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A CHANGE OF MIND



Brandon Staglin experienced many symptoms before getting schizophrenia.

DE-ANNE FITZMAURICE

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Scientists are learning to predict psychosis years in advance—and possibly prevent it

By **Jennifer Couzin-Frankel** | Nov. 16, 2017, 12:30 PM

Rachel Loewy was an undergraduate in 1995 when she answered a flyer seeking students to assist with a research study. A couple of floors up in a psychology department building, Loewy sat, clipboard in hand, interviewing teenagers whose brain health was beginning to falter. Some heard whispers. Others imagined that their teachers could read their minds, or that fellow students stared at them and wished them harm as they walked down the halls.

The teenagers had been diagnosed with schizotypal personality disorder, a condition that can precede schizophrenia. Among the most debilitating and stigmatized psychiatric diseases, schizophrenia can rob sufferers of their self and their future, often in early adulthood.

Although these teens didn't have schizophrenia, the researchers believed that some would later deteriorate and be diagnosed with the disorder. But when Loewy met them they were lucid and self-aware. And they were frightened that their mind sometimes spun out of control.

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Doctors routinely assess a patient's risk of heart attack, various cancers, and diabetes, often intervening to slow or stop disease before it strikes. But preventing psychiatric conditions, from anxiety to depression to schizophrenia, has received scant attention.

The reasons are many. "With all due respect to cardiologists," the brain "is a very, very complex organ," says Jacob Vorstman, a Dutch pediatric psychiatrist who relocated this fall to The Hospital for Sick Children in Toronto, Canada. There, he's setting up a clinic to assess and follow young people genetically at risk of psychiatric disorders, including schizophrenia. Though the brain is better understood than it was a generation ago, Vorstman says, how its intricate dance of chemical and electrical signals gives rise to mind and personality remains mysterious.

Stigma is also a powerful barrier to prevention. Schizophrenia is marked by episodes of psychosis as well as cognitive and social problems, and it's deeply feared and often misunderstood, even by many physicians. That makes it ethically dicey, some believe, to label young people at risk when not all of them will develop the disease. "It's easier to say, 'I am a patient with asthma,' than to say, 'Listen, I have psychotic breaks,'" Vorstman suggests.

But change is afoot. In recent years, brain specialists have refined their ability to anticipate who's at highest risk of psychosis—a defining feature of schizophrenia—identifying subtle signs in some children and more vivid precursors in late adolescence. And increasingly, researchers feel they'd be derelict not to pursue prevention. Tests of preventive measures are up and running, ranging from cognitive therapies to pregnancy supplements for the fetal brain to psychiatric drugs. Last month, a German pharmaceutical company enrolled the first volunteer into what is intended to be a 300-person randomized clinical trial testing an experimental drug to prevent psychosis in those at extremely high risk. It's believed to be the first time a company has poured millions of dollars into an effort like this one.

“ If we knew then what we know now, we would have had much better clarity about what the symptoms we were seeing meant. ”

Garen Staglin

The quest to untangle schizophrenia's roots began in earnest in the 1980s. Researchers decided that "we ought to get as close as we possibly can to the onset of the illness," says Robert Heinssen of the National Institute of Mental Health in Bethesda, Maryland. At the time, that was considered the first psychotic break, when an individual cannot distinguish reality from fantasy.

But when physicians interviewed patients hospitalized after their initial psychotic episode, they were startled to learn that in many cases, "people began experiencing changes in cognition, behavior, and perception for months or years" before psychosis struck, Heinssen says. "That led to this idea that there's an emerging risk state that precedes" schizophrenia.

Brandon Staglin was 14 years old when he experienced this "emerging risk state" first-hand. Living with his parents and 6-year-old sister in Lafayette, California, a scenic town east of San Francisco, he was a science fiction fan who aspired to explore the galaxy and devoured Isaac Asimov books. "I was a little less social perhaps than some of the other students," Brandon says now, but nothing that triggered alarms.

At the time, his grandfather was near death from leukemia. One night, Brandon began wondering what it would mean for him to be gone. "I was pondering these deep thoughts and fell asleep," he remembers. "I opened my eyes 5 minutes later and couldn't tell the difference between whether I was dreaming or awake. It was very scary."

