How Scary Things Get That Way

Researchers are closing in on the mechanisms by which the brain learns to interpret certain situations as fearful—with hopeful indications for anxiety sufferers

You come home at night and find your front door wide open and the house dark. Warily, you enter, heart pounding, mouth dry. Expecting to find a knife-wielding intruder around any corner, you jump out of your skin when the cat brushes by your legs. Half an hour later, with the lights on, the doors locked, and the house found to be empty and undisturbed, your heart rate has slowed, and the cat's touch is familiar and comforting.

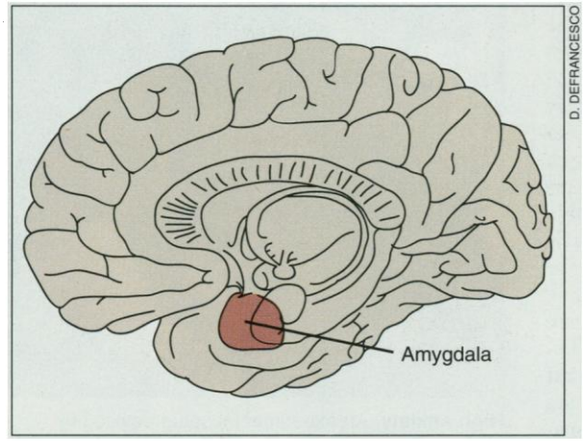
If you have ever been in a predicament like this one—and everyone has—you were experiencing "learned fear." That is, the situation doesn't contain anything that is intrinsically threatening, yet it's bristling with signs we have learned to associate with danger. The brain responds to those signs by revving up the body's systems into an energized state.

For the past decade, a handful of research laboratories have been probing the brain mechanisms that underlie this kind of learning. As several intriguing presentations at a recent Cold Spring Harbor meeting on learning and memory* made clear, they are closing in on how the process works. And, by understanding the phenomenon, they hope to gain insight into how it goes awry—for example in the case of people with generalized anxiety, who find themselves in a heart-pounding state of panic even when the house is safe and secure, or the Vietnam veterans whose post-traumatic stress causes something as commonplace as the smell of Chinese food or the sound of a helicopter to throw them into paroxysms of terror.

The key to fear learning seems to be a small structure deep in the brain called the amygdala, which appears to be capable of linking a variety of emotions—including fear—to certain memories or situations. Remove a rat's amygdala, for example, and the benighted creature, bereft of its all-important sense of fear, will walk up to a sleeping cat, and even nibble on its ear. Stimulate the amygdala of an epilepsy patient during brain surgery, on the other hand, and he will report a surge in anxiety not produced by tweaking other parts of his brain.

None of this evidence implies that the amygdala is where memories are made or stored—but it does seem to be where they get their emotional clout, says University of California, Irvine, neuroscientist James McGough: "If I say today is Friday, you will probably remember that....But if I say today is Friday and it is the last day of your life, you'd certainly pay attention to that. My view is that the amygdala got excited when I said that to you, and it plays a role in influencing the storage of that information. It gives it some weight." And fear-charged memories are among the weightiest of all, says Michael Davis, who studies fear learning at Yale. "If you touch a scalding radiator when you are 3 years old, you never touch a radiator again." There must be "very profound" changes in the brain, he adds, to create such lasting associations.

Participants at the Cold Spring Harbor meeting heard Davis and Joseph LeDoux of New York University (NYU), key players in the field, talk about how animal models—including rats, rabbits, and mice—are shedding light on the formation of fearful memories. Davis, LeDoux, and the others working in this area use an approach in which the animal is taught to associate a signal, such as a tone or light, with an unpleasant stimulus, such as a shock. After that conditioning, the animal's state of fear in response to the signal is measured by such things as a change in heart rate, jumpiness, or a tendency to freeze in place. The experimenters can then use drugs, electrical stimulation, or surgery to alter the animals' brains, and see how those changes affect the learned fear.



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Fearful symmetry. In the amygdala, "fear learning" takes place as stimuli are endowed with anxious overtones.

In the late 1970s, Bruce Kapp of the University of Vermont began using this approach to track the neural circuitry important to fear learning. Kapp worked with rabbits, and as a sign of fear he monitored their heart rates, which paradoxically slow down in frightening situations. Kapp's rabbits would hear a tone on a loudspeaker, then get a shock from the metal floors of their cages. After a short time, when the rabbits heard the tones their heart rates slowed, signaling anticipation of the shock. "The animal is learning that the tone predicts the occurrence of this uncomfortable tingling," says Kapp.

