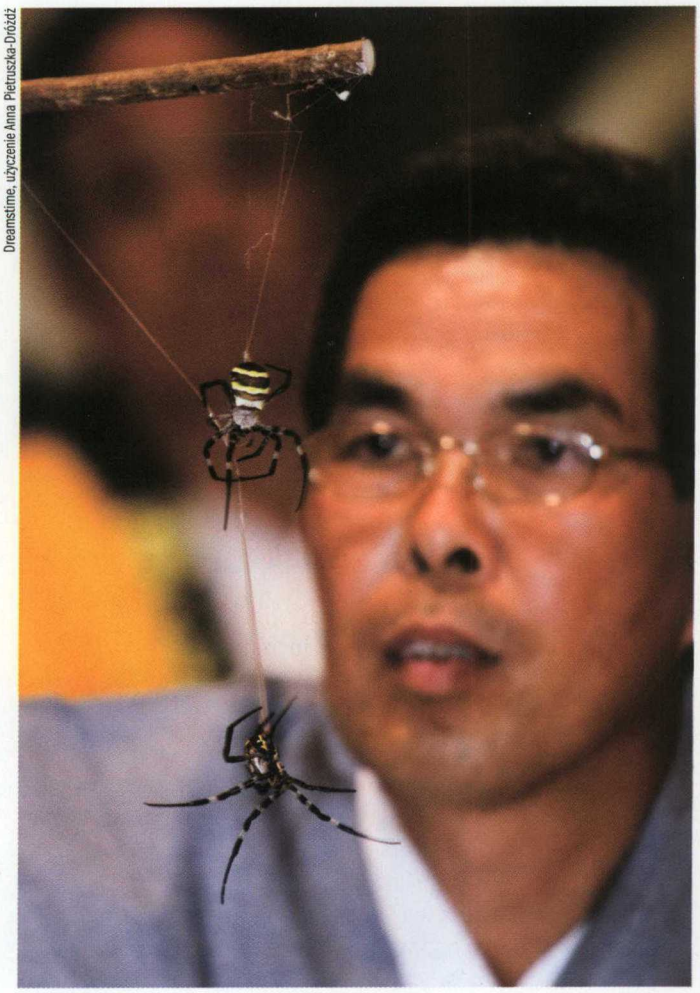
While the mechanisms of acquiring and expressing fear responses have been studied in detail, we have a much poorer understanding of the mechanisms underlying fear extinction and the processes that cause previously extinguished fear responses to return. It is known that the LA and BL nuclei are essential in fear extinction. The fact that a previously extinguished fear response may reappear suggests that both memory traces - those concerning the stimuli that trigger fear and the memory of the extinguished fear response triggered by those stimuli - exist in parallel, and it will be the context that decides which one will be called up at a given time. Context information is controlled by the prefrontal cortex and the hippocampus. The prefrontal cortex includes two regions with distinct functions - an increase in the activity of the infralimbic (IL) region leads to the recollection of the extinguished fear memory, while an increase in the activity of the prelimbic (PRL) region results in the reactivation of the fear memory.

Recent research indicates that changes in an animal's behavior, corresponding to low and high fear levels in an extinguished and renewed response, respectively, are related to changes in the stimulation in two separate neuronal populations in the BL. These populations are characterized by different connections with the prefrontal cortex and the hippocampus. Our research used c-Fos protein expression for brain

activity imaging (the protein regulates the activity of various genes playing a role of a coordinator of complex cellular function in active neurons), which allows for simultaneous imaging of the activity of several brain structures with resolution at cellular levels. We have shown that fear extinction and renewal largely involve different neuronal networks within the prefrontal cortex, the amygdala and the hippocampus. Recently, we have also studied the relative share of projections from the IL and PRL regions of the prefrontal cortex and the hippocampus on neurons within the amygdala that are activated during fear extinction and renewal. The results obtained indicate the presence of two discrete populations of neurons in the LA involved in retrieval of extinguished fear and contextually driven renewal of fear. These subpopulations can be distinguished through their different connections with the IL and PRL regions of the prefrontal cortex and the ventral part (IL) of the hippocampus.

Curing fear

Eliminating memory traces of dangerous situations linked with learned fear responses (as in the film "Eternal Sunshine of the Spotless Mind," where a team of technicians simply erases the client's specific memories on request and for a fee) seems the only foolproof method of eradicating anxiety disorders. However, the concept remains in the realm of fiction for now, since its execution would require an understanding of the functioning of the entire brain on an individual neuron level. In the meantime there are other methods of intervention - for example pharmacological - in the processes controlling retrieval of extinguished fear memories. Recent experimental therapeutic attempts have focused on pharmacological enhancement of the fear extinction processes using compounds such as D-cycloserine, yohimbine and prazosin. However, the effectiveness of such interventions remains low, it is only applicable to certain disorders, and in some cases it can even exacerbate the disorder, which may be due to high variability between individuals in terms of extinguishing fear responses. Due to our modest understanding of the process of renewal of fear responses, the therapeutic potential of intervening in the course of such responses remains unknown. It may be broadly speculated that the deterioration of certain aspects of brain function (resulting in the reappearance of fear responses) may be technically simpler than improving results during fear extinction. In any case intervention in the reappearance of fear responses as a therapy for anxiety disorders remains but a dream. However, due to the limited effectiveness of other therapies, its potential should be investigated - and the first step along the way should be gaining an in-depth understanding of the basis of the renewal of fear responses. ■



Dreamstime, użyczenie Anna Pietruszka-Dróżdż

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Further reading:

Knapska E., Maren S. (2009). Reciprocal patterns of c-Fos expression in the medial prefrontal cortex and amygdala after extinction and renewal of conditioned fear. *Lear Mem.*, 16(8), 486-93.

Maren S. (2011). Seeking a spotless mind: extinction, deconsolidation, and erasure of fear memory. *Neuron*, 70(05),830-45.