He put on a Bruce Springsteen song he'd always loved. "I didn't feel any of the emotions it [usually] stirred up in me," he says. Instead, he felt nothing. "That was even scarier." Although Brandon didn't recognize these dissociations as related to psychosis, he knew that something was terribly wrong. He woke his parents, who calmed him down, and he went back to sleep. The episode ended there: The next morning all was normal.

"These kids know something is not right," Loewy says. "They say, 'I'm hearing things,' and it freaks them out."

Through her mentor, psychologist Elaine Walker at Emory University in Atlanta, Loewy also met middle-aged adults with severe schizophrenia who struggled to maintain their grip on reality and couldn't carry on a conversation. She was struck by the disparity between the 15-year-olds and the 50-year-olds, and wondered about the path from early foreboding to serious illness. "Can't we do something?" she asked herself.

More than 20 years later, Loewy is a psychologist at the University of California, San Francisco, and that question has defined her career. With a small group of brain experts worldwide, she is trying to bring prevention to the field of psychiatry—one of the few medical specialties that hasn't managed to incorporate it.



Psychologist Rachel Loewy has been considering how to prevent psychosis in young people for years. Here she shows her research coordinator Mayra a new software program that involves cognitive training.

SUSAN MERRELL/UCSF

Four years later, as a freshman at Dartmouth College, Brandon was hit by an onslaught of symptoms that this time didn't dissipate on their own. A nightmare that he was embedded inside a tree, with one eye poking out and swiveling around, frightened him for days and left him convinced it carried a spiritual meaning. He heard voices telling him he was "a mixed-up kid."

That summer, he suffered a full-blown psychotic break and was diagnosed with schizophrenia. He was 18 years old.

"If we knew then what we know now, we would have had much better clarity about what the symptoms we were seeing meant," his father, Garen Staglin, says more than 25 years later. "He was such a superbright individual. We attributed his quirkiness and his behaviors to the Albert Einstein effect—he just couldn't be bothered with day-to-day things."

In 1996, not long after Brandon was diagnosed, a pair of Australian psychiatrists named Alison Yung and Patrick McGorry developed a model for the risk state Brandon experienced. They suggested that young people skate toward psychosis and then away from it, just as Brandon did that night his grandfather was dying. They may withdraw socially, suffer sleep disturbances, or stop doing schoolwork. Later work estimated that 20% to 35% of these people would suffer a psychotic break within 2 years.

But why does one person with these early signs develop psychosis and not another? Brain studies have yielded some clues. In healthy kids, "the brain dynamically changes" during adolescence, says Akira Sawa,

a psychiatrist at Johns Hopkins University in Baltimore, Maryland. In particular, widespread "synaptic pruning"—a sort of scaling down of connectors between neurons—**reshapes the brain as a child transitions to adulthood**. MRIs of some people with schizophrenia show that parts of their brain are smaller than normal, a feature associated with overactive synaptic pruning in adolescence.

Recent genetic research lends credence to this theory. In January 2016, a landmark study in *Nature* from the Broad Institute in Cambridge, Massachusetts, reported that **a set of genes associated with schizophrenia can contribute to synaptic pruning**.

So far, genetic studies have done more to elucidate biology than to identify people at high risk. Although schizophrenia has a strong inherited component—about 10% of those with an affected parent and 50% with an affected identical twin will be diagnosed—the genetics are "humbly complex," says Tyrone Cannon, a psychologist at Yale University with a longstanding interest in prevention. "It's not just one mechanism, it's thousands of genes."

The life and habits of an average teenager may amplify risk in those already tilting toward disease. Smoking marijuana, for instance, has been associated with psychotic episodes. Stress modulates hormones that are thought to affect pruning, and stressful events often precede a psychotic break. This was true for Brandon, as he struggled with his first year away at college and a breakup with a girlfriend before descending into psychosis.

Researchers who have sifted through medical records of people with schizophrenia from before the disease struck, or medical records of their children, recognize subtle signs even earlier. "We're looking back using the army records from Israel to see what happens before onset, or birth registries from Scandinavia," says Iris Sommer, a psychiatrist at the University Medical Center Groningen in the Netherlands. She and others have found what she calls a "huge trajectory" of symptoms arcing toward psychosis. This trajectory begins very young and becomes more pronounced, if vague, as a child grows.