Kapp's group found, however, that if they damaged part of the amygdala, the rabbits no longer showed the learned-fear response. In other experiments, they trained the rabbits to distinguish between a tone that preceded a shock and one that didn't. The researchers found that rabbits' hearts slowed only when they heard the tone that had been coupled to the shock—and they were able to identify neurons in the amygdala that fired specifically in response to that tone. The neurons only increased their firing after the animal was trained to associate the tone with the shock, indicating that something was changing in the amygdala as the rabbit learned to anticipate the shock.

But what? The complete answer isn't in yet, but some findings suggest the amygdala-based change is a familiar phenomenon called long-term potentiation, or LTP, which has been studied in another brain structure associated with learning: the hippocampus. Several years ago, Paul Chapman, then a postdoc with Tom Brown at Yale, found that LTP, which is a form of strengthening of neural connections, could be experimentally triggered in slices of amygdala; LeDoux's group showed the same effect in whole animals. Now Davis and his colleagues at Yale have shown that just as infusions of an LTP-blocking drug into a rat's hippocampus will block hippocampus-based learning, infusion of the same drug into the amygdala blocks fear learning.

But creating associations between certain situations and deep-rooted anxiety is only part of the amygdala's role in fear learning. It also has to get that fearful message out to the rest of the body. And a complex physiological message it is. Frightened animals and humans share symptoms ranging from diarrhea to jumpiness and shortness of breath. Over the past decade, researchers have found that

*"Learning and Memory," Cold Spring Harbor, 30 September to 4 October 1992.

the amygdala is indeed wired to all the parts of the brain needed to produce this gamut of fearful behaviors. "The anatomy is known on the output side," says Davis. "Evolution has hardwired in all the connections between the central nucleus of the amygdala and all these target areas that are involved in the specific signs and symptoms of fear."

Finding the wiring on the output side leaves researchers the task of understanding the incoming wiring—the neurons that bring in the information needed for the amygdala to form its angst-ridden connections. LeDoux and his colleagues at NYU have been unraveling that story. The NYU researchers trained rats to expect a shock when they hear a tone, and then traced the neural pathways by which news of the tone reaches the amygdala. They got a shock themselves: It was not the expected route.

Taking a direct route

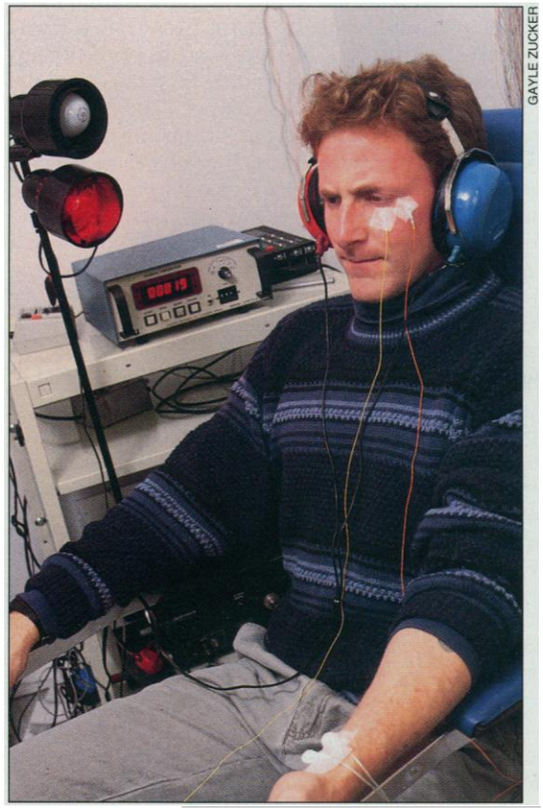
Common wisdom says all nerve impulses carrying sound sensations go through a processing area called the auditory cortex before being shunted off to other sites such as the amygdala. But LeDoux's team found they could destroy the entire auditory cortex, yet the rats would still learn to be fearful of the tone. It turned out that the information was taking a direct route from ear to amygdala, traveling through the brain's lower auditory segments but skipping higher level processing. The unprocessed information can't be very detailed, says LeDoux, but for the purpose of providing a warning it is probably sufficient. "You don't need to know exactly what something is to know that it may be dangerous," he notes.

