



MEMORIES

OF

FEAR

**AN NYU RESEARCHER
PROBES THE NATURE
OF MEMORIES
ASSOCIATED WITH
SEVERE STRESS
AND HOW THEY CAN
BE UNDONE.**

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▶ **HUMANS EXPERIENCE TWO MAJOR PROBLEMS WITH MEMORY, NEUROSCIENTIST JOSEPH LEDOUX, PHD, LIKES TO TELL HIS**

AUDIENCES: “Sometimes we can’t remember, and sometimes we can’t forget.” Brushes with danger have a way of creating some of our most intractable memories, he adds, because fear is closely linked to survival.

“Evolution places a high value on not having to relearn about danger,” says Dr. LeDoux, University Professor and the Henry and Lucy Moses Professor of Science in the Center for Neural Science, and director of the Emotional Brain Institute at the Nathan S. Kline Institute for Psychiatric Research. More to the point, when these indelible fear memories are triggered, they take over our brains and, through the fight-or-flight mechanism, our entire bodies.

While fear may be an essential survival tool, it can also undermine some people’s ability to function, wreaking havoc with their lives. But what if therapies could be developed that relieve their suffering by erasing specific fear memories? This is the tantalizing promise of Dr. LeDoux’s research. It’s also why, over the past decade, his work has attracted attention from clinicians who treat an array of fear-related maladies, including phobias, panic attacks, social anxiety, and post-traumatic stress disorder (PTSD).

Dr. LeDoux’s research focuses on the neurological underpinnings of fear in rats—especially the role that a small almond-shaped structure called the amygdala, buried deep within the brain, plays in storing fear memories and activating fear responses. His groundbreaking work to understand the neural pathways that stimuli (such as sounds or sights) activate in rats’ brains and how these nerve impulses are consolidated in the brain as long-term memories has changed the way scientists think about memory itself.

The common perception is that a memory is more or less fixed, and that each time we bring it to the fore we are retrieving the same original memory. Based on his work with animal models,

however, Dr. LeDoux believes that after a memory is activated, there is a period of time during which it is reconsolidated as a new long-term memory. During that period, it is vulnerable to drugs that can chemically block the reconsolidation process, effectively eliminating the memory and the fear response it triggers.

Daniela Schiller, PhD, a postdoctoral student who collaborates with Dr. LeDoux, draws an analogy to a word-processing file: when you open it up and then hit “save,” the previous form of the file is gone, replaced by something new.

To understand the neurological basis for the consolidation and reconsolidation of fear memories, Dr. LeDoux created a simple experiment. It starts with fear conditioning, in which a rat is exposed to a 30-second tone followed by a half-second shock to the feet. The animal is videotaped, and its fear response is measured by a set of uniform criteria. The next day, the tone by itself elicits the fear response.

Through a long series of experiments that included disabling specific brain regions before observing the rats’ behavior, inserting probes into the brains to measure electrical activity in specific regions, and dissecting the brains of dead fear-conditioned rats to examine their neural pathways

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A SNAPSHOT OF FEAR IN ANY GIVEN YEAR... *

Anxiety Disorders

Approximately 40 million American adults age 18 and older, or about 18.1% of people in this age group, have an anxiety disorder.

Panic Disorder

Approximately 6 million American adults age 18 and older, or about 2.7% of people in this age group, have panic disorder.

Obsessive-Compulsive Disorder (OCD)

Approximately 2.2 million American adults age 18 and older, or about 1.0% of people in this age group, have OCD.

Post-Traumatic Stress Disorder (PTSD)

Approximately 7.7 million American adults age 18 and older, or about 3.5% of people in this age group, have PTSD.

Joseph LeDoux, PhD, in his office at NYU’s Center for Neural Science.



under an electron microscope, Dr. LeDoux was able to show that there is a high-speed connection to the amygdala that bypasses the cerebral cortex. Certain regions of the amygdala store emotional memories such as fear, he found. When these areas are triggered, they begin to send alarm signals to the rest of the body before the slightly slower pathways of the cerebral cortex—the part of the brain associated with thought, decision making, and language—can catch up.

To illustrate this, Dr. LeDoux points to an amateur video made in the vicinity of the bombing at the 1996 Summer Olympics in Atlanta. First everyone freezes (an involuntary response) before the thinking about which way to run kicks in. If memories associated with basic emotions such as fear can trigger responses independently of the cerebral cortex, he notes, one consequence for humans is that “you can have an emotional response that you don’t understand. You could go to therapy for 95 years and never figure it out because you can’t verbalize it.”