Most of these signs are nonspecific and carry only a small increase in risk, and many people who are diagnosed later display none of them. Studies of pregnant women have found that some who suffer serious infection are more likely to have a baby who grows up to develop schizophrenia. In elementary school, children at risk can harbor irrational thoughts, like believing they're being spied on. They may make involuntary motor movements, or hold their limbs or head in awkward positions. Walker collected home movies of children who developed schizophrenia as adults, along with videos of age- and sex-matched siblings. The children were under 10, but in retrospect, the crystal ball was already clear. "Undergrads," says Loewy, who was one when she watched the movies, "could reliably tell which one was going to develop schizophrenia."

Arcing toward psychosis

Scientists are trying to decipher early signs that may indicate risk of psychosis later on, and they are testing ways to reduce that risk. Right now, most signs are very vague and nonspecific, and the vast majority of kids who exhibit them stay healthy.

- Risk factors
- Possible signs
- Possible interventions

Prenatal

Genetics

Serious second trimester infection

Preterm birth

Birth complications

Choline prenatally

Good prenatal care



8 years

Abuse

Head injuries

Being bullied



Being bullied

- Involuntary motor movements
- Unusual thoughts
- Many have no symptoms.

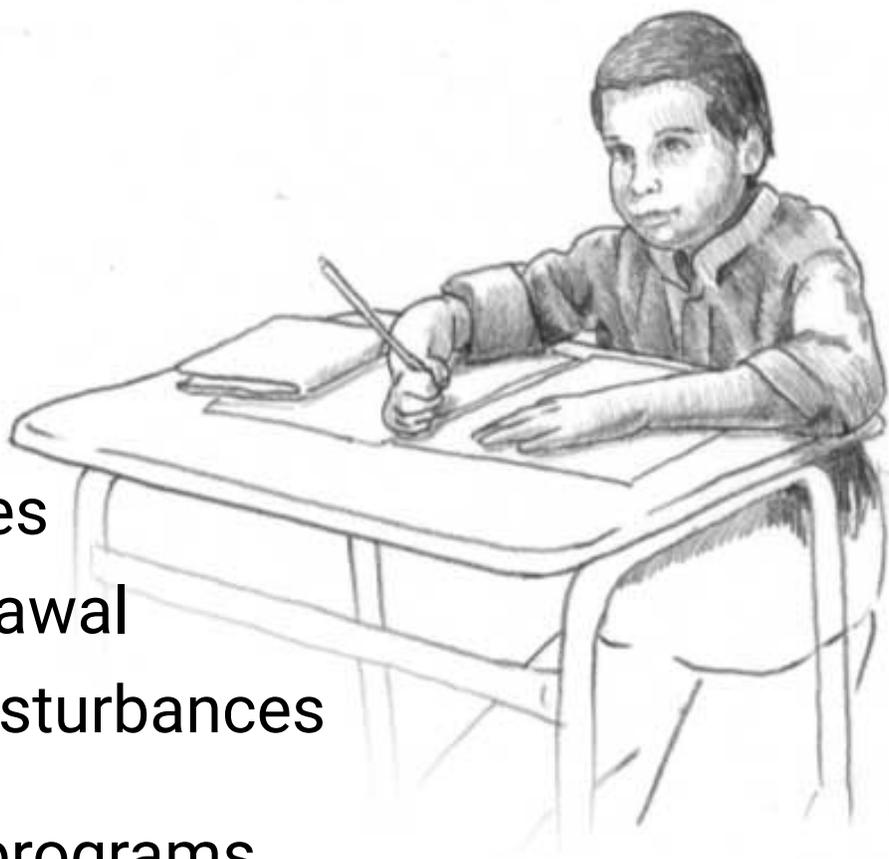
- Family therapy
- Prevent bullying at school.



