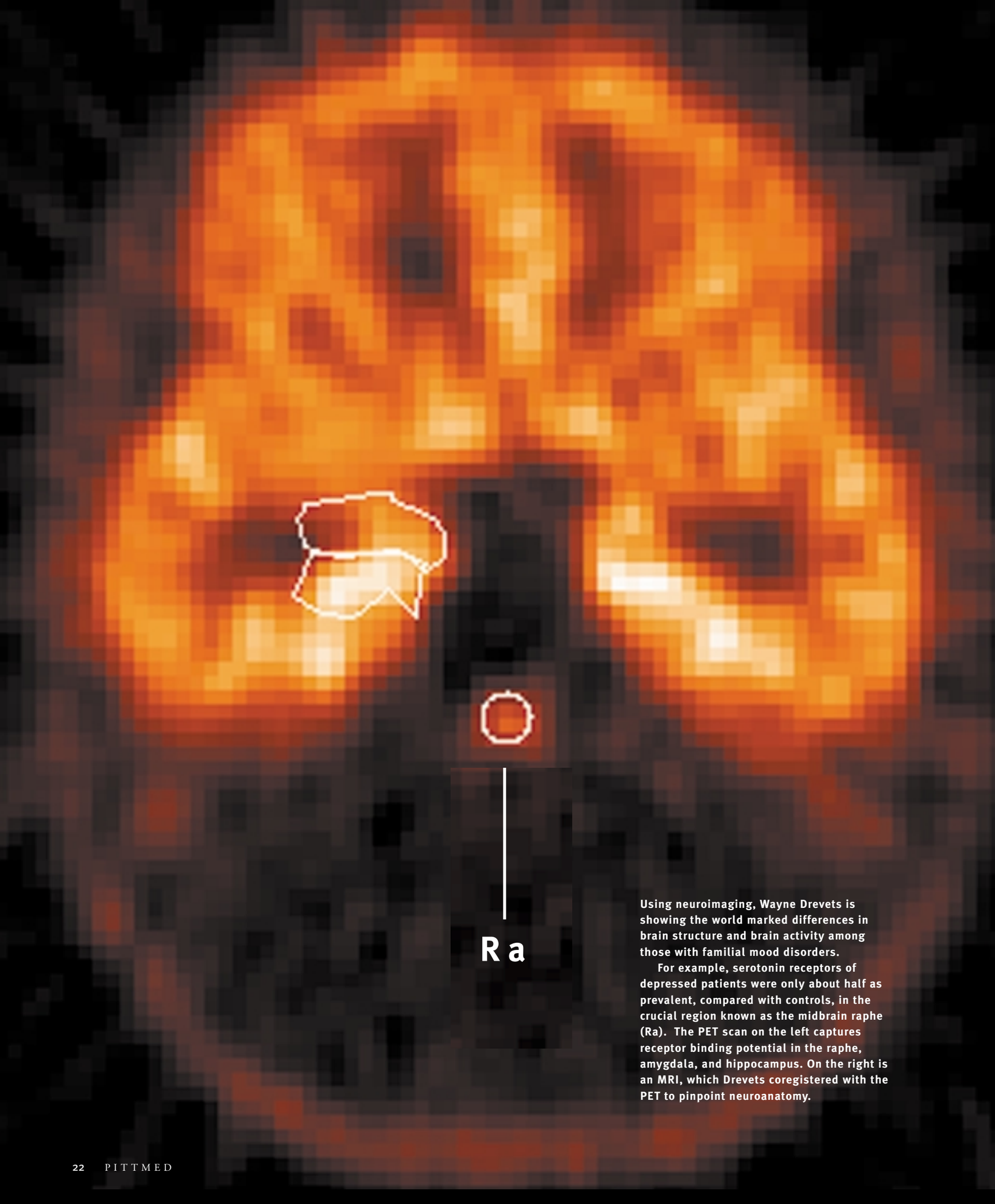
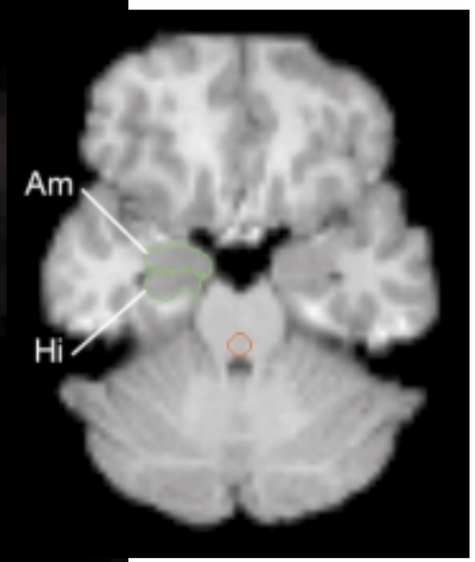


Using neuroimaging, Wayne Drevets is showing the world marked differences in brain structure and brain activity among those with familial mood disorders.

