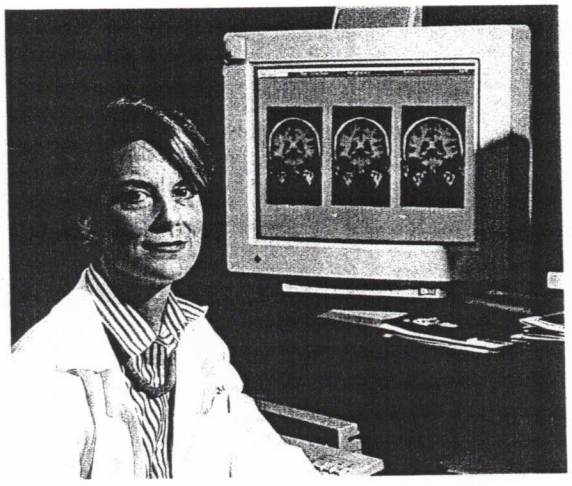
Telltale

Recurrent Depression Leaves Its Mark On The Brain

By the time Sylvia Carr Hiles was 26 years old, she had been married for seven years and had nine pregnancies and eight miscarriages. Although she gave birth to one healthy child, a son, Hiles was grief-stricken over those she had lost.



Yvette I. Sheline, MD, has found that recurrent depression in patients causes atrophy of the hippocampus, which is part of the brain's limbic system, a group of structures important to emotion and motivation.

"I desperately wanted children," she says. "After the last miscarriage, I couldn't take any more. And that's when my problems began."

What she had accepted as grief slowly turned into anxiety, fatigue and an inability to concentrate — red flags that Hiles immediately recognizes today as incapacitating indicators that a bout with depression is coming her way.

"I know I'm in trouble when I start to lose the ability to focus," says Hiles, who has battled clinical depression for 35 years. "I begin to have trouble organizing and sorting things. I can't sort socks or mail; balancing the checkbook is impossible. Activities that you normally do automatically take me forever. Everything you do — even opening a door — takes effort and becomes a conscious act."

Hiles, 60, estimates that her depressive episodes occur about every 10 years, and they can last for years at a time. She recalls one event lasting four years.

Experts say it is fairly typical for depressive episodes to recur, and that many people suffer from depression several times during the course of their lives.

Hiles, who is a retired grade school teacher, says that at one point her depression was so severe that she attempted suicide by taking an overdose of tranquilizers.

"I was sick of trying to cope," she recalls. "I don't think I really wanted to die. I just wanted the pain and confusion to be over. I had so much trouble organizing my life and making decisions — I couldn't live that way anymore."

Minutes after taking the potentially deadly pills, Hiles says her thoughts turned to her 10-year-old son and she picked up the

An arrow points to the hippocampus (red-orange), a seahorse-shaped brain structure involved in learning and memory.

By Jim Dryden

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telephone and called her minister. Since that time, she has received psychiatric therapy and she now takes the anti-depressant drug Prozac when she feels an episode coming on. Although she has been free of depression for two years, Hiles knows that her disease can return.

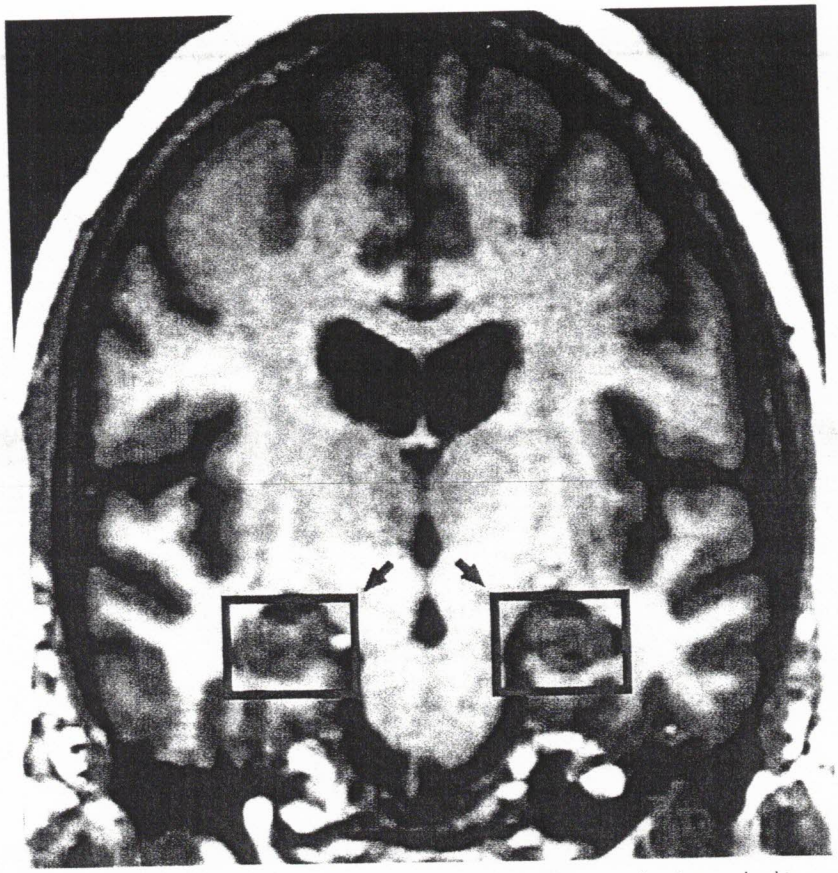
What causes depression to recur is a question with which researchers at the School of Medicine have been wrestling. Recently, they identified an anatomical difference in the brains of depressed women that may help explain why some get depressed many times during the course of their lives.

