

Stressed-Out Memories

A little stress sharpens memory. But after prolonged stress, the mental picture isn't pretty

By Robert M. Sapolsky

Your first kiss. Your wedding ceremony. The time the car spun out of control and just missed the oncoming truck. Where you were when the earthquake hit, when Kennedy was shot, on 9/11. Each detail of such life-changing events is etched forever in your mind, even though you may not recall the slightest thing about the 24 hours beforehand. Arousing, exciting, momentous occasions, including stressful ones, get filed away very readily. Stress can enhance memory.

We've all had the opposite experience when under stress as well. The first time I met my future wife's family, I was nervous as hell; during a frantically competitive word game after dinner, I blew the lead of the team consisting of my future mother-in-law and me by my utter inability at one criti-

cal juncture to remember the word "casserole." Some instances of failed memory revolve around infinitely greater traumas: the combat veteran who went through some unspeakable battle catastrophe, the survivor of childhood sexual abuse—for whom the details are lost in an amnesic fog. Stress can disrupt memory.

For researchers like me who study stress, this dichotomy is quite familiar. Stress enhances some function under one circumstance and disrupts it under another. Recent research shows just how short-term stressors of mild to moderate severity enhance cognition and memory, whereas major or prolonged stressors disrupt them.

Memory Basics

To understand how stress affects memory requires some background on how memories are formed (consolidated), how they are retrieved and how they can fail.

Memory is not monolithic but comes in different flavors. One particularly important di-

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chotomy distinguishes short-term versus long-term memories. With the former, you look up a phone number, sprint across the room before you forget it, then punch in the digits. And then the number is gone forever. In contrast, long-term memory refers to recalling what you had for dinner last night, how many grandchildren you have, where you went to college.

Another important distinction is that between explicit (also known as declarative) and implicit (which includes an important subtype called procedural) memory. Explicit memory concerns facts

Parisian dancers; it wasn't Degas [two more networks pulled in]. Wow, remember that time I was at the museum and there was that really cute person I tried to talk to in front of one of his paintings ... oh, what was the stupid pun about that guy's name, about the train tracks being too loose?" With enough nets working, you finally stumble into the one fact at the intersection of all of them: Toulouse-Lautrec.

Neuroscientists have come to think of both learning and storing of memories as involving the "strengthening" of some network branches rather

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and events, along with your conscious awareness of knowing them: I am a mammal, today is Monday, my dentist has thick eyebrows. In contrast, implicit procedural memories are about skills and habits, about knowing how to *do* things, even without having to think consciously about them: shifting the gears on a car, riding a bicycle, doing the fox trot. Given enough practice, such memories can be transferred between explicit and implicit forms of storage.