After instilling a fear response in a rat, Dr. LeDoux then eliminated it. He and his colleagues discovered that when a fear response is activated, there is a window of up to six hours during which the memory is reconsolidated. By strategically administering drugs that interfere with the synthesis of proteins used by the brain to establish long-term memories, he was able to disrupt the reconsolidation process and, in a relatively short time, transform rats that freeze at the sound of the tone to rats that don’t, essentially unfreezing fear.



▶ **DR. LEDOUX, WHO GREW UP THE SON OF A BUTCHER**

in a small Louisiana town, began his academic career with two degrees in marketing.

Along the way he discovered a passion for psychology that led to graduate studies in neuroscience. When his advisor told him that nobody in the field was grappling with emotions, he was off and running. Today, his work on fear is generating intense interest, which isn’t surprising, given that 40 million Americans suffer from anxiety disorders, at an annual cost of \$50 billion in terms of treatment and lost productivity. Then, of course, there is the human anguish. “As bad as anxiety is for those of us who are quote unquote normal, it’s really bad for people who have anxiety disorders,” he says.

Dr. Schiller is part of a lab that is taking Dr. LeDoux’s findings on involuntary fear responses in rats and seeing if they apply to humans. Her work on emotional learning in her native Israel led her to NYU, she said, because Dr. LeDoux and Elizabeth Phelps, PhD, his former postdoctoral fellow, who is now a professor of psychology and runs her own lab, are at the cutting edge of their field. Dr. Schiller’s subjects are usually NYU students who have agreed to let themselves be shocked with a mild electrical current. The stimulus is paired with the display of a yellow square, and the students’ responses are recorded through highly calibrated measurements of perspiration. Like the auditory stimulus in the rats, the visual stimulus of the yellow square soon elicits a fear response without the shock.

“We have two goals, which are not mutually exclusive,” said Dr. Schiller, whose interest in fear was motivated in part by her own experiences with skydiving. “We want to understand how memory works in the normal brain with regard to how emotions are represented, and we want to see if we can make use of this knowledge to improve treatment.”

The standard approach to treating certain fear disorders is extinction therapy, which involves repeatedly pairing anxiety-provoking situations with benign or even positive outcomes until over time, the impact of those stimuli is diminished. New understandings of the plasticity of memories and the fact that they can actually be altered or even erased could lead to much more effective use of extinction therapy. If indeed there is a very specific time window during which memory reconsolidation occurs, then much more precise and effective therapies could potentially be developed that use the principles of extinction therapy to target debilitating memories. This could be done through talk therapy or with drugs that inhibit reconsolidation of a memory that has been deliberately activated in a therapeutic setting.

The idea of using drugs to erase memories draws criticism from some ethicists, who say that our memories are at the core of who we are. Dr. Schiller counters this concern by pointing out that while pain plays a vital role in survival, nobody wants to do away with painkillers. “At a certain point, pain loses its function—it’s not effective anymore, and you just suffer.” She believes the same is true of maladaptive memories. “You have a natural process that allows you to overcome fear and to continue functioning normally despite the bad memory,” said Schiller, “but if the memories are so bad that they affect your everyday functioning, this is where you need treatment.”

Aside from their scientific collaborations, Drs. LeDoux and Schiller conspire to make rock and roll music together as part of an all-scientist band that Dr. LeDoux started several years ago with NYU biology professor Tyler Volk, PhD. The Amygdaloids perform original songs with themes that originate in the lab, and have played venues ranging from the 92nd Street Y and the Kennedy Center in Washington, D.C., to Kenny’s Castaways on Bleecker Street. The refrain from “Memory Pill,” one of the songs on their first album, *Heavy Mental*, goes, “Just give me a pill, oh yes oh please. Just give me a pill, wash away my memories.” Their new CD, which will be out in June, features Rosanne Cash on two songs.

The author of two popular books (*The Emotional Brain*, Simon & Schuster, 1996, and *Synaptic Self*, Viking, 2002) and dozens of scientific articles, Dr. LeDoux addresses the propriety of altering or erasing memories head on. “We’re changing memories every time a person meets someone or goes to therapy or reads a book,” he says, so why not try to eliminate memories that interfere with our ability to function? Looking ahead to the future of his field, Dr. LeDoux says, “My fondest hope would be that we get to the point where the ethicists are *really* worried—in other words, where we really can alter these debilitating memories.” ●

AND...

Generalized Anxiety Disorder (GAD)

Approximately 6.8 million American adults age 18 and over, or about 3.1 % of people in this age group, have GAD.

Social Phobia

Approximately 15 million American adults age 18 and over, or about 6.8 % of people in this age group, have social phobia.

Agoraphobia

Approximately 1.8 million American adults age 18 and over, or about 0.8 % of people in this age group, have agoraphobia without a history of panic disorder.

Specific Phobia

Approximately 19.2 million American adults age 18 and over, or about 8.7 % of people in this age group, have some type of specific phobia.

* National Institute of Mental Health