

## **STRESS AND YOUR SHRINKING BRAIN**

**by Robert M. Sapolsky**

***War, rape, sexual abuse, and other severe trauma -- even a car accident -- could make part of your brain disappear.***

Every now and then, someone with a medical problem needs a CT scan or MRI of the brain. With luck, the test rules out a threatening disease, and in the resultant relief, the doctor shows the patient the scan. If it's his or her first one, the patient will probably get the willies. Unlike pictures of other organs, which inspire a bemused response ("Hey, lookie here, that's my liver"), brain scans provoke awe. That's your brain in there, with its convoluted surface and all those mysterious subsections. Rookie med students feel the same disquiet in anatomy class when they first hold a cadaver's brain in their hands. The same uneasiness makes neurosurgeons joke, "There go the piano lessons," when they cut into gray matter. The brain, after all, is the Seat of the Soul, the Big Enchilada of Consciousness, the organ of Me-ness. From this mass of tissue resembling marinated tofu emanates a person.

By the time a child's body stops growing, the brain has long since settled into its adult size. Which is why it's mighty interesting when the size of some part of the brain changes dramatically in an adult. Check out the brain of a chronic alcoholic and you'll often find a particular region badly disintegrated; autopsy someone who was exposed to lots of organic toxins and you'll see damage in another brain area. And a third brain region has attracted a lot of attention recently because it may atrophy in response to a certain type of serious stress.

Take a green 18-year-old, stick him in a uniform, ship him off to a war, and expose him to something truly horrific even by the standards of human violence--say, a battle in which he's the only soldier in his entire unit to survive. Some rare, inexplicable supermen may come out of such an experience unfazed or even strengthened, having found life's meaning during that moment when the world melted around them. But the average guy comes out a lot worse. He may suffer from nightmares for a while. He may feel estranged from loved ones who can't understand what he's been through. And that's if he's lucky. Some survivors are apparently damaged for decades.

During the First World War the phenomenon was called shell shock; it produced men who even as octogenarians would shake and leap for cover when a door slammed. Something similar was called battle fatigue in World War II. And in modern psychiatric parlance, the long-lasting residue of horror is called post-traumatic stress disorder. It's not just restricted to combat trauma, either. Gang rape, childhood sexual abuse, the carnage of yet another choirboy next door going postal with an automatic weapon, imprisonment in Auschwitz – all are experiences that have produced the broken person labeled with the acronym PTSD.

According to the American Psychiatric Association, patients with PTSD suffer from flashbacks, nightmares and other sleep problems, emotional numbness or outbursts, loss of pleasure, an inappropriate startle reflex, and problems with memory and concentration. Those last two symptoms have prompted recent brain-imaging studies.

Memory problems might arise from subtle microscopic conditions: something wrong in the way a few critical neurons produce or use a particular neurotransmitter, or trouble with the enzymes that degrade a neurotransmitter, or with the receptor for it or the intracellular messengers it triggers. In the last few years, however, some neuroscientists have begun to look at the bigger picture, generating magnetic resonance images of PTSD patients' brains and carefully measuring the volumes of the organs' many bewildering regions. The researchers have dotted their *i*'s and crossed their *t*'s like good scientists, controlling for the depression and substance abuse that often

accompany PTSD and controlling for total brain size, age, sex, and education. Recently, groups working independently at Yale Medical School; the Veterans Administration Medical Center in Manchester, New Hampshire, and Harvard; and the University of California at San Diego reported that in afflicted individuals an important region of the brain called the hippocampus is smaller than average.

To the cognoscenti, that was big news. Unlike some brain regions, which have been swallowing up earnest grad students like quicksand for decades without yielding a clue to their functions, the hippocampus is well-explored territory. We use it to form long-term memories, retrieve old ones, and manage explicit, conscious memory. When repeatedly stimulated pairs of hippocampal neurons and their connections become stronger, more excitable: shazam – those neurons have learned something. Surgically destroy the hippocampus, as has been done in a zillion lab rats and in one famous neurological patient known only as HM, and some major types of memory will be gone for good. Similar problems result when Alzheimer's disease ravages the hippocampus.

