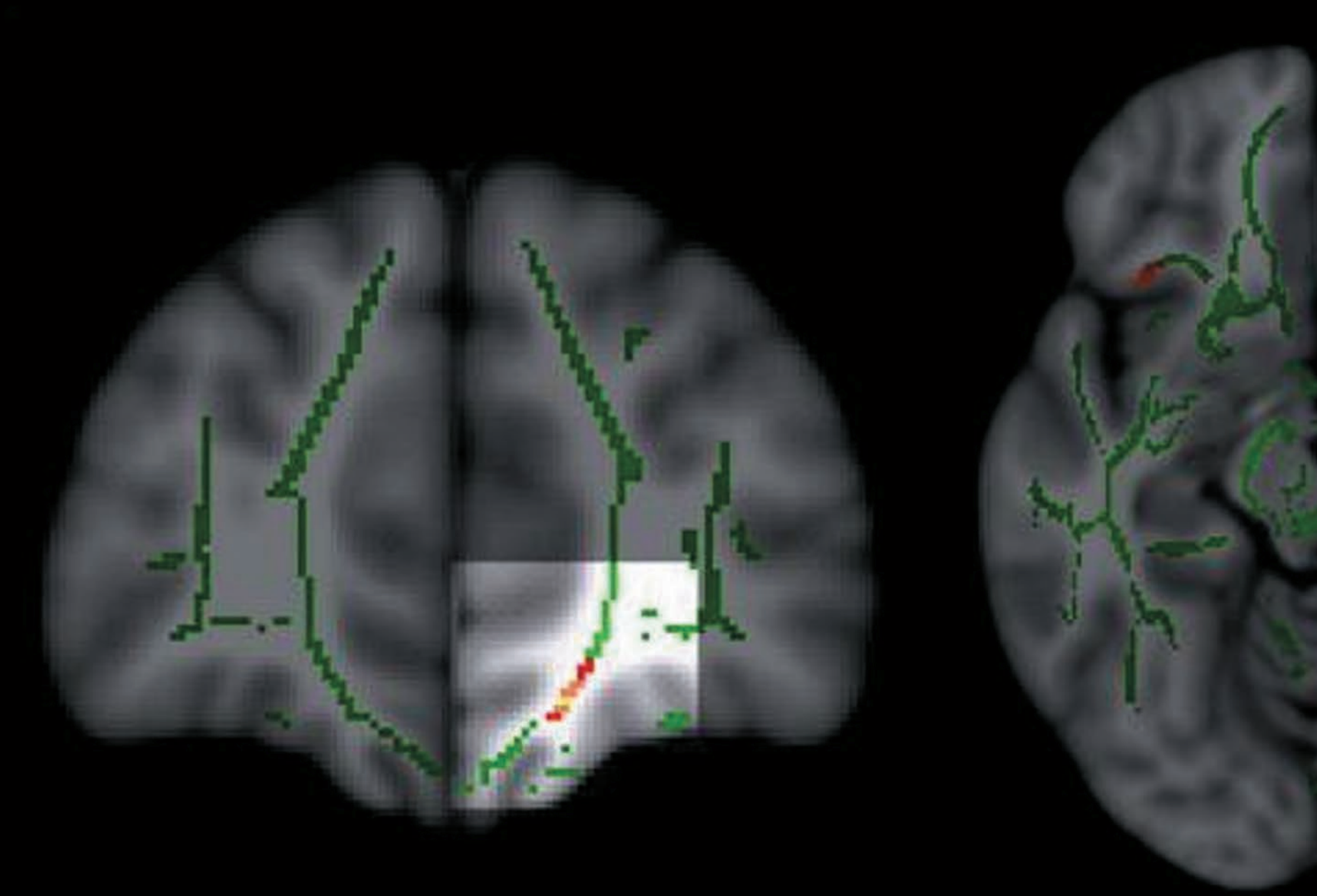