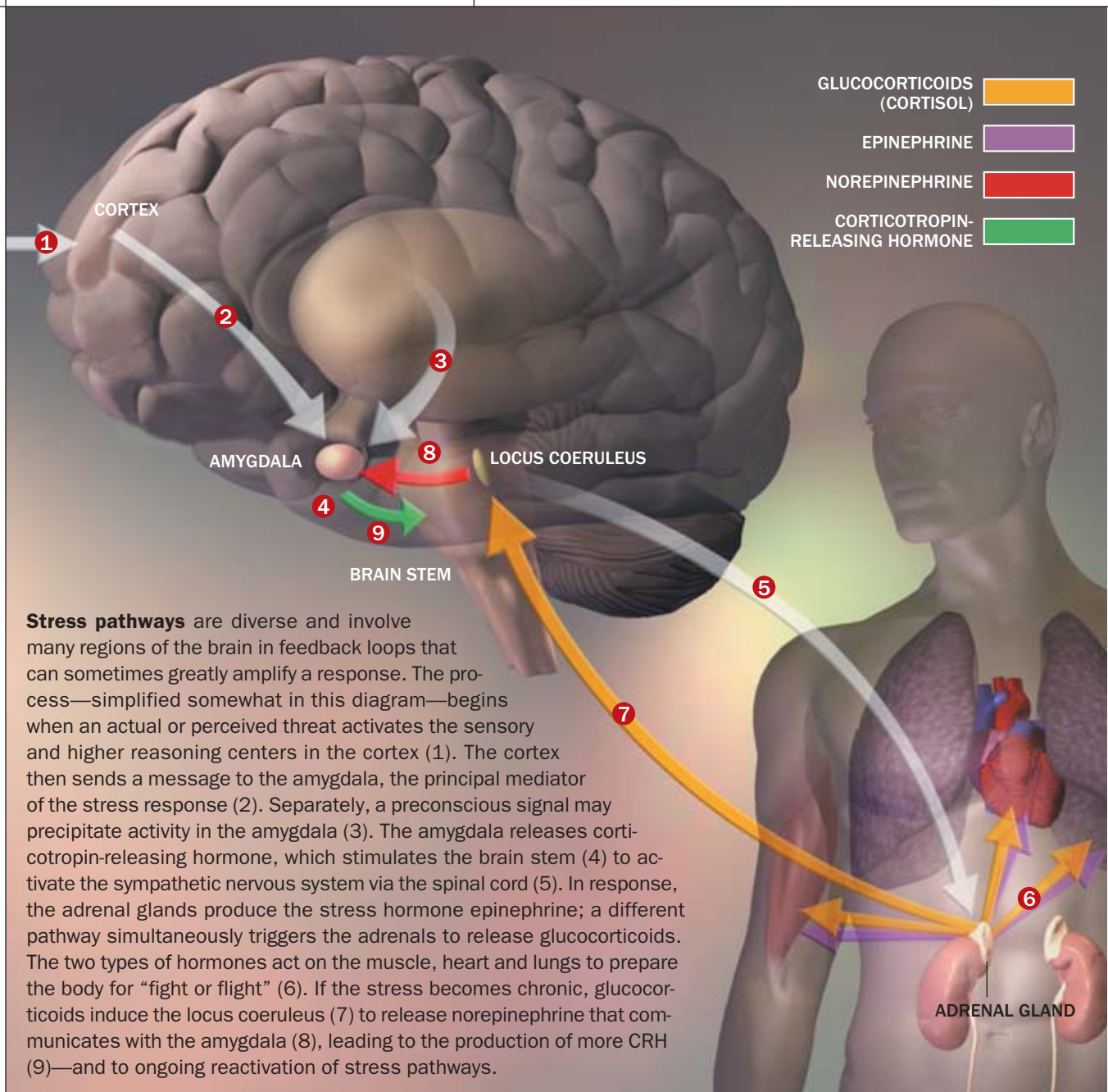
Just as there are different types of memory, different areas of the brain are involved in information storage and retrieval. One critical site is the cortex, the vast and convoluted surface of the brain. Another is a region tucked just underneath part of the cortex, called the hippocampus. If you want a totally simplistic computer metaphor, think of the cortex as your hard drive, where memories are stored, and your hippocampus as the keyboard, the means by which you place and access memories in the cortex. Last, brain structures that regulate body movements, such as the cerebellum, are involved with implicit procedural memory.

Now let us shift to the next magnification to examine what goes on at the level of clusters of neurons within the cortex and hippocampus. Knowledge is stored in the patterns of excitation of vast arrays of neurons—in trendy jargon, in neuronal “networks.” We take advantage of such convergent networks whenever we are trying to grasp a memory that is almost, almost there. Suppose you are trying to remember the name of a painter, that guy, what's his name? “He was that short guy with a beard [activating your “short guy” and your “bearded guy” networks]. He painted all those

than others. To see how that occurs, we switch to a final level of magnification, to consider the tiny gaps between the thready branches of two neurons, called synapses. When a neuron wants to pass on some fabulous gossip, when a wave of electrical excitation sweeps over that brain cell, this wave triggers the release of chemical messengers—neurotransmitters—that float across the synapse and excite the next neuron. Dozens, probably hundreds, of kinds of neurotransmitters exist, and synapses in the hippocampus and cortex disproportionately make use of what is probably the most excitatory neurotransmitter, called glutamate.

“Glutamatergic” synapses have two properties critical to memory. First, they are nonlinear in their function. In a run-of-the-mill synapse, a little bit of neurotransmitter from the first neuron causes the second to get a little excited; if a smidgen more neurotransmitter becomes available, a smidgen more excitation occurs and so on. With glutamatergic synapses, some glutamate is released, and nothing happens. A larger amount is released, and still nothing happens. But when a certain threshold is passed, all hell breaks loose in the second neuron, and a massive wave of excitation follows. And this wave is what learning is about.

The second feature is even more important. Under the right conditions, when a synapse has had a sufficient number of superexcitatory glutamate-driven experiences, it becomes persistently more excitable. That synapse just learned something; that is, it was “potentiated,” or strengthened. From then on, it takes less of a signal to recall a memory. We can now see what happens when the system reacts to stress.