11 years

- Abuse
- Being bullied
- Hearing voices
- Social withdrawal
- Perceptual disturbances

- Antibullying programs
- Drug abuse prevention



16 years

Smoking marijuana

Excess stress

Abuse

Withdrawing socially

Hearing voices

Distorted thoughts

Depression

Anxiety

Sleep disturbances

Difficulty with schoolwork

Cognitive behavioral therapy*

Family psychoeducation and support*

Physical exercise

Substance abuse



*Positive results

Anyone with young children might read this and worry—and that is exactly the challenge those seeking to prevent psychosis confront today. It's all well and good to decipher biology and study the health records or home movies of children who later develop psychosis. But that leaves out many others who stay healthy. Hearing voices at age 11 indicates a 16-fold increased risk of schizophrenia—but the overwhelming majority of these kids will never develop it.

To prevent disease, specialists must be able to pinpoint who is hurtling toward it. An international consortium is studying people with a genetic syndrome called 22q11.2 deletion syndrome, which puts them at about a 25% chance of a psychotic disorder. Researchers hope these patients, many of whom were recruited as children, will offer a clearer window into early cognitive and emotional changes that precede the illness. In another effort, Australia and six European countries are running a 10-site project called PRONIA, which began in 2013. PRONIA is recruiting 1700 people who are at high risk of psychosis, who have early-stage psychosis, or who have early-stage depression, in part to compare the trajectory of the two illnesses. Participants are offered a battery of tests over time, including neuropsychological testing, MRI scans, DNA sequencing, and analysis of blood samples for biomarkers, such as those reflecting stress response. In the United States, a long-running study called the North American Prodrome Longitudinal Study (NAPLS) is doing something similar across nine centers.

Finding these youngsters isn't easy. Pediatricians and school counselors may see teenagers whose grades have slipped or who have stopped socializing. But "people aren't really thinking, 'This could be a budding psychotic process,'" says Cannon, who spearheaded NAPLS 14 years ago. "It's only after somebody who's trained to ask these questions asks them, 'Are you hearing anything that is unusual, or having some ideas that are bothersome?' And it's at that point they tell you, 'I've heard a voice call my name.'"

Cannon and his colleagues reach out to schools, hospitals, churches, and other groups. And they handle a high-risk diagnosis sensitively. They don't lead off with the words psychosis or schizophrenia, but explain that the child is experiencing certain symptoms that may worsen—although they also have a high likelihood of improving.

"We grapple with, 'Can I do harm by saying something so uncertain?'" says Kristen Woodberry, a psychologist at Harvard Medical School in Boston. "And yet, you do harm by not saying anything." In part that's because the more quickly a psychotic break is detected and treated with antipsychotics and other therapies, the better the long-term prognosis. Woodberry thinks of a 16-year-old she treated, whose psychiatrist had overlooked emerging psychosis for years because "this was a very bright kid, and a very high-functioning family. ... He was writing in his poetry, 'I think I'm losing my mind,' and nobody picked up on the fact that he is losing his mind."

Increasingly, projects like NAPLS and PRONIA are clarifying what happens in the months and years before psychosis strikes. One of the big discoveries of NAPLS is that people who progress to psychosis suffer a

loss of gray matter in their brain over about a year. Another is that blood markers of inflammation, perhaps driven by a mix of genetics and external risk factors, may both boost risk and predict that gray matter loss.

Last fall, Cannon and others in the NAPLS consortium published a risk calculator based on 596 people who were followed for up to 2 years. They found that lower memory and verbal learning scores and a decline in social functioning were strong predictors of a psychotic break, along with severity of precursor symptoms, such as unusual thoughts. The result is a calculator, designed for professionals experienced in identifying those at high risk, which NAPLS has made available online. The researchers believe it can reliably detect up to a 50% risk of psychosis in the next year.

When it comes to prevention, "I'm not expecting a miracle," Sommer says. But "we should start."

Research projects are gearing up, and some begin before birth. At the University of Colorado in Denver, Camille Hoffman, a maternal-fetal medicine specialist, launched a randomized trial this summer that aims to test a supplement, choline, in 250 pregnant women to improve brain health and mitigate various diseases in the babies. A pilot trial, published in December 2013 in *The American Journal of Psychiatry*, suggested that choline supplementation in healthy moms-to-be improved "auditory gating" in their babies, which helps filter out background noise. Poor auditory gating is correlated with later psychosis and other psychiatric illnesses. By 4 years old, the children were also more attentive and interactive. To Hoffman, the improvements make sense: Choline activates a brain receptor that helps with brain "scaffolding"—the fundamental arrangement of neurons during fetal development.