For example, serotonin receptors of depressed patients were only about half as prevalent, compared with controls, in the crucial region known as the midbrain raphe (Ra). The PET scan on the left captures receptor binding potential in the raphe, amygdala, and hippocampus. On the right is an MRI, which Drevets coregistered with the PET to pinpoint neuroanatomy.

NOW WE CAN SEE—DEPRESSED BRAINS ARE BIOLOGICALLY DIFFERENT | BY EDWIN KIESTER JR.

LOOK AGAIN



When the cable arrived, my wife and I both cried, "How can I tell you that David is gone, never to return?" The message read, in words still burned into my brain: "Sunday night he took his life."

David was 49. He was our closest friend, a backpacking buddy, a brilliant editor and writer, *magna cum laude* from Harvard, creative in every way, loyal to my wife, and a pal to our son. But we also, painfully, saw David's other side—deep, dark, despairing moods that alternated with bursts of almost boundless, unstoppable energy. We knew about the medication he swallowed in an effort at a more serene, stable life; we also knew about his close relatives who sought to end their own anguish by poison or a bullet. David chose a noose. His death was devastating, but it was scarcely a total surprise.

NEUROIMAGING | COURTESY OF DREVETS
PHOTOGRAPHY | CRAIG THOMPSON

Serious depression, officially known as unipolar or major depressive disorder (MDD), touches more than 10 million American adults each year. Manic-depressive illness—bipolar disorder, characterized by drastic swings of mood—affects more than two million, according to National Institute of Mental Health (NIMH) estimates. Many people plunge into darkness again and again. In families like David's, the illness runs through the generations like an ominous black thread. Counting milder forms of depression, NIMH estimates, 10 percent of the population is afflicted, and antidepressants are among the most-prescribed drugs in the physician's armamentarium. For all their prevalence, however, the exact whys and wherefores of mood disorders have remained a tragic and recalcitrant puzzle.

At the University of Pittsburgh School of Medicine, however, Wayne C. Drevets, an MD and associate professor of psychiatry and radiology, has been fitting illuminating pieces into that puzzle. Using positron emission tomography (PET) and magnetic resonance imaging (MRI), he has demonstrated that the brains of those with familial mood disorder, both unipolar and bipolar, function abnormally during depressive episodes, and portions of their brains are actually diminished in size. One of the areas where these differences occur is a part of the forebrain the size and shape of an index finger. This area, located behind the eyes and between the brain's two hemispheres, is known as the subgenual prefrontal cortex (PFC). This region serves as a way station between what might loosely be called the "thinking" part of the brain, where information is received and processed, and the "feeling" part, the lower-order centers where inputs are interpreted in emotional terms. Depression, in the words of one researcher, results from "imperfect traffic" between these two areas. In Drevets's words, depressed persons lack "an effective set of brakes" for checking persistent and inappropriate emotional responses to a given experience.

Overlaying the two sets of images, Drevets could see that in the bipolar group the subgenual prefrontal cortex was 39 percent smaller than in the control group, and in the unipolar group it was 48 percent smaller.

That the brains of those suffering from what has been called "a malignant sadness" are visibly different is obviously a key discovery in the mood-disorder puzzle. Seated under mounted slides of brain cross sections in his office at the UPMC Health System PET Facility, Drevets sums up his pathbreaking findings in somewhat more technical language:

"We have been able to identify circuits of the brain that function abnormally in depression and have also been able to show actual decreases in volume in a number of key structures involved in inhibiting emotional expression or stress responses. That seems to be the neural model for individuals who have mood disorders that run in families, so that they get stuck in a persistent pattern of negative emotions that they find difficult to control and that the medication we use to treat these illnesses does not cure."