Add a Little Stress ...

The first point, of course, is that mild to moderate short-term stressors enhance memory. This is the sort of optimal stress that we would call “stimulation”—it makes us feel alert and focused. Larry Cahill and James McGaugh of the University of California at Irvine carried out one particularly elegant study in this realm. Test subjects who heard a tale with an exciting passage remembered the emotional components better than subjects who heard a uniformly dull story. The study also indicated how this effect on memory works. Hear a stressful story, and a stress response is initiated [For more on stress pathways, see illustration above].

The sympathetic nervous system kicks into gear, pouring epinephrine and norepinephrine into the bloodstream. Sympathetic stimulation appears to be critical, because when Cahill and McGaugh gave subjects a drug (the beta blocker propranolol, the same medication used to lower blood pressure)

(The Author)

ROBERT M. SAPOLSKY is professor of biological sciences and neurology at Stanford University and a research associate at the National Museum of Kenya, where he has studied a population of wild baboons for more than 25 years. He earned a Ph.D. in neuroendocrinology from the Rockefeller University in 1984. Sapolsky’s research interests include neuronal death, gene therapy and the physiology of primates.

ALFRED T. KAWAJIAN

Healthy neurons of the hippocampus of a rat (left) shrink after prolonged stress (right).

to stall the system's activation, the experimental group did not remember the livelier story any better than the controls remembered theirs. It's not that propranolol obstructs memory formation. Rather the drug disrupts stress-enhanced memory formation. In other words, the experimental subjects did as well as the controls on the boring parts of the story but didn't get the boost in memory for the emotional section.

The sympathetic nervous system indirectly arouses the hippocampus into a more alert, activated state, which in turn facilitates memory consolidation. This involves an area of the brain that is also central to understanding anxiety, the amyg-



dala. The sympathetic nervous system also helps the energy needs of potentiating neurons to be met by mobilizing glucose into the bloodstream and increasing the force with which blood is pumped into the brain. An important class of hormones released in response to stress are glucocorticoids. Secreted by the adrenal gland, they often act in ways similar to their more famous cousin, epinephrine (also known as adrenalin). Epinephrine acts within seconds; glucocorticoids back up this activity over the course of minutes or hours.

As it happens, a mild elevation in glucocorticoid levels smoothes the progress by which synapses in the neocortex and hippocampus become more sensitive to glutamate signals, the long-term potentiation that is the building block of learning.

A mild elevation in glucocorticoid levels smoothes the progress of long-term potentiation in the hippocampus as well. Finally, there are some obscure mechanisms by which moderate, short-term stress makes sensory receptors more sensitive. Taste buds, olfactory receptors, the cochlear cells in the ears all require less stimulation under moderate stress to get excited and pass on the information to the brain.

Too Much of a Good Thing

We can now look at how memory formation and retrieval go awry when stressors become too

big or prolonged. Numerous studies with lab rats—using an array of stressors, including restraint, shock, exposure to the odor of a cat—have shown a resulting decline in explicit memory. A similar deficit appears when high doses of glucocorticoids are administered to rats. Other aspects of brain function, such as implicit memory, remain fine.

The picture is much the same in humans. Problems with explicit memory appear in patients who suffer from a disorder called Cushing's syndrome, in which tumors cause the secretion of tons of glucocorticoids. Prolonged treatment with synthetic glucocorticoids, which are often administered to people to control autoimmune or inflammatory disorders, results in explicit memory problems as well. As the clearest evidence, just a few days of high doses of synthetic glucocorticoids impairs explicit memory in healthy volunteers.

How does prolonged stress disrupt hippocampus-dependent memory? A hierarchy of effects has been shown in laboratory animals.

First, hippocampal neurons exposed to high glucocorticoid levels no longer work as well. Stress can disrupt long-term potentiation in that brain region even in the absence of glucocorticoids (as in a rat whose adrenal glands have been removed). Extreme arousal of the sympathetic nervous system seems responsible for this effect.

In the mid-1980s Ron de Kloet of the University of Utrecht in the Netherlands discovered the mechanisms behind the disruption caused by exposure to high glucocorticoid levels. The hippocampus has large amounts of two types of glucocorticoid receptors. Notably, the hormone is about 10 times better at binding to one kind (a "high-affinity" receptor) than the other. If glucocorticoid levels rise only a little bit, most of the hormone effect in the hippocampus is mediated by that high-affinity receptor. In contrast, the hormone released during a major stressor activates a lot of the low-affinity receptor. And, logically, it turns out that activation of the high-affinity receptor enhances long-term potentiation, whereas the low-affinity one does the opposite.