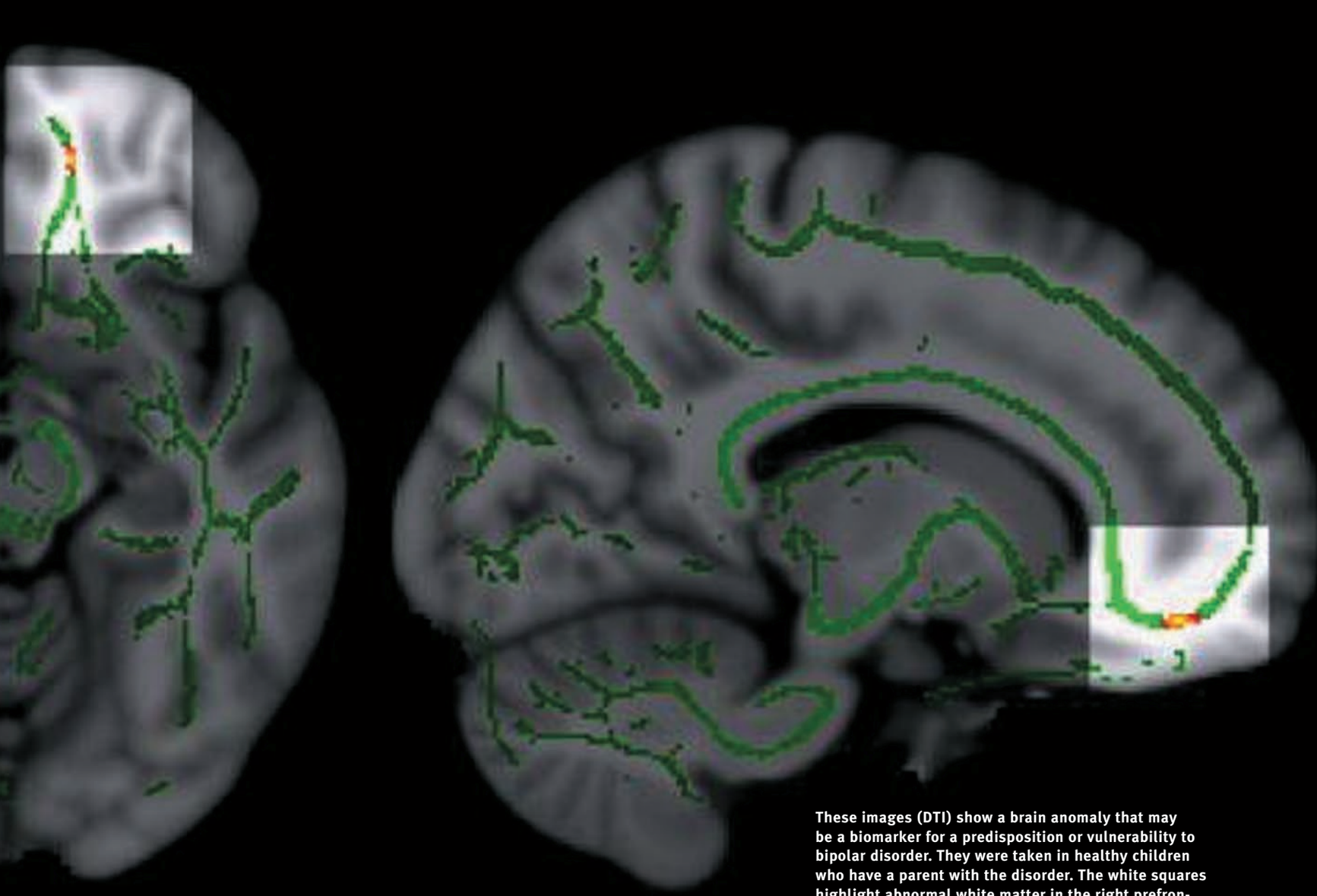