In Drevets's ongoing neuroimaging research, adult patient volunteers are selected from those just entering an episode of depression but not yet receiving antidepressant medication. Two out of three are women, reflecting the caseload in the mood-disorder population. After being infused with a radioactive form of oxygen, they travel supine through a humpbacked, tunnel-like machine to trace brain blood flow and glucose metabolism (glucose is the brain's fuel). The radioactive oxygen emits positrons, or positive electrons, which collide with electrons in the body to give off gamma rays. The PET scanner encircling the patient detects the gamma rays and creates a continuous, multicolored image of the region where the reaction is occurring, providing a millisecond-by-millisecond visual record of brain activity.

A few years ago, Drevets conducted a study with depressed patients and other persons serving as nondepressive controls. Some patients were characterized as unipolar, others as bipolar. PET images of the two groups showed that the depressed patients metabolized glucose in the subgenual PFC at a rate 12 percent lower than the control group did—with the striking exception of bipolar patients in the manic phase, whose rates were actually higher. PET images were then matched with those obtained by MRI, which can produce more minutely detailed images of brain anatomy. Overlaying the two sets of images, Drevets could see that in the bipolar group the subgenual PFC was 39 percent smaller on average than in the control group, and in the unipolar group it was 48 percent smaller.

"The changes were subtle," Drevets says. "It's not like traditional radiology for tumor or stroke, where they jump right out at you." Yet the results were unmistakable. The depressed person's brain was clearly different.

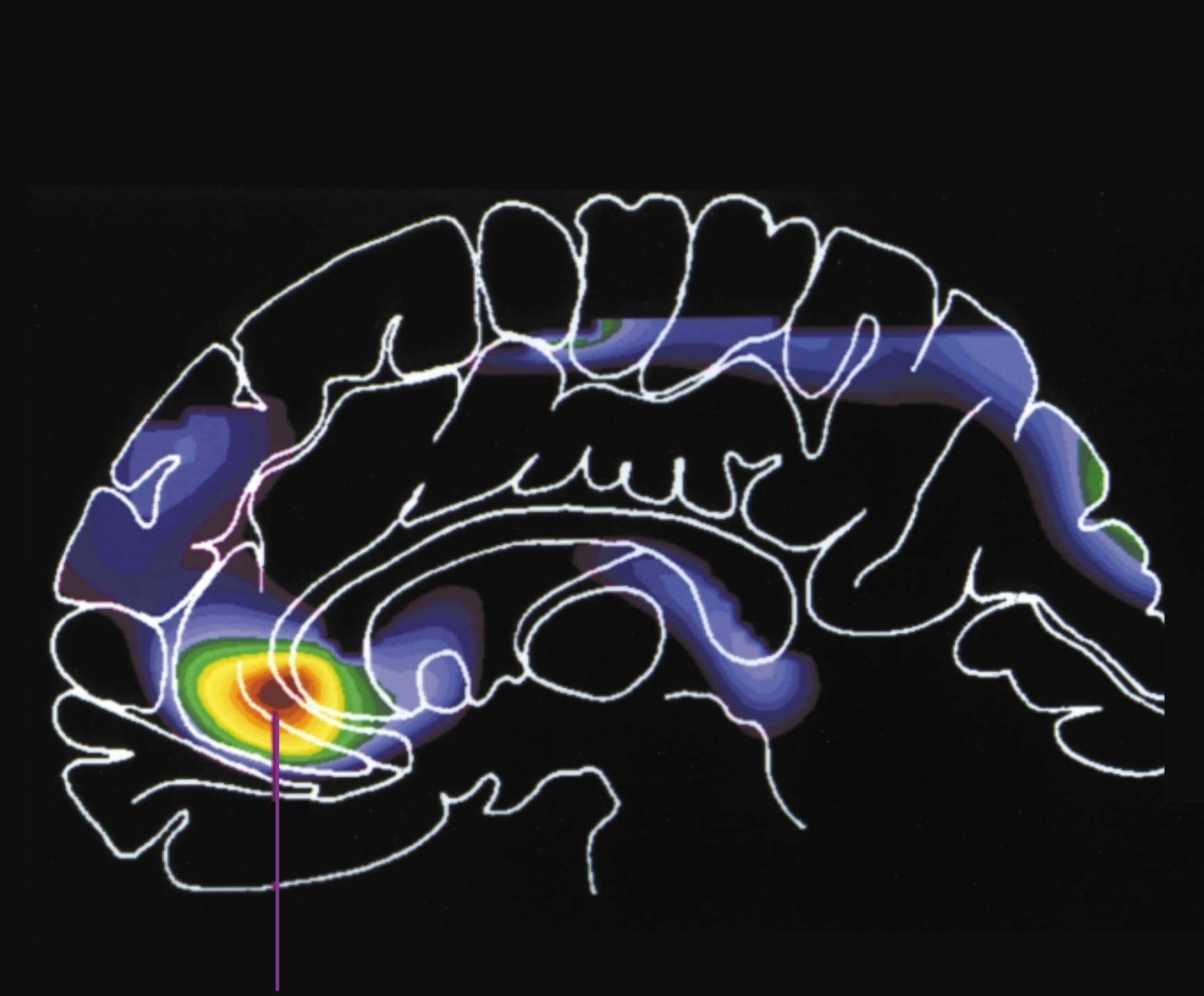
Drevets and colleagues published their findings in *Nature* (April 24, 1997), immediately causing a stir among neuroscientists and bringing him worldwide television exposure, including, he notes a bit shyly, interviews on the BBC. "Drevets has done first-rate work," declared Frederick K. Goodwin, former NIMH director and a leading voice in depression research. Antonio Damasio, of the University of Iowa, another commanding pres-