Not all of the inputs to the amygdala are so direct. Russell Phillips, a student with LeDoux, found that the cues that make the rat afraid of the cage where it gets shocked are processed in the hippocampus—a site of spatial learning—before reaching the amygdala.

Besides the sensory inputs to the amygdala, LeDoux has investigated other inputs, some of which seem to play a role in the "unlearning" of fear associations that are no longer relevant—a very important process, according to Davis. "Clinically, one of the most interesting questions is how do you inhibit fear?" Davis says. "The real problem for people with anxiety disorders seems to be that they cannot turn off or inhibit their anxiety."

LeDoux's group is using the same basic experimental setup—with a different twist—to test the unlearning of fearsome associations. In this case, once the rat is trained to associate the tone with a shock, the experimenters begin to play the tone without the shock. As the rat repeatedly hears the tone, but never gets a shock, it gradually becomes less fearful. This unlearning seems to depend not just on the amygdala but also on a part of the prefrontal cortex of the brain, according to work presented at Cold Spring Harbor by graduate student Maria Morgan of LeDoux's group. After damaging an area in the prefrontal cortex, Morgan found that the rats continued to react fearfully to the tone for nearly twice as long as their peers with intact brains.

Davis says this type of animal study could improve the understanding of human anxiety disorders and might even lead to better tailored treatments. For example, he says, one type of anxiety disorder may be due to an amygdala that is chronically revved up, even in the absence of any danger, while another may come from an inability to turn down the amygdala when a frightening situation no longer represents a threat. "You can imagine that there would be very different brain systems involved," says Davis.



GAYLE ZUCKER

High anxiety. An experimental setup devised by Michael Davis and Christian Grillon of Yale to measure fear learning in human subjects.

To begin to try to analyze human anxiety disorders, Davis and Christian Grillon, also of Yale, developed a human fear-learning test analogous to those used on rats. Human subjects are seated in front of a board with a red and a green light, and a device is strapped to one wrist from which, they are told, they can expect a painful shock at some time while the red light is on. The longer the red light is on, they are told, the greater the chance of a shock—and the stronger the shock will be. When the green light is on, they are assured, they will not be shocked.

At several times in the test, the subjects are startled with a sudden noise, and the degree of their startle response is measured by how hard they blink their eyes. Not surprising, says Davis, "the amplitude of the startle gets progressively larger the longer the red light is on. As soon as the green light, which is their safety signal, comes on, the startle goes right down."

But that's not the case in patients with anxiety disorders. Though the results are preliminary, Davis says, he and Grillon already have some intriguing findings in patients with post-traumatic stress syndrome. Tested in a laboratory where they have never been told they would be shocked, these patients have a normal startle response. But once in a lab where they expect a shock, they have an exaggerated startle response—and the response can't be turned off normally. "Even though the instructions say that when the green light comes on you definitely won't get a shock," says Davis, "they are not appropriately responding to that safety signal. They feel like they are at risk all the time."

Such experiments could lead the way to new and more specific treatments for such types of anxiety, says Davis. For example, if an inability to turn off fear turns out to be a key in post-traumatic stress, that might suggest that people with the syndrome have a problem in the areas of their prefrontal cortex that seem to be involved in that turning off. "Maybe drugs that would activate those areas would be particularly selective anxiolytic compounds," Davis posits.

Although clinical payoffs are still in the future, University of California, San Diego, neuroscientist Larry Squire, co-organizer of the Cold Spring Harbor meeting, has high praise for the work that's untangling the biology of fear learning and unlearning. "It's another case of the triumph of modern neuroscience," he says, "a long-term research program that has developed into a full-bodied story." And the body in question, remarkably enough, is that tiny, anxiety-ridden nugget buried deep in the brain: the amygdala.

–Marcia Barinaga

Additional Reading

J.E. LeDoux, "Brain Mechanisms of Emotion and Emotional Learning," *Curr. Opin. Neurobiol.*, **2**, 191 (1992).

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P. Gloor, A. Olivier, L.F. Quesney, F. Andermann, and S. Horowitz, "The Role of the Limbic System in Experiential Phenomena of Temporal Lobe Epilepsy," *Annals of Neurology*, **12**, 129 (1982).