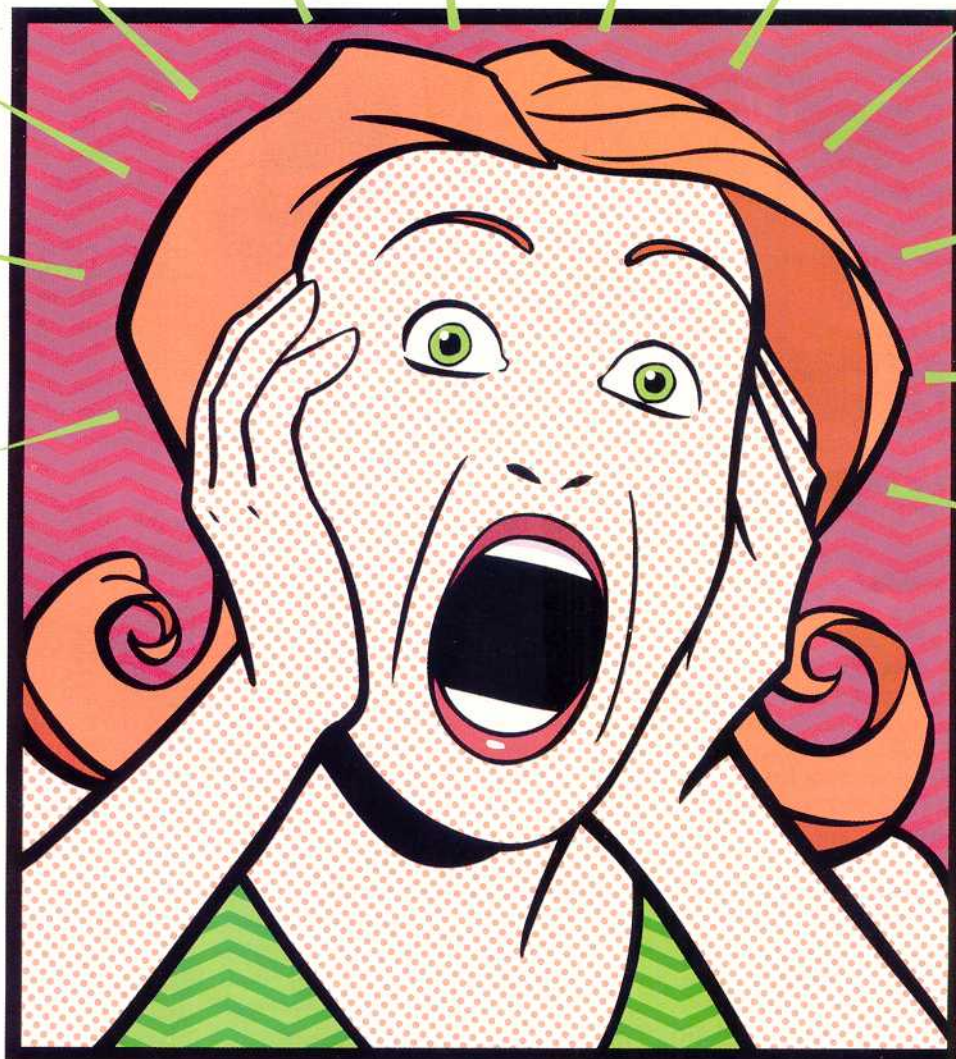


# SCIENCE NEWS

THE WEEKLY NEWSMAGAZINE OF SCIENCE

sex-change specialists  
solid behaving fluidly  
planet heats its star  
clue to mussel's glue

[www.sciencenews.org](http://www.sciencenews.org)



**fear-less**



# FEAR NOT

Scientists are learning how people can unlearn fear

BY JOHN TRAVIS

**W**hat are you afraid of? Do snakes or spiders get your heart racing? Or do your palms begin to sweat if you have to fly or give a public presentation? For many people, these situations trigger the adrenaline-fueled stress reaction that's hardwired into all animals. This fear response kicks into overdrive even though there's no immediate danger. Such phobias aren't the only fear disorders to strike people. Some individuals experience panic attacks for no apparent reason. Others faced with the horrors of war, natural disasters, or physical abuse develop posttraumatic stress disorder, a sometimes-debilitating condition that can include horrific nightmares and flashbacks. All told, the National Institute of Mental Health in Bethesda, Md., estimates that 19 million people in the United States suffer from disorders that include inappropriate fear responses.