A HOLY GRAIL UNEARTHED

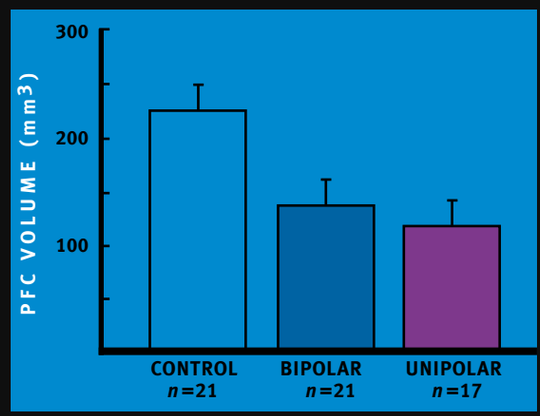
If you want to see depression in action at the neurobiological level, you might start at the thalamus and head south a bit. Here, in the midbrain raphe, is where serotonin is synthesized. For years, scientists' ability to measure accurately how serotonin receptors bound in the raphe of living persons was, to say the least, elusive. As Wayne Drevets puts it, this was one of clinical neuroscience's holy grails.

However, further developing a novel radioligand (i.e., a radioisotope used to tag and measure binding activities), first applied in England, changed all that. Recently, Drevets, Ellen Frank, Chet Mathis, and others in Pitt's Departments of Psychiatry and Radiology found that the binding potential of serotonin 1A receptors was reduced by almost half (42 percent) in the raphe of depressed persons compared with a control population. The binding potential in limbic and neocortical areas of depressed patients also was less than optimal: 25 and 33 percent lower, respectively. What's more, those discrepancies were found among patients with both unipolar (major-depressive) and bipolar (manic-depressive) familial mood disorder—the same subgroups falling under the umbrella of illnesses known as "depression" that Drevets had identified earlier as having smaller subgenual prefrontal cortexes. ***—EL***

Wayne Drevets with the PET scanner. He keeps handing in more evidence for neurobiological explanations of familial mood disorder.



In the subgenual prefrontal cortex, Wayne Drevets found that metabolic activity is reduced during depressive episodes. Colors show decreased glucose metabolism—the red/yellow end of the spectrum indicates the highest difference in activity relative to controls. The low activity is at least partly explained by the smaller subgenual prefrontal cortexes (PFCs) in depressed persons. The bar graph compares subgenual PFC volume in Drevets's nondepressed control group with that of bipolar (manic-depressive) and unipolar subjects during depressed episodes. The reduction is 39 percent in the bipolar and 48 percent in the unipolar.



Experts point to a subtext in the research. The fact that recurrent familial bipolar and unipolar disorder both show abnormalities in the same part of the brain indicates they are "close cousins." Physicians should consider that relationship when choosing treatment.

ence in neuroscience, similarly praised Drevets's research in an editorial accompanying the *Nature* paper. Of the PFC discrepancies reported by Drevets, he wrote, "Drevets et al. have identified a key player in one of the several systems that underlie emotional processing—a valuable finding indeed."

For 30 years, evidence has been mounting for a neurobiological explanation of familial mood disorder. In other words, "It's not just a matter of how your parents raised you," to quote Goodwin, the former NIMH director and author with Kay Redfield Jamison of *Manic-Depressive Illness*. Indeed, the drugs that are the basis of treatment are aimed at correcting a presumed defect in the brain's chemistry by boosting the available supply of the neurotransmitter serotonin, one of the chemicals that enable brain cells to communicate with one another.