Most of the recent PTSD imaging studies have found atrophy only in the hippocampus; the rest of the brain is fine. The damage, however, is not trivial. For example, Tamara Gurvits, Roger Pitman, and their colleagues at the Manchester VA Medical Center and Harvard Medical School have studied combat PTSD patients and reported that one side of the hippocampus was about 25 percent smaller than expected. Twenty-five percent! That's like reporting that an emotional trauma eliminates one of the four chambers of the heart. These hippocampi are seriously out of whack. Research by J. Douglas Bremner and his colleagues at Yale Medical School supports that notion. Typically, when a person is given a memory task, the metabolic rate of the hippocampus increases, reflecting the energy it takes for that brain region to kick into gear. In people with PTSD, though, the same memory task fails to speed up hippocampal metabolism, a finding that fits with the memory deficits typical of PTSD sufferers.

While neuroscientists agree that an atrophied hippocampus and PTSD go together, there is a lot of debate over why. One possible explanation, favored by Bremner, involves a class of steroid hormones called glucocorticoids; most people are familiar with hydrocortisone, the glucocorticoid found in humans. During stress, whether of a physical or a psychological nature, a person's adrenal glands secrete loads of these chemicals. Glucocorticoids are necessary for surviving a stressful sprint across the savanna with a hungry leopard on one's tail. They help send energy to the thigh muscles, and they shut down nonessentials, such as growth or reproduction, that can wait for more auspicious times. But however useful glucocorticoids can be in the face of an acute physical stressor, too much of the hormones--during chronic psychological stress, for example--can be a trigger for all sorts of stress-related conditions, including high blood pressure.

Because the hippocampus has lots of receptors for glucocorticoids, it's the part of the brain most sensitive to the hormones. Glucocorticoids can damage neurons in the hippocampi of rodents and primates. Researchers in my laboratory and elsewhere have found a number of ways in which this happens. For starters, a few days' worth of elevated glucocorticoid levels can endanger a hippocampal neuron, making it less likely to survive a seizure, a period without oxygen and glucose, as occurs during cardiac arrest. Next, over a few weeks or months, glucocorticoids shrivel the branchlike connections between hippocampal neurons; once the stress or glucocorticoid exposure ends, the branches slowly grow back. Finally, when glucocorticoid levels stay high enough for long enough--months or years--they can destroy hippocampal neurons.

These findings have unnerved some clinicians because patients with a variety of diseases are treated with high-dose glucocorticoids for long periods (even though the treatment is known to cause memory problems) and because the body itself secretes a ton of these hormones during neurological crises. Can excessive glucocorticoids damage the human hippocampus? Maybe.

Consider Cushing's disease, in which any of several types of tumors produce astronomically high glucocorticoid levels. Monica Starkman and her colleagues at the University of Michigan have found atrophied hippocampi on MRI scans of people with this disease. The rest of the brain is fine, but the higher the levels of glucocorticoids in the bloodstream, the smaller the hippocampus and the more memory problems the patient experiences. When the tumor is corrected and glucocorticoid levels go back to normal, the hippocampus slowly returns to normal size, suggesting that the shriveling was reversible and the branches grew back.

Is this what happens in PTSD? The model fits best if we imagine neuron loss (instead of just shriveling), because the atrophy can persist for years or decades after the trauma. Still, no one really has a clue if this is what's going on. Researchers need to study actual brain tissue, instead of pictures, to determine whether PTSD patients really have fewer neurons in their hippocampi than healthy individuals. Moreover, no one knows how high glucocorticoid levels get during a rape or a bombing.

An alternative model comes from Rachel Yehuda and her colleagues at Mount Sinai School of Medicine and the Bronx Veteran Affairs Medical Center in New York. They have examined patients' glucocorticoid levels once post-trauma problems emerge. To everyone's surprise, they and others have observed that levels are not higher than normal but lower. Their careful work has shown that this might be because the brain is more sensitive to the regulatory effects of glucocorticoids, resulting in less secretion (rather like making a thermostat more sensitive to minor changes in temperature). Thus, they explain the syndrome not by excessive stress hormones during trauma but by excessive sensitivity to these hormones after the trauma. In either model, what's interesting is that scientists have identified a likely culprit, a stress-related hormone known to do bad things to the hippocampus and memory under other circumstances.

