THE ROOTS OF RESILIENCE

Most people bounce back from trauma — but some never recover. Scientists are trying to work out what underlies the difference.

BY VIRGINIA HUGHES

On a chilly, January night in 1986, Elizabeth Ebaugh carried a bag of groceries across the quiet car park of a shopping plaza in the suburbs of Washington DC. She got into her car and tossed the bag onto the empty passenger seat. But as she tried to close the door, she found it blocked by a slight, unkempt man with a big knife. He forced her to slide over and took her place behind the wheel.

The man drove aimlessly along country roads, ranting about his girlfriend's infidelity and the time he had spent in jail. Ebaugh, a psychotherapist who was 30 years old at the time, used her training to try to calm the man and negotiate her freedom. But after several hours and a few stops, he took her to a motel, watched a pornographic film and raped her. Then he forced her back into the car.

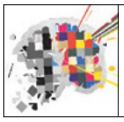
She pleaded with him to let her go, and he said that he would. So when he stopped on a bridge at around 2 a.m. and told her to get out, she thought she was free. Then he motioned for her to jump. "That's the time where my system, I think, just lost it," Ebaugh recalls. Succumbing to the terror and exhaustion of the night, she fainted.

Ebaugh awoke in freefall. The man had thrown her, limp and handcuffed, off the bridge four storeys above a river reservoir. When she hit the frigid water, she turned onto her back and started kicking. "At that point, there was no part of me that thought I wasn't going to make it," she says.

Few people will experience psychological and physical abuse as terrible as the abuse Ebaugh endured that night. But extreme stress is not unusual. In the United States, an estimated 50–60% of people will experience a traumatic event at some point in their lives, whether through military combat, assault, a serious car accident or a natural disaster. Acute stress triggers an intense physiological response and cements an association in the brain's circuits between the event and fear. If this association lingers for more than a month, as it does for about 8% of trauma victims, it is considered to be post-traumatic stress disorder (PTSD). The three main criteria for diagnosis are recurring and frightening memories, avoidance of any potential triggers for such memories and a heightened state of arousal.

Ebaugh experienced these symptoms in the months after her attack and was diagnosed with PTSD. But with the help of friends, psychologists and spiritual practices, she recovered. After about five years, she no longer met the criteria for the disorder. She opened her own private practice, married and had a son.

About two-thirds of people diagnosed with PTSD eventually recover. "The vast majority of people actually do OK in the face of horrendous stresses and traumas," says Robert Ursano, director of the Center for the Study of Traumatic Stress at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. Ursano and other researchers want to know what underlies people's mental strength. "How does one understand the resilience of the human spirit?" he asks.



STRESS AND RESILIENCE
The links between adversity and mental illness. nature.com/stress

Since the 1970s, scientists have learned that several psychosocial factors — such as strong social networks, recalling and confronting fears and an optimistic outlook — help people to recover. But today, scientists in the field are searching for the biological factors involved. Some have found specific genetic variants in humans and in animals that influence an individual's odds of developing PTSD. Other groups are investigating how the body and brain change during the recovery process and why psychological interventions do not always work. The hope is that this research might lead to therapies that enhance resilience.

A NATURAL RESPONSE

Although no one can fully understand what was going on in Ebaugh's mind during her attack, scientists have some idea of what was happening to her body. As soon as Ebaugh saw her attacker and his knife, her brain's pituitary gland sent signals to her adrenal glands, atop the kidneys, to start pumping out the stress hormones adrenaline and cortisol. In turn, her pulse quickened, her blood pressure rose and beads of sweat formed on her skin. Her senses sharpened and her neural circuits formed strong memories, so that if she ever encountered this threat in the future, she would remember the fear and flee.

The repercussions were profound. For the first week after the abduction, "I felt like a newborn baby", Ebaugh says, "like I had to be held, or at least be in the presence of somebody". She shivered constantly, was easily startled and felt only fear. She could not go near the grocery store.

Nearly every trauma victim experiences PTSD symptoms to some degree. Many people who are diagnosed with the disorder go on to have severe depression, substance-abuse problems or suicidal thoughts. PTSD can take

a horrific toll. Between 2005 and 2009, as a growing number of soldiers faced multiple deployments in Iraq and Afghanistan, suicide rates in the US Army and Marines nearly doubled.

Over the past two decades, researchers have used various kinds of imaging techniques to peer inside the brains of trauma victims. These studies report that in people with PTSD, two areas of the brain that are sensitive to stress shrink: the hippocampus, a deep region in the limbic system important for memory, and the anterior cingulate cortex (ACC), a part of the prefrontal cortex that is involved in reasoning and decision-making. Functional magnetic resonance imaging (fMRI), which tracks blood flow in the brain, has revealed that when people who have PTSD are reminded of the trauma, they tend to have an underactive prefrontal cortex and an overactive amygdala, another limbic brain region, which processes fear and emotion (see 'The signature of stress').