Drevets keeps handing the neuro community more evidence. In recent research, he focused on receptors for serotonin, which allow the neurotransmitter to be taken up and reused by cells. Accurately measuring receptor action had long been a murky region of study—sort of a holy grail for clinical neuroscience. Drevets et al.'s PET scans showed marked differences in serotonin receptors for patients with familial mood disorder. Drevets also has conducted postmortem studies on brain tissue from depressed persons who died of suicide or other causes (in collaboration with Joseph Price of Washington University in St. Louis, Missouri). Sure enough, the subgenual PFCs of depressives turned out to be smaller than the subgenual PFCs of controls.

Before David J. Kupfer, chair of Pitt's Department of Psychiatry, recruited him four years ago from Washington University, Drevets, at 39, already had earned a national reputation in neuroscience research and received a Career Development Award. Meanwhile Pitt was seeking to strengthen its acknowledged leadership in neuroscience research, especially neuroimaging.

"It was the premier psychiatry department in America," Drevets notes in describing his decision to join Pitt's faculty. "They saw early on that receptor imaging was going to be very important in psychiatry, and they had assembled the radiochemists and physicists to enable them to do it. Plus, it was about three times larger than Wash U."

The workings of the human brain had intrigued Drevets since he was a junior at Wheaton College volunteering at Elgin State Hospital in Illinois.

"I developed this enduring fascination for what caused psychiatric illness," he recalls. Drevets comes from a family of internists, and he had planned to practice cardiology. But on psychiatric rotation at the University of Kansas Medical School, he got his first glimpse of the potential of brain imaging.

"I quickly saw it as a way to understand the pathophysiology of psychiatric disorder," he says.

At "Wash U," he was mentored by Marcus Raichle, whom he recognizes as "one of the true pioneers of imaging." Drevets spent 10 years in St. Louis, then moved to Pitt's School of Medicine.

Since then, Drevets has done his part to stir up conventional wisdom. His postmortem studies revealed a striking finding: The depressed brain had lost glial cells, yet the functioning neuron count was normal. That was big news. Glia have long been considered scaffolding that supports functioning neurons, yet they appear to do much more than science had recognized. Researchers have found that among other responsibilities, these numerous cells store glucose and play a role in neuronal metabolism. Some types equipped with serotonin receptors help to innervate the brain with that important neurotransmitter. If the brain loses glia, less serotonin might be available, and thus the brain might not be as well equipped to right itself from attacks of depression.

The link between loss of glia and depression isn't clear, Drevets says, "but what we know is that in depression, there are too few glia."

All this raises one of those chicken-or-egg questions: Does an episode of depression trigger changes in the brain, such as lower glia counts and subgenual PFC volumes; or is depression brought on by existing brain abnormalities? Or rather, is "malignant sadness" caused by an interaction between the two? Drevets is now aggressively seeking those answers, studying the same patients when they are depressed and when they have emerged from depression. Preliminary results seem to indicate that some abnormalities are persistent and may serve as markers for the illness. He also has begun to perform PET and MRI imaging on "high risk" young adults (meaning people who have more than one family member affected) to see whether abnormalities might predate the first episodes of depression.

Other questions arise, too. Do repeated episodes of depression cause damage in other parts of the body, the way hypertension or diabetes assaults the blood vessels, the heart, and the kidneys? Is there a way to target drugs directly to the deficient areas where they are needed? Finally, is there some distinct anatomical or neurochemical marker detectable with a brain image by which those vulnerable to depression could be picked out in advance?

The benefits of Drevets's research to diagnosis and treatment of mood disorders will be played out largely in the future. Yet Goodwin, who is now director of the psychopharmacology research center at George Washington University, points to a subtext in the research of potential importance to treatment now. The fact that recurrent familial bipolar and unipolar disorders both show abnormalities in the same part of the brain indicates they are "close cousins." Physicians should consider that relationship when choosing treatment. They should also note, Goodwin cautions, that both conditions are different from what happens when a man suffers from a single bout of depression after losing his job.

"Our work in imaging has led us to clues we knew nothing about beforehand," Drevets says.

"We don't yet know what sets what in motion. We now know the important things to study. The kind of information we're getting may well account for why treatments work. [It] may also lead to an understanding of how we should be treating people more effectively in the future."

Let's hope that understanding will save the lives of future Davids. ■