Psychologists and neuroscientists, however, are making progress at understanding how to conquer fear. It's not a simple matter of erasing scary memories. Instead, it seems that people can learn to suppress a fright reaction by repeatedly confronting, in a safe manner, the fear-triggering memory or stimulus. For specific phobias, up to 90 percent of people can be cured through such exposure therapy, says David Barlow, director of Boston University's Center for Anxiety and Related Disorders.

In a symposium at last November's Society for Neuroscience annual meeting in New Orleans, researchers described recent studies of how this process, known as fear extinction, works in animals and people. For example, investigators have begun to home in on the neural circuitry required for extinction. "There must be some structure in the brain that inhibits fear," says Gregory Quirk of the Ponce School of Medicine in Puerto Rico.

Such research may have already produced a dramatic payoff. From their studies of rodents, scientists have identified a well-known drug that seems to speed fear extinction. Indeed, in a test on people who were afraid of heights, the drug—an antibiotic—dramatically reduced the amount of exposure therapy needed to

overcome the phobia. If larger studies confirm the drug's promise, investigators envision combining it with exposure therapy to treat a wide range of psychiatric disorders, including posttraumatic stress disorder.

"Extinction is at the heart of lots of psychotherapy," notes Michael Davis of Emory University in Atlanta.

**SCARING LITTLE ALBERT** Many phobias and other fear disorders, suggest researchers, can be considered a type of conditioned response. About a century ago, the Russian physiologist Ivan Pavlov drew attention to such responses with his studies of slobbering dogs. By ringing a bell whenever he gave the animals food, Pavlov quickly trained dogs to salivate at the mere sound of the bell. This proved that animals can be taught, or conditioned, to provide a specific physiological response to a given stimulus.

What do slobbering dogs have to do with a person's most dreaded fears? Consider the infamous story of Little Albert and the white rat. About 80 years ago, U.S. psychologist John Watson and his assistant Rosalie Rayner used Pavlovian-style conditioning to instill fear in a baby named Albert. They chose the 11-month-old infant because he was typically calm and unafraid of most things, including the laboratory's animals.

Watson and Rayner changed that. They presented a white rat to Albert and, whenever the boy reached for the animal, they struck a metal pipe with a hammer. The loud sound, coming from close behind the baby, terrified Albert, who soon began to cry or move away whenever the rat came close. Albert also began to exhibit fearful reactions to a rabbit, a dog, a fur coat, and a Santa Claus mask with a white beard.

To most psychologists, Little Albert's story is a classic example of a conditioned-fear response. Researchers today, being less inclined than their forebears to frighten babies, study such responses by training mice and rats to associate a modest electric shock with a light or sound. After several training sessions, the rodents quickly halt and brace for the foot shock whenever they see the training light or hear the sound. At that point, a fear memory has lodged in the animals' brains, researchers presume.

The scientists can quell that memory by retraining the apprehensive rodents, repeatedly exposing them to the light or sound without an accompanying foot shock. The animals slowly stop



**SCARY TIMES** — In a famous psychology experiment in the 1920s, John Watson and his assistant Rosalie Rayner made a terrifyingly loud noise whenever a baby boy named Albert began to play with a white rat. In this way, they trained the infant to fear the rodent.



freezing in response to the conditioning stimulus. But if the animals are stressed or placed in a new environment, they often return to freezing in reaction to the light or sound.

Such relapses are among the evidence indicating that even though extinction training suppresses the original fear conditioning, the fear memory remains within an animal's brain. "Extinction is a paradigm of inhibitory learning," says Mark Barad of the University of California, Los Angeles. "It's not an erasure of the original fear."

Barad, who organized the New Orleans symposium, recently showed a way in which fear extinction deviates from other learning. In general, learning happens most readily when training sessions occur at intervals. "It's a very solid learning rule," says Barad, noting that it may explain why cramming before a test doesn't often work.

He and his colleagues expected to see the benefits of intermittent training when they recently conditioned rats to fear a noise that had been paired with a foot shock. The next day, the researchers sought to extinguish that fear by presenting the noise repeatedly without the shock. If the shockfree noises were spaced 10 or 20 minutes apart, however, the training did little to eliminate the rodents' fear of the noise. In fact, some of the animals became even more apprehensive. But sounding the same number of noise cues at just 5-second intervals produced a strong, long-lasting extinction of the animals' fear, the researchers report in the October 2003 *Journal of Experimental Psychology: Animal Behavior Processes*.

"This was a big surprise," says Barad. One practical implication of this work may be that exposure therapy for phobias would work best if performed intensely over a few hours, rather than in shorter sessions spread over days or weeks.