NEW ANATOMICAL EVIDENCE OF BIPOLAR DISORDER | BY ELAINE VITONE

TRAPPED MINDS



These images (DTI) show a brain anomaly that may be a biomarker for a predisposition or vulnerability to bipolar disorder. They were taken in healthy children who have a parent with the disorder. The white squares highlight abnormal white matter in the right prefrontal cortex. This anomaly is similar to what is seen in adults who have been diagnosed with bipolar disorder.

COURTESY CLINICAL AND TRANSLATIONAL AFFECTIVE NEUROIMAGING PROGRAM

About 15 years ago, Colin Davies (we've changed his name), an Oxford-educated Londoner in his early 20s, became depressed and went to see a psychiatrist. His doctor gave him a prescription, and once the pills started to work, things were glorious.

Not only had the crushing weight of his darkened mood vanished, but in its place came a feeling so incredible he couldn't cram all his enthusiasm into the daylight hours. He hardly slept or ate, but he didn't feel tired or hungry. He binged, partied, and took everything and everyone in his life for granted—but he was too euphoric to notice.

And then, months later, all the joy rushed out of him. He told his doctor the medication wasn't working anymore and asked for another. Once those pills kicked in, the unstoppable Super Colin Davies was back … for a while. He raged on like this, caught in a cycle of self-sabotage, for a decade. When he was feeling high, he cheated on his partner, shouted, and even struck his child. And then there were months when he was so low he could barely function.

"It was so tragic," says psychiatrist Mary Phillips, who began treating Colin when he was in his mid-30s. "He ended up with no job, no partner, no access to his children, and this awful mood disorder."

But Phillips realized Davies' disorder wasn't clinical depression, as his previous doctors had assumed. By the erratic way he behaved in her office, it was clear to her that he had bipolar disorder, one of the most severe of all psychiatric illnesses.

Marked by swings between mania and depression, bipolar disorder affects 2 percent of the population and is notoriously difficult to diagnose. When people with bipolar disorder seek help, it's almost always when they're depressed, rather than when they're high. (Phillips' exam with Davies was a rare exception.) At the clinic, they're virtually indistinguishable from people with unipolar depression. If misdiagnosed and given antidepressants, those suffering from bipolar depression turn manic, then swing between emotional extremes even more drastically. The would-be cure brings out the worst in the disease.

Virginia Woolf wrote of how the family curse of mental illness plagued him with "violent states of excitement and states of utter apathy."

People with bipolar disorder commonly spend a decade trying to get the right diagnosis. By that time, many end up like Davies.

"With very good training and a lot of experience, you can hone your skills and get a very good idea of what diagnosis the person may have," says Phillips, who treated many mood-disorder patients in London throughout the 1990s. "But it takes a long time to ask all the right questions. We desperately need biological tools."

Phillips has been a leader in the field of psychiatric neuroscience since it began 25 years ago with the emergence of brain-imaging technologies. In 1997, she published a paper in *Nature* on the neurobiology of the emotion of disgust. It was the first study ever to link an emotion to a site in the human brain.

After investigating obsessive-compulsive disorder and schizophrenia for several years, Phillips came to the University of Pittsburgh in 2003 to focus primarily on bipolar disorder. She's now a professor of psychiatry, director of the Functional Neuroimaging Program, and codirector of the Brain Imaging Research Center. (She's also a consultant/professor for Cardiff University's Department of Psychological Medicine in Wales and a visiting professor at the Institute of Psychiatry in London.) Of the numerous neuroimaging studies she has published in the field's premier journals, her September 2009 *Biological Psychiatry* paper stands out. It established, for the first time, a pattern of distinguishing anatomical characteristics that separate bipolar disorder from unipolar depression.

Phillips is 5-foot-10 with long brown hair; a quick, alto-pitched British accent; and an obsession with her e-mail account. To stay in touch with her armies of collaborators around the world, as well as mentees and colleagues down the hall, she's plugged in from 6 a.m. to midnight, seven days a week.

She's been pleased to find that her work is more valued in the States than back home. Across the United Kingdom, many psychiatrists openly decry psychiatric neuroimaging as an unjustifiable expense—why do it when you can diagnose patients by talking to them? Others call brain scans superficial snapshots that can't even scratch the surface of the complex human mind.

Phillips says that if you had chest pains, or a broken limb, or a serious problem with any other part of your body, your doctor wouldn't just ask you where it hurts and treat you based on that. So why should the brain be any different? The expense of neuroimaging is coming down, she reports. And she asks us to consider the toll on these patients and their families as they struggle through years of anguish. Some of these cases result in suicide, she reminds.

When the *Pittsburgh Post-Gazette* reported her landmark study this summer, she received dozens of e-mails of support.

My poor son/daughter/husband/wife is sick but can't get the right diagnosis, said some.

