

A new look at how and when schizophrenia starts

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Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

The traditional view was that schizophrenia, the most devastating of mental illnesses, struck young people on the cusp of adulthood, often without much warning.

In their late teens or early 20s, previously healthy men and women would suddenly begin hearing voices no one else could hear and withdrawing from a world teeming with delusional threats. They faced a lifetime of disability even with strong medication and - in a country without adequate care - of increased risk of homelessness, suicide and prison.

Raquel Gur, a University of Pennsylvania neuropsychiatrist and nationally known expert on schizophrenia, is at the forefront of the new way of thinking about the disorder, which affects 1 percent of the population.

Scientists now view it as a neurodevelopmental condition that begins years before its most disturbing symptoms appear, in much the same way that heart disease begins long before the first heart attack.

Gur's painstaking work, done with the help of 9,500 Philadelphia children and their families, finds that those at risk for psychosis diverge from their peers in important ways as early as age 8. The differences in brain functioning - these are thinking skills, not psychosis - widen in the mid-teens.

The tantalizing question is whether early identification and treatment can delay or prevent the onset of psychosis, allowing young sufferers time to build a firmer foundation for life.

It's early, but there is some evidence that the answer is yes.

Schizophrenia experts are excited by promising results for [cognitive behavioral therapy](#) and, surprisingly, fish oil.

Work on the first stages of schizophrenia - what is often called the prodrome - is unfolding at a time when scientists are learning the brain is a far more dynamic organ than was once thought. True, the brains of

people with schizophrenia do not look or function normally, but all of our brains are changing more than we realize.

"Most people have gotten far more hopeful that we will be able to use experience or training or something else to help the brain rewire," said Thomas Insel, director of the National Institute of Mental Health (NIMH).

He sees hope in teaching people with schizophrenia how to focus and control their thoughts. Lack of cognitive control, he said, "is the on-ramp to psychosis."

Gur's work, undertaken with \$26 million in NIMH funding since 2009 and help from Children's Hospital of Philadelphia, is an ambitious effort that is following children over time to see how psychotic illnesses unfold. Four percent of the teenagers had symptoms of psychosis. The rates were higher for 8- to 10-year-olds, but Gur chalks some of that up to "vivid imagination." Because of funding constraints, Gur's team is closely following only 250 at-risk children and 250 who are normal.

The researchers are analyzing genes and brain images, family history, neighborhood environment, and early life experiences as well as measures of perceptual and cognitive abilities and emotion processing. While much previous research has focused on positive symptoms - hallucinations and delusions - in schizophrenia, there is growing recognition that negative symptoms - problems with working memory, advanced decision-making and social skills - are equally disabling.

Gur's husband, Ruben, a brain/behavior expert at Penn who collaborates with her, will soon start testing the theory that acting may help at-risk youths recognize and express emotions better. Raquel Gur will test cognitive retraining as a therapy. That program will focus on improving attention, working memory (the ability to hold thoughts in your head

while working with them) and problem-solving. Gur hopes for results within a year.

Like other experts, she thinks early intervention will be better for schizophrenia, as it is for so many other diseases.

"If you want somebody to continue on a fairly normal trajectory of development," she said, "you need to capture them before they fall off the track so much that it's difficult to bring them back."

If schizophrenia strikes before victims have grown up, it's hard for them to catch up later. "They're not equipped to become adults," she said.

William Carpenter, a well-known schizophrenia researcher at the University of Maryland, says that, even if early treatment only delays the worst symptoms, it has to be better to have more time to develop life skills and relationships. Those make it easier to cope.

"If you have to become psychotic," he said, "it's a whole lot better to do it after you've finished school and got a job and got married."

Carpenter chaired the American Psychiatric Association committee that decided not to list "attenuated psychosis syndrome," a term for people with psychoticlike symptoms that are not strong enough to meet the definition of schizophrenia, in the official list of psychiatric disorders last year. The group questioned whether most therapists could identify the condition properly. There were also worries about stigmatizing [young people](#) and exposing them to antipsychotic medications, which don't work in this group.

And, there was the problem of false positives. Only about 30 percent of people who get what Carpenter called the "placeholder diagnosis" progress to having psychosis within two years. In Gur's sample, about

half the children who had [psychotic symptoms](#) at intake still had persistent or worsening symptoms two years later. Among those who at first seemed normal, 17 percent later developed sub-psychotic or psychotic symptoms. One of the things she's learning is that a surprising number of children have perceptual problems that go away or don't become severe.

Her study could help define who is most likely to become schizophrenic as well as factors common in those who are most resilient.

"It will become a national resource," she said.

What she knows already is that the children most likely to have serious problems are different from an early age. If you look back at family pictures taken at 7 or 8, these are kids who are always at the corner, looking down. They often start to experience more serious interpersonal problems, perception changes and heightened anxiety two to three years before they have a "break" or become actively psychotic.

"It's not overnight," she said. "It's insidious."

In a paper published early this year, Gur's group found a delay in cognitive growth in children on the "psychosis spectrum" or those with relatively mild perceptual changes. Based on an hourlong test of a variety of thinking skills, they were six to 18 months behind peers. The delay widened around age 16. "This is when they fall off the curve," Gur said.

Her team has found that, even before the youths become fully psychotic, their brain functioning is similar to that of people already diagnosed with schizophrenia.

Parents often seek help only when their child's behavior gets too strange to be ignored. Maybe they're talking when they're alone in their room, or

they're overtly paranoid.

Everyone expects a little eccentricity in adolescence and, perhaps, parents don't want to know.

"There's a stigma that's associated with it," Gur said. "People are afraid."

Children who are at risk may begin doing worse at school or becoming less interested in hobbies. They get more isolated and anxious. Some have trouble sleeping. They lack motivation and their thoughts become more concrete. They are less emotionally expressive. "You talk to them and their face is wooden," Gur said.

Kids say they felt bewildered and disconnected in those early years. They may catch "dreamlike," fleeting glimpses of things they know aren't real. (People with full [psychosis](#) have more frequent and intense hallucinations. They have more trouble knowing what is and isn't real.)

Some kids grow out of it. Gur said strong family support improves resilience. She is more hopeful when she sees a family arrive together. "It's a good predictor that the child will do better," she said.

Among adult patients, she said, schizophrenia isn't as bad as many assume. True, about one-third of patients function poorly. Another third are stable and do OK. The rest, she said, improve and are able to do quite well. Some function so well that most people wouldn't know they have [schizophrenia](#).

While many of her young patients will never seem normal, she thinks they might have enough reserve in their brains to compensate. "It might be good enough for them to reach independence and get a job ... and feel like they're part of society," she said.

"People can have a good outcome."

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