**SHUTTING OFF FEAR** Scientists propose that fear conditioning establishes a new memory in the brain, and many studies in animals and people place that fear memory in the brain region known as the amygdala. Until recently, it's been less clear what parts of the brain are involved in fear extinction.

Over the past few years, Quirk's group and other researchers have made the case that a brain area called the medial prefrontal cortex (mPFC) provides a home for the fear-inhibiting memories created by extinction training. It has the right connections to shut off the fear response. Nerves from this cortical area project into the amygdala and brain stem, says Quirk.

Fear-extinction training doesn't work on rats with mPFC lesions. To be more accurate, it has an initial effect that doesn't last. Rodents with damage to the mPFC stop their conditioned fear response to a sound if it's given repeatedly without the shock, but their fear returns by the next day.

Quirk's hypothesis is that the fear-quelling memory—the "I'm safe" signal—forms in the same area of the amygdala in which the original fear memory resides. But this safety memory then transfers to the mPFC for storage, called consolidation. Damage to the mPFC therefore doesn't prevent the creation of the safety signal,

but it does limit its life span.

In the Nov. 7, 2002 *Nature*, Quirk's group showed that nerve cells in the mPFC fire in response to a tone that rats had been conditioned first to fear and then to consider safe. However, those same nerve cells weren't active during the original fear conditioning or the extinction training, supporting Quirk's theory that the cortex stores a safety memory that's created elsewhere in the brain.

The investigators even showed they could mimic extinction training by pairing a tone that rats were conditioned to fear with electric stimulation of the mPFC. After the stimulation, the animals froze much less often in response to the sound.

Recent work from Quirk's group also supports the theory that the mPFC suppresses the activity of fear-generating nerve cells in the amygdala and elsewhere. In the Sept. 24, 2003 *Journal of Neuroscience*, the investigators reported that electrically stimulating the mPFC reduces the responsiveness of nerve cells in the amygdala's central nucleus.

"The [medial] prefrontal cortex does inhibit the output of the amygdala," says Quirk. In other words, the fearful memory is still stored, probably elsewhere in the amygdala, but the mPFC prevents the memory from generating anxiety.

Quirk's research may apply beyond fearful rats. Several brain-imaging studies have suggested that people with posttraumatic stress disorder have an abnormally small or inactive mPFC. In the July 22, 2003 *Proceedings of the National Academy of Sciences*, for example, a research team from Japan reported that a portion of the mPFC called the anterior cingulate cortex had a volume that was smaller than normal in nine people who developed posttraumatic stress disorder after surviving the 1995 attack on the Tokyo subway by terrorists using the poison gas sarin.

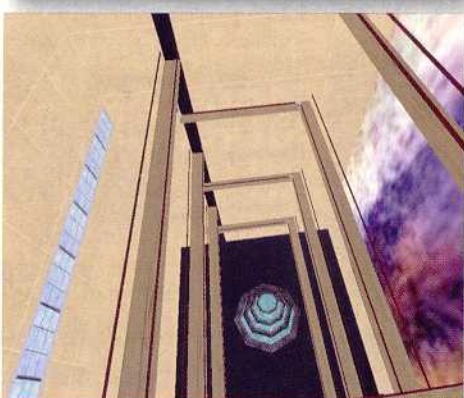
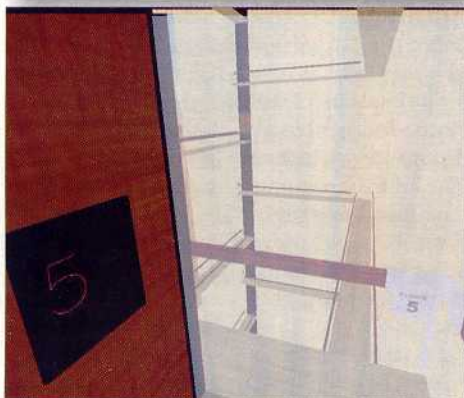
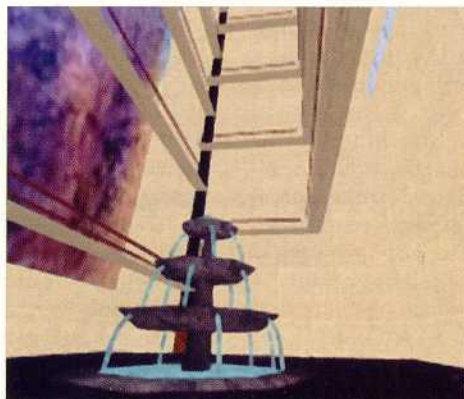
"There is homology between the areas involved in [fear] extinction in rats and the areas involved in posttraumatic stress disorder in humans," says Quirk.