Others said they suspected they themselves had bipolar disorder. They asked: *Can I come in and see someone? Can I have a brain scan?*

And they wrote: *Thank you for helping me understand that it's not my fault and that I'm not a bad person.*

Phillips wrote each correspondent back, connecting them with local resources and, when requested, with members of her staff who screen and coordinate study participants. She also thanked them.

"All of it's been incredibly positive and very touching," she says. "It's made me think I must be doing something right."

In Phillips' *Biological Psychiatry* study, participants sat in a scanner and looked at a series of pictures—faces exhibiting extreme emotions like fear, anger, happiness, and sadness. About half of the participants were in a state of depression and had previously been diagnosed with bipolar I—the most severe form of the disorder. The other half were controls.

Facial expressions have universal meanings for all of us, regardless of language or culture. It's a gift of our evolution as primates, a way to pass on essential messages quickly and without uttering a sound. The simple act of looking at a face evokes a powerful empathetic response in the brain—emotional contagion, as it's called—whether the person realizes it consciously or not. Phillips was one of the first to use contagion to map emotions in the brain, a technique that's widely used today.

As the test subjects completed the exercise, Phillips' team paid close attention to the uncinate fasciculus, one tract in the vast network of wiring that enables brain regions to communicate with one another. The uncinate fasciculus connects the amygdala (an almond-shaped bulge at the bottom of the brain that helps us process the emotional impact of our experiences) to the orbital prefrontal cortex (a region at the front of the brain that helps us control our behavior). The orbital prefrontal cortex regulates the amygdala as brakes do on a car.

In an earlier study, Phillips and Pitt's Amelia Versace found that in people with bipolar disorder, the fibers of the uncinate fasciculus were thinner than normal on the left side of the brain, the side that's generally associated with positive emotions. This anomaly may explain the difficulty in putting the brakes on positive feelings. Hence mania.

On the right side of the brain, which is associated with negative feelings, the uncinate fasciculus fibers were thicker and more criss-crossed than normal. This suggests a tendency to get caught in a loop of negativity. Hence depression.

In another imaging study of unipolar depression, Phillips and Versace found no abnormalities on the right side of the brain—and on the left, the uncinate fasciculus was *thicker* than normal, not thinner.

"That kind of makes sense," says Phillips. "Too much of a brake on that side means [people with unipolar depression] are always going to have difficulty feeling positive."

Phillips has been awarded funding from the National Institute of Mental Health to use brain imaging to further identify and confirm abnormalities that could help distinguish between bipolar and unipolar depression.

Her team uses a combination of imaging technologies: fMRI (functional magnetic resonance imaging), which tracks blood-flow increases throughout the brain, and DTI (diffusion tensor imaging), which maps the wiring that connects brain regions. DTI is a much newer technique and a welcome one. Blood flow alone can't tell the whole story.

If there's a glitch affecting one region of the brain, to some extent, another region (or regions) will pick up the slack. Phillips' team is showing how these altered networks behave by imaging both function and fine-detail structure at once and in real time. Their hope is that imaging could eventually help psychiatrists not only diagnose mood disorders, but also prescribe and refine treatments, as well as track patients' progress—a potentially life-changing prospect for people who struggle through the frustrating process of finding just the right drug combination and dosage.

Jorge Almeida, a Pitt postdoctoral associate, began his research career under Phillips' wing four years ago. Back then, he expected the pathophysiology of psychiatric disorders would be his focus—and the idea of his work having any clinical implications in the foreseeable future didn't even occur to him. Since working with Phillips, neurological biomarkers have become his mission. "It's all happening so fast," he says. "It's like cancer research was 30 years ago."

Phillips mentors more than 20 emerging researchers and does a bang-up job in spite of the breakneck speed at which their projects are growing and evolving, her protégés say. When they present their work at conferences, Phillips makes sure to introduce her mentees to all the big names. When they knock on her door seeking advice, she welcomes them in with a smile. And her e-mail replies are lightning-fast.

"I don't know how she does it," Almeida says, laughing. "I try at different times of the day, I try on weekends. She always writes back right away with helpful comments on the papers we're working on."