People who experience trauma but do not develop PTSD, on the other hand, show more activity in the prefrontal cortex. In August[1], Kerry Ressler, a neuroscientist at Emory University in Atlanta, Georgia, and his colleagues showed that these resilient individuals have stronger physical connections between the ACC and the hippocampus. This suggests that resilience depends partly on communication between the reasoning circuitry in the cortex and the emotional circuitry of the limbic system. "It's as if [resilient people] can have a very healthy response to negative stimuli," says Dennis Charney, a psychiatrist at the Mount Sinai School of Medicine in New York, who has conducted several brain-imaging studies of rape victims, soldiers and other trauma survivors.

ENVIRONMENTAL PROTECTION

After her abduction, Ebaugh began seeing a psychotherapist and several alternative-medicine practitioners. But more than anything else, she attributes her resilience to being surrounded by caring people — beginning within minutes of her escape.

After Ebaugh crawled up the rocky riverbank, a truck driver picked her up, took her to a nearby convenience store and bought her a cup of hot tea. Police, when they arrived, were sympathetic and patient. The doctor at the hospital, she says, treated her like a daughter. A close friend took her in for a time. And her family offered reassurance and emotional support. "For the first month, I almost had to tell people to stop coming because I was so surrounded by friends and community," she says.

Studies of many kinds of trauma have shown that social support is a strong buffer against PTSD and other psychological problems. James Coan, a psychologist at the University of Virginia in Charlottesville, has done a series of experiments in which women lie in an fMRI scanner and see 'threat cues' on a screen. They are told that between 4 and 10 seconds later, they may receive a small electric shock on the ankle. The cue triggers sensory arousal and activates brain regions associated with fear and anxiety, but when the women hold the hands of their husbands[2] or friends[3], these responses diminish.

Social interactions are complex and involve many brain circuits and chemicals; no one knows exactly why they provide relief. Being touched by someone is thought to stimulate the release of natural opioids, such as endorphins, in the brain. The ACC is packed with opioid receptors, suggesting that touch could influence its response to stress.

Other clues come from the hormone oxytocin, which courses through the brain during social interaction and has been shown to boost trust and reduce anxiety. In one imaging study[4], participants viewed frightening images after receiving nasal sprays of either oxytocin or a placebo. Those who sniffed oxytocin showed reduced activation in the amygdala and weaker connections between the amygdala and the brainstem, which control some stress responses, such as heart rate. The oxytocin surge that comes from being around other people could, like endorphins, help to reduce the stress response.

Past social interactions may also affect how a person responds to trauma. Chronic neglect and abuse unquestionably lead to a host of psychological problems and a greater risk of PTSD. Ressler, however, points to a factor that is well recognized but poorly understood: 'stress inoculation'. Researchers have found that rodents[5] and monkeys[6], at least, are more resilient later in life if they experience isolated stress events, such as a shock or a brief separation from their mothers, early in infancy.

Ebaugh says that early stress — and the confidence she gained in conquering it — helped her to recover from her traumatic abduction. She was born with a condition that made her feet turn inwards. At age ten, she underwent surgery to rebuild her knees followed by a year of intensive rehabilitation. "It wasn't foreign to me to be hurt and have to walk the walk of being strong again," she says. "It's like a muscle, I think, that gets built up."