But because psychosis rarely manifests before the teens, Hoffman's trial won't show whether choline given during pregnancy actually prevents disease. Instead she will rely on markers of behavior, stress hormones, and other measures in early childhood.

Sommer is encountering similar challenges. For older children, being bullied is a risk factor for later psychosis, and it's hard to argue against antibullying programs. But when Sommer proposed a study to test an antibullying program for children hearing voices, her grant application was turned down. "This type of research is very expensive," she says. "You need to target a lot of children, only a few will go on to develop schizophrenia," and they must be followed for years.

Others are looking at cognitive behavioral therapy (CBT) to help at-risk youth reframe their thinking. Several trials have shown that CBT can reduce the risk of developing psychosis by about 50% in the following year, Heinssen says, though it's not clear whether treatment prevents or delays disease. Either way, researchers also believe the intervention can ease current symptoms, which makes offering it as a preventive much easier to justify. Various international agencies recommend CBT as treatment for high-risk young people, says Paolo Fusar-Poli, a psychiatrist at King's College London whose office is in an unmarked building so families will feel more comfortable. Though he embraces CBT, Fusar-Poli acknowledges that its link to disease biology is a black box. "Whether it is effective in changing the neurobiology and course of the disorder" is unknown, he says.

The most potent prevention strategy is also the most controversial: psychiatric drugs. Over the years, doctors have tried to head off psychosis with the same antipsychotic drugs used to treat full-blown illness. But the jury is still out on whether these drugs prevent a psychotic break, and they come with many side

effects. "We were young and enthusiastic and didn't realize how difficult it would be," says Scott Woods, a psychiatrist at Yale who studied an antipsychotic years ago in high-risk individuals.

Woods is hopeful again. He's consulting with Boehringer Ingelheim, a pharmaceutical company headquartered in Germany, where scientists this fall began offering an experimental drug to people at very high risk of psychosis who are eligible based on the severity of their symptoms. The drug is not an antipsychotic, but instead strengthens the signaling of glutamate, a neurotransmitter that's impaired in people with schizophrenia and those at risk. The company was trying it for cognitive problems in schizophrenia, and expanded into prevention.

Last month, at sites across the United States, the United Kingdom, and Canada, the first of 300 people signed on to be randomly assigned to the drug or a placebo. Like other prevention trials, Boehringer's is examining whether its treatment can ease current symptoms, as well as prevent psychosis.

When asked about the ethics of offering a drug to people who may never get the disease it's designed to prevent, Michael Sand, the Boehringer scientist overseeing the clinical trial, acknowledges that psychosis risk prediction is far from perfect. But, he says, we welcome prevention in other diseases, like cancer and heart attacks, even for those whose risk is only modest. To Sand, the stigma and tragedy that mark a schizophrenia diagnosis, and our ability to identify those at substantial risk, make preventing it with safe and effective therapies even more urgent.



Brandon Staglin at 12 with his younger sister.

Brandon Staglin, now more than 2 decades into life with schizophrenia, suggests that reducing that stigma may make the disease easier to combat, for example by helping affected teens speak up about their symptoms. Despite two psychotic breaks and several years unable to work, he is now doing well on medication and is happily married, getting a master's degree in health administration, and assisting with a new California program to build a network of early psychosis treatment centers. Not everyone with schizophrenia is as healthy as he is—but not everyone is as incapacitated as even doctors often imagine.

"Brandon is a different great now" than he used to be, his father says. "He's not a Ph.D. rocket scientist ... which is what he wanted to do. But he's got a great life. It's just a different life."

A few years after Brandon was diagnosed, his parents formed a nonprofit now called One Mind. One Mind has raised millions of dollars for research on a host of brain illnesses. One of its earliest grants was to Cannon, for psychosis prevention.

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Jennifer Couzin-Frankel

Staff Writer

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