"Because [Phillips] has worked in other disorders, she's able to come up with more general theories that might apply," says Natalia Lawrence, a former-mentee-turned-collaborator at Cardiff University's Wales Institute of Cognitive Neuroscience.

Phillips' team is working on studies of bipolar II disorder, the less severe version of the disorder that is even more elusive. For these individuals, the depression side is evident, but the other extreme, dubbed hypomania, can be tough to pin down.

Hypomania, as its name suggests, can manifest as a toned-down version of mania—a hyper, life-of-the-party feeling—but it can also feel more like irritability and anger on a short fuse. Even after finally arriving at a diagnosis, people with bipolar II often have a very hard time accepting that they have it and taking medications. The mood-stabilizer drugs used to treat bipolar disorder can cause patients to feel emotionally flat, drowsy, or nauseated or to experience other unpleasant side effects.

"As far as they're concerned, they've just got to wait to find the right antidepressant," Phillips says. But when she's shown patients their scans and explained the results, the reaction has been quite different. "It helps people more readily accept the appropriate treatments if they know there's a scar or a broken circuit."

Bipolar disorder is an ailment of many guises, a range of combinations of symptoms in varying degrees. Psychiatrists who've labored to decipher these subtleties know well that it's probably overly simplistic to say that there are only two types of bipolar disorder, either I or II. More likely, there's a whole spectrum of gradients in between, each with its own set of symptoms and pathologies, though this has yet to be proven. Phillips hopes to pursue this hypothesis with Holly Swartz, also in the Department of Psychiatry.

As if bipolar disorder weren't devastating enough, it often comes with other problems—namely, insomnia and risk-taking behavior. That can add up to a real powder keg. No one knows why these particular issues are such common twofers or threefers—comorbidities, in clinical parlance. To get to the bottom of it, Phillips' team is comparing the genetics of mood control and sleep problems with brain imaging.

A century before Colin Davies' illness took hold of him, a fellow countryman named James Kenneth Stephen—a first cousin of novelist Virginia Woolf—began acting odd. Woolf wrote of how the family curse of mental illness plagued him with both "violent states of excitement and states of utter apathy."

During his monthslong manic periods, Stephen blew his money on useless trinkets and strange clothing. He rode around Cambridge all day in a horse-drawn cab, then arrived home, wild-eyed and frenzied, and rushed inside, leaving his father with the bill. At one point, he ran through the streets stark naked. He was institutionalized soon after, in November of 1891.

At first, he lashed out, destroyed the furniture, and struck a staff member. Then came depression. Then a cheerful and vigorous phase. Then irritability.

In mid-January, the depression returned, and Stephen fell into an unyielding trap of the mind; he couldn't eat or sleep. His face sallow, his pulse racing, he lay there mumbling, "It's too late," as he wasted away. He died on Feb. 3, 1892.

In the days before lithium, this is how many people with severe bipolar disorder spent their final days. One 1933 study found that 40 percent of bipolar patients who died in the hospital succumbed to "manic exhaustion," like Stephen. Suicide also was common.

Today we know that, if left untreated, bipolar disorder causes deterioration—tiny lesions in the wiring of the brain—that worsens over time. The earlier treatment begins, the less deterioration patients will suffer throughout their lives. And the better they'll respond.

What if bipolar patients could confront the disorder as early as childhood or adolescence? What if they could contain bipolar disease before it had a chance to rob them of even one day of healthy adult life?

Phillips' lab is partnering with the Child and Adolescent Bipolar Services Clinic at Western Psychiatric Institute and Clinic of UPMC, which is devoted exclusively to the treatment and study of bipolar disorder in the youngest populations. Working with Boris Birmaher, Pitt's endowed professor of early onset bipolar disease and a professor of psychiatry, and David Axelson, director of the clinic and Pitt professor of psychiatry, she's beginning to look at the brains of children who have just received a diagnosis, as well as children who are at risk because of a family history.

They're charting out how it all begins, watching what changes from the very first manic and depressive episodes.

Phillips reminds us that scientists are just beginning to pierce the mysteries of the mind.

"We really only know, I would guess, about 5 or 10 percent of what there is to know in terms of brain circuitry problems—at most," she says.

Still, she's unfazed.

"We have a lot of work to do; so no weekends off." ■