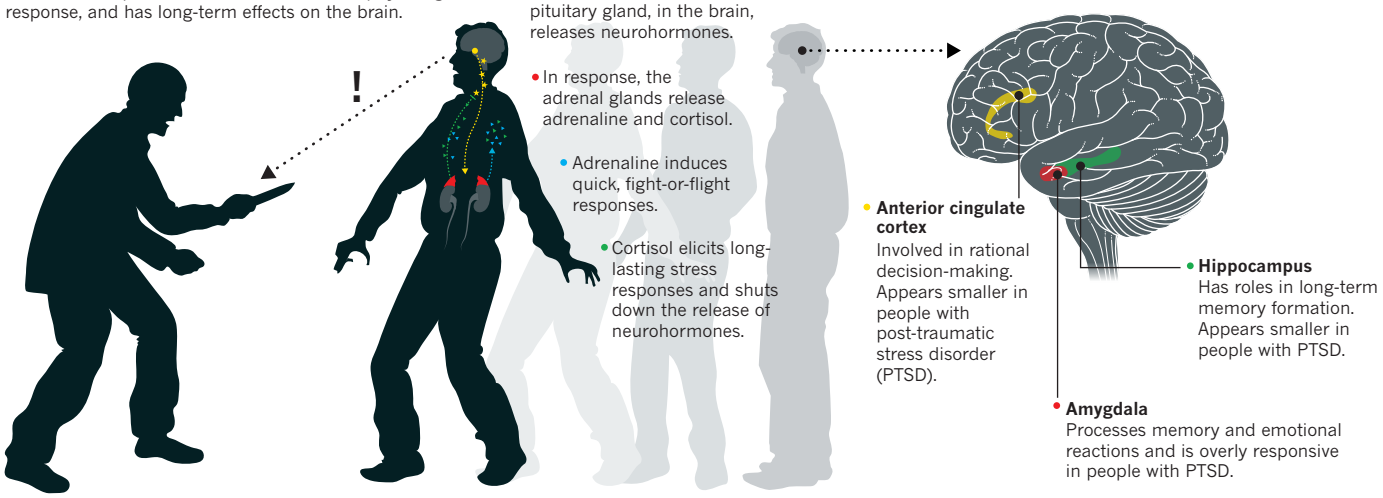
RESILIENT BY NATURE

Although most people, like Ebaugh, recover from trauma, some never do. Some scientists are seeking explanations for such differences in the epigenome, the chemical modifications that help to switch genes on and off (see page 171). Others are looking in the genes themselves. Take, for example, *FKBP5*, a gene involved in hormonal feedback loops in the brain that drive the stress response. In 2008, Ressler and his colleagues showed that in low-income, inner-city residents who had been physically or sexually abused as children, certain variants in *FKBP5* predisposed them to developing PTSD symptoms in adulthood. Other variants offered protection[7].

The most talked-about biological marker of

THE SIGNATURE OF STRESS

A traumatic experience elicits an immediate physiological response, and has long-term effects on the brain.



resilience is neuropeptide Y (NPY), a hormone released in the brain during stress. Unlike the stress hormones that put the body on high alert in response to trauma, NPY acts at receptors in several parts of the brain — including the amygdala, prefrontal cortex, hippocampus and brainstem — to help shut off the alarm. "In resiliency, these brake systems are turning out to be the most relevant," says Renu Sah, a neuroscientist at the University of Cincinnati in Ohio.

Interest in NPY and resilience took off in 2000, partly because of a study of healthy US Army soldiers who participated in a survival course designed to simulate the conditions endured by prisoners of war, such as food and sleep deprivation, isolation and intense interrogations[8]. NPY levels went up in the soldiers' blood within hours of the interrogations. Special Forces soldiers who had trained to be resilient had significantly higher NPY levels than typical soldiers.

Researchers are now conducting animal experiments to study how NPY works. In one experiment, a team at the Indiana University School of Medicine in Indianapolis restrained a rat in a tight-fitting plastic pouch for 30 minutes, then released it into a box with another rat[9]. The restraint made the rat so anxious that it avoided interacting with the other animal for 90 minutes. But when rats were injected with NPY before the treatment, they interacted with cage-mates as if nothing had happened.

The work could lead to treatments. Charney's group at Mount Sinai is carrying out a phase II clinical trial of an NPY nasal spray for individuals with PTSD. Others are investigating small molecules that can cross the blood–brain barrier and block certain receptors that control NPY release.

CONFLICT RESOLUTION

The US military is leading the hunt for additional biological markers of resilience. Since 2008 — driven in part by soaring suicide rates among soldiers — the US Army has collaborated with the National Institute of Mental Health and several academic institutions on a US$65-million project called Army STARRS (the Study to Assess Risk and Resilience in Servicemembers). The project has many parts, including a retrospective look at de-identified medical and administrative records for 1.6 million soldiers, in search of early warnings of suicide, PTSD and other mental-health problems. STARRS scientists are also collecting data — such as blood samples, medical histories and cognitive testing results — on tens of thousands of current soldiers. The researchers expect to publish their first findings early next year.

The military also funds research into animal models of resilience. Most rodents will quickly learn to associate painful foot shocks with a certain cue, such as a tone or a specific cage. After they have learned the association, the rodents freeze on experiencing the cue, even without the shock. Several years ago, Abraham Palmer, a geneticist now at the University of Chicago in Illinois, made a line of resilient mice by selectively breeding mice that froze for abnormally short periods of time. After about four generations, he had mice that froze for about half the time of typical animals[10]. The effect was not due to a difference in pain sensitivity or general learning ability. This month, Luke Johnson, a neuroscientist at the Uniformed Services University, will present data at the Society for Neuroscience meeting in New Orleans, Louisiana, showing that these mice have uncommonly low activity in the amygdala and hippocampus, consistent with human studies of PTSD resilience. They also have low levels of corticosterone, a stress hormone, in their urine.

"They have a quieter system, even at rest," says Johnson. "It suggests that there are underlying biological traits that are associated with the capacity of the animal for fear memory." In future experiments, Johnson plans to use the mice to study NPY and potential new therapies.

Ebaugh, who now specializes in therapy for trauma victims, agrees that drug-based treatments could aid in recovery. But some people may find relief elsewhere. Religious practices — especially those that emphasize altruism, community and having a purpose in life — have been found to help trauma victims to overcome PTSD. Ebaugh says that yoga, meditation, natural remedies and acupuncture worked for her.

Today, she buys groceries at the plaza where she was abducted, and she drives over the bridge she was thrown from as though it were any other road. She says that she has forgiven the man who abducted her. When she reflects on what he did, it's not with anger, sadness or fear. "It doesn't feel like it affects my life at all at this point, at least not in a negative way," she says. "In a positive way, it's been a huge teacher." ■

ERIKA LARSEN/REDUX

Elizabeth Ebaugh is finally comfortable visiting the bridge from which she was thrown 26 years ago.

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