Researchers are exploring whether they can extinguish fear in people by directly stimulating the mPFC. They've considered a technique called transcranial magnetic stimulation (*SN: 9/23/00, p. 204*), says Quirk, but it doesn't penetrate deeply enough into the brain to reach the mPFC regions that his team has implicated in

extinction. The group is now looking for more-accessible brain regions that contribute to the extinction process.

**HAVE A SAFE FLIGHT** There may be a way for researchers to induce extinction without shooting magnetic pulses into people's brains. Davis and his colleagues are studying the role of the amygdala in learning, and they've found that blocking a protein called the N-methyl-D-aspartate (NMDA) receptor within this brain tissue prevents fear extinction in rodents. This protein sits on the surface of nerve cells, where it responds to the neurotransmitter called glutamate.

As Quirk does, Davis theorizes that the amygdala is where fearful memories originate and where the extinction process initially



**GOING UP** — People have overcome their fear of heights with the aid of a virtual reality simulation that mimics a glass-elevator ride up the inside of a tall hotel. Within the simulation, participants can walk out on a crosswalk and look down on a fountain in the lobby.



STATS

19  
million

People in the  
United States  
who suffer from  
fear-related  
disorders

creates a safety memory. Since compounds that inhibit the NMDA receptor thwart fear extinction, Davis reasoned that compounds that facilitate the protein's response would speed it. He and his colleagues therefore turned to D-cycloserine, a compound best known as an antibiotic for treating tuberculosis.

D-cycloserine also binds to the NMDA receptor and, according to animal studies, enhances learning. Physicians have been so impressed with such studies that they've tested the drug in people with schizophrenia or

Alzheimer's disease—though with mixed results.

Davis started his investigation of D-cycloserine's effect on fear by conditioning rats to associate a foot shock with a bright light. He and his colleagues then measured how often the light startled rats before and after 30, 60, or 90 presentations of the light without the shock. While 30 shockfree presentations brought a 50 percent reduction in the number of startles triggered by the light, it typically took at least 60 presentations before the animals had completely lost their fear. Injecting D-cycloserine into a rodent's bloodstream or amygdala before this training sped up the extinction process, the researchers reported in 2002. The animals required fewer shockfree presentations to overcome their fear, Davis says.

Encouraged by these results and the drug's record of safe use as an antibiotic, Davis' team joined forces with Barbara Rothbaum, who leads a group at Emory University that treats people's phobias with virtual reality-based exposure therapy.

The researchers recruited 30 volunteers who were terrified of heights. "They didn't want to drive over high bridges. They didn't want to fly in airplanes. They didn't want to go up in elevators," says Davis.

Such people typically overcome much of their phobia with about eight, hour-long virtual reality sessions, says Rothbaum. Patients don goggles that present images of a glass elevator rising inside a tall hotel. They ride the elevator up as far as they can, usually going higher each session, and stroll out onto virtual catwalks.

In an experiment in which half the volunteers took a pill containing D-cycloserine right before each of two therapy sessions, the people who got the drug reported a much greater reduction in their fear of heights than did those who had received a placebo. Neither the volunteers nor their therapists knew whether the pill taken contained the drug. The volunteers' behavior in the next 3 months confirmed their initial subjective report: The D-cycloserine-treated individuals exposed themselves to heights in the real world, such as by flying or by driving over tall bridges, twice as often as did volunteers not given the drug.

The people who had taken D-cycloserine before their two therapy sessions had about the same improvement as did people who completed eight full sessions without taking the drug, says Davis.

"We were very pleased," says Rothbaum. She and Davis already have plans to test the drug on people who are trying to overcome their fear of public speaking. Volunteers will take D-cycloserine and then talk in front of virtual audiences.

Barad, who is also looking for drugs that speed fear extinction, notes that many people don't complete exposure therapy because it's costly and can take months. Use of D-cycloserine could partially overcome those obstacles, he says.

Davis predicts that the drug could also treat people with post-traumatic stress disorder or obsessive-compulsive behaviors. And investigators at the Massachusetts General Hospital in Boston recently launched a trial to see whether D-cycloserine can speed the behavioral therapy of people with panic disorders.

"It's very exciting," says Barlow. "Here you have a drug whose very action seems to be to facilitate the [fear-]extinction process. If that's true, then we have a powerful new combination treatment." ■