In the second of the hierarchy of effects, during major stressors the amygdala sends a large, influential neuronal projection to the hippocampus. Activation of this pathway seems to be a prerequisite for stress to disrupt hippocampal function. Destroy a rat's amygdala or sever its connection to the hippocampus, and stress no longer impairs the kind of memory that the hippocampus mediates, even amid high glucocorticoid levels.

Third, neural networks in the hippocampus start to become disconnected. Bruce S. McEwen of

the Rockefeller University has shown that in a rat, after as little as a few weeks of stress or exposure to excessive glucocorticoids, cellular communication cables known as dendrites begin to shrivel, atrophy and retract [see illustration on opposite page]. Fortunately, it seems that at the end of the stressful period the neurons can dust themselves off and regrow those connections. Memories are not lost, just harder to access.

Fourth, prolonged stress inhibits the birth of new neurons in the hippocampus, which was recently discovered to be one of only two sites in the adult brain where new neurons can arise. When the stress stops, does neurogenesis recover and, if so, how fast? No one knows. Also, does it matter that stress hinders adult neurogenesis? Intrinsic in this

and glucocorticoids are often highly effective treatments. Potentially, the memory problems are a particularly grim and unavoidable side effect.

Neurologists also use synthetic versions of glucocorticoids (such as hydrocortisone, dexamethasone or prednisone) to reduce brain swelling after a person has had a stroke. Glucocorticoids do wonders to block the edema that occurs after something like a brain tumor, but it turns out that they don't do much for poststroke edema. Worse, there is increasing evidence that these famously anti-inflammatory compounds can actually be pro-inflammatory in certain types of injured brains. An even more troubling implication of these findings is that what we think of as typical amounts of brain damage after a stroke or seizure are actually worsened

(There simply has not been much evolutionary pressure to make the body's response to massive neurological injury more logical.)

question is the larger issue of what adult neurogenesis is good for. The jury is still out on this one, too.

Fifth, if hippocampal neurons experience an insult (such as from a stroke or seizure), stress makes them more susceptible to dying. By about 30 minutes into a continuous stressor, glucose delivery is no longer enhanced and has returned to normal levels. If the stressor continues, the delivery of glucose to the brain becomes inhibited. My lab and others have shown that the relatively mild energy problem caused by that inhibition makes it harder for a neuron to contain the eleventy things that go wrong during neurological insults.

Finally, some studies appear to suggest that glucocorticoids and stress may even kill neurons outright, although the results are preliminary and controversial.

These findings have some disturbing implications. About 16 million prescriptions are written annually in the U.S. for glucocorticoids. Much of the use is benign—a little hydrocortisone cream for some poison ivy, a hydrocortisone injection for a swollen knee, steroid inhalants for asthma. But hundreds of thousands of people take high doses of glucocorticoids to suppress the inappropriate immune responses in autoimmune diseases (such as AIDS, lupus, multiple sclerosis or rheumatoid arthritis). So should you avoid taking glucocorticoids for your autoimmune disease to avoid the possibility of accelerated hippocampal aging down the line? Almost certainly not: these are often devastating diseases,

by the natural release of glucocorticoids as part of the stress responses our bodies have at such times.

Consider how bizarre and maladaptive this is. Lion chases you, and you secrete glucocorticoids whose primary effects on metabolism throughout the body are to divert energy to your thigh muscles for sprinting: great move. Go on a blind date, get nervous and you secrete glucocorticoids to divert energy to your thigh muscles: probably irrelevant. Have a grand mal seizure, secrete glucocorticoids to divert energy to your thigh muscles—and your brain damage becomes more severe.

How did such maladaptive responses arise? The most likely explanation is that the body simply has not evolved the tendency *not* to secrete glucocorticoids during a neurological crisis. Stress-induced glucocorticoid secretion works roughly the same in all mammals, birds and fish, and only in the past half a century have Westernized versions of just one of those species had much of a chance of surviving something like a stroke. There simply has not been much evolutionary pressure to make the body's response to massive neurological injury more logical.

We are now 50, 60, years into thinking about ulcers, blood pressure and aspects of our sex lives as being sensitive to stress. We also now recognize the ways in which stress can interfere with how we learn and remember. The noted neuroscientist Woody Allen once said, "My brain is my second-favorite organ." My guess is that most of us would rank our brains even higher up on the list.

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