Footprints In The Brain

In the April 30 issue of the *Proceedings of the National Academy of Sciences*, principal investigator Yvette I. Sheline, MD, assistant professor of psychiatry, reported that the size of the brain's hippocampus is smaller in women who have been clinically depressed than in women who have never suffered a depressive episode.

The hippocampus is a seahorse-shaped brain structure involved in learning and memory. It is part of the brain's limbic system, a group of structures important to emotion and motivation. Using high resolution magnetic resonance imaging (MRI), Sheline's team also found that the more times a woman had been depressed, the smaller her brain's hippocampus was likely to be.

"We looked exclusively at women because statistically they are twice as likely as men to suffer from clinical depression," Sheline says. "We also excluded women with other medical illnesses to lessen the chance that something other than depression accounted for the changes."



Left and right hippocampal volumes (boxed) were measured in depressed and normal subjects.

A condition called hypercortisolemia may contribute to the atrophy in the hippocampus. Research has shown that the stress hormone cortisol is released in large amounts in the brain during depressive episodes. Sheline believes the excess cortisol may damage or even kill neurons and cause the volume reductions she observed in MRI scans.

Recent animal studies lend support to this view. Re-search has shown that rats injected with high levels of cortisol develop neuronal loss in the hippocampus. Rats exposed to stress and to low levels of the same hormone also suffer atrophy in the hippocampus.

"If the same mechanism is at work in humans, that could at least partly explain what we've seen in the MRI scans," Sheline says.

If that is the case, Sheline says the atrophy of the hippocampus in depressed women could mean that depressive episodes relate to one another. A depressive episode could leave "footprints" in the form of damaged neurons. Such damage may make a patient vulnerable to future depression, which would explain why the illness recurs in some people months or years after they are treated.

"For many years, depression has been thought of as a functional illness caused by a temporary chemical imbalance," Sheline explains. "When the depression remits, that's the end of it, unless another chemical imbalance causes a future episode. Our study indicates we might need to look a step further."

Researchers compared high-resolution MRI scans from 10 women who never had been depressed with scans from 10 others who had suffered multiple depressive episodes. None of the patients, who averaged 60 years of age, were depressed at the time of the study.

Hiles, who was among the women Sheline studied, sees Sheline's research as further confirmation that depression is a disease rather than a weakness or a character flaw. She says her mother

thought her depression was some kind of punishment. "My mother was ashamed that I was depressed, and I always thought I was crazy, and I would really hurt when I was depressed.

"I remember it was such a relief when I finally learned that depression had physical causes, just like any other illness," she says. "Like a broken leg or a fever, depression may incapacitate you for a time, but I want other depressed people to know that it's something you can recover from."

"Many people still don't understand that this is a very serious illness that makes people very sick," Sheline explains. "When you compare the functional outcome, depression has morbidity and mortality rates comparable to heart attacks and other diseases better understood by the public."

Depression is the most common psychiatric illness, affecting about 15 percent of all people at some point in their lives. It has enormous economic consequences — treatment, hospitalization and lost work time cost the U.S. economy about $20 billion annually.

The Next Step

Past research has shown that chemical and hormonal imbalances in the brain contribute to depression, but Sheline's is the first study to suggest that those irregularities cause permanent damage in patients screened to exclude physical illness and risk factors for brain damage. Recently, the journal *Science* cited Sheline's report as one of a handful of groundbreaking papers to demonstrate how stress can harm the brain.

In a parallel study, similar changes were found in the hippocampus of posttraumatic stress disorder patients. That study from researchers at Yale University found that combat veterans had volume decreases in the hippocampus on the right side of the brain. Posttraumatic stress and depression involve the release of large amounts of the hormone cortisol.

When Sheline's team examined MRI scans from the depression study, they noted that while total brain volume was comparable in the two groups of patients, the hippocampus was about 12 percent smaller in patients who had been depressed than in control subjects.

Sheline says the subtle nature of the atrophy could explain why the changes have not been found in the past. "Although we favor the notion that depression causes hippocampal changes, we cannot exclude the possibility that some people are born with a smaller hippocampal region which, in turn, makes them more vulnerable to bouts of depression," she explains.

In a larger study, Sheline will look at that "chicken and egg" question as she studies greater numbers of depressed women ages 30 to 80. She also plans to follow subjects over time.

If a small hippocampus puts patients at risk for depression, Sheline says she would expect to see volume differences in study subjects at a very early age and observe little change over time. If, however, depression causes the hippocampus to shrink, she would expect to see only minor differences in young subjects with large differences in older ones.

To answer these questions, Sheline has begun a five-year study of depressed women. She thinks that she will ultimately find that hormones released during major depression cause the hippocampus to shrink. The researchers will also conduct neuropsychological studies to test brain function in patients who have experienced depression.

If researchers find that depression is damaging the hippocampus, Sheline says a small loss in volume probably will not cause major impairment. New drugs and therapy can help relieve the symptoms of depression in a short time.

"What would be exciting is to find a treatment which could alleviate some of the potential for ongoing damage," Sheline says. "Anti-depressants alleviate the symptoms, but they are not sufficient to prevent the actual brain damage that occurs."

If researchers can show that stress hormones selectively kill neurons in the hippocampus during depression, Sheline says it may be possible to develop a therapy that protects those neurons. ●