Naturally, the idea that trauma could cause a brain to shrink could be completely wrong, the sort of chicken-and-egg mess that often trips up scientists just when they think they've found a clue. Put a bunch of soldiers through some unspeakable hell of combat and typically only a subset of them, 15 to 30 percent, get PTSD. Maybe we have the story backward. Maybe the person with a small hippocampus who goes into a trauma is the one vulnerable to PTSD. Maybe that person processes information differently, forms memories differently, and is more at risk for flashbacks. Pitman and his colleagues have reported that soldiers who wind up with PTSD were likely to have had a higher-than-average rate of what are called "soft" neurological signs--not out-and-out neurological diseases but some minor red flags such as delayed developmental landmarks or a higher than average rate of learning disorders.

Some researchers are trying to figure out whether a small hippocampus predisposes someone to PTSD. Pitman, Arieh Shalev, and their colleagues are doing a prospective study, examining MRIs of people who have just undergone a trauma and following up with later scans. The neuroscientists will examine the before-and-after images to see whether a small hippocampus really does precede and predict who will get PTSD, or if hippocampal volume decreases in the later picture.

Meanwhile, Thomas Freeman, a psychiatrist at the North Little Rock Veterans Administration Medical Center, is taking another approach to untangling the question of cause and effect. If the hippocampus shrinks after the trauma, especially if it does so as a function of the ongoing post-trauma period, the extent of atrophy should be more dramatic in survivors of older disasters than of recent ones. Freeman and his colleagues are comparing brain scans of PTSD victims from the Gulf War, Vietnam, Korea, and so on.

So we've got scientists disagreeing, experiments to be done, grants to be written. What does all this mean? Let's start with what it doesn't mean. At present, there isn't a shred of evidence to link everyday stress--traffic jams, money worries, crummy bosses, unhappy relationships--to neurons keeling over dead. Those stressors are not good for things like blood pressure and may result in hippocampal neurons not functioning at their best, but the neurons almost certainly remain intact.

Another caveat: The business about the branches that connect neurons in the hippocampus shriveling up from stress and later recovering has provided an irresistible metaphor to some folks who believe in "recovered memory." The term describes a controversial scenario in which victims of horrendous traumas utterly repress all memory of the experience, only to recover it years or decades later. Lives have been destroyed over this incendiary issue--either those of the trauma victims (in one interpretation), left to wait decades for justice because of the workings of memory, or, in the counterview, those of the victims of false accusations, consumed in this season's witch-hunt. Civil war has nearly broken out among neuropsychologists over this issue, so let me tread lightly here--I will simply say that I have seen no scientific evidence for how such recovered memories might work, no supposed cases of it documented to be legitimate in a way that should satisfy a rigorous scientist, and plenty of scientific explanations for why various claims have not been legitimate.

Although the recent hippocampal research has little to say about everyday stress and recovered memory, it does have some valuable practical lessons for us. If a small hippocampus is indeed a risk factor for PTSD, neuroanatomy should be taken into account when we decide whom to ship off to battle, the same way we'd consider the presence of a heart murmur. And if the atrophy is a consequence of the trauma or the post-trauma period, scientists have their usual marching orders: figure out how the process works so we can learn how to prevent it.

But these findings should mean something larger as well. For most of us, all the alarming lectures in the world about how we are endangering our environment don't have the power of that first, iconic picture from the moon of Earth--tiny, vastly alone, fragile. Reading about the Nazis can't take our breath away like a visit to the U.S. Holocaust Memorial Museum, with its room filled beyond number with the shoes of the murdered. We need concrete images when trying to grasp the ungraspable. And thus a thousand people writing a thousand words each about the consequences of human violence may not have the impact of a single picture, like a brain scan. Look what they did to my brain. Look what they did to me.

PHOTO (COLOR): An American soldier on the Taegu front in the Korean War sobs with fatigue at a battlefield collecting station.

PHOTO (BLACK & WHITE): The hippocampus, a structure that occurs in each brain hemisphere, plays a vital role in forming and retrieving memories. In these MRI scans, a PTSD patient's; left

PHOTO (BLACK & WHITE): hippocampus (above left, outlined in red) is much smaller than that of a normal subject. (The left hippocampus appears on the right because the patients are facing the viewer.)