

## Pattern of Brain Activity Signals Danger of Schizophrenia

### *Therapeutic Focus Shifting to Earliest Stages of Disease*

For many people, schizophrenia descends not all at once but in bewildering bits and pieces.

“You think a television is talking to you or about you, but then you say, ‘Well, not really—that doesn’t make sense,’” said [Larry Seidman](#), HMS professor of psychology in the Department of Psychiatry at Beth Israel Deaconess Medical Center. Some people experience occasional strange thoughts or perceptions and never succumb to full-blown disease, but for others, the visions, voices and feelings of paranoia will visit more often. They may be joined by other strange behaviors—lapses of memory, jumbled and nonsensical thoughts, extreme sensitivity to others, depression, a tendency to withdraw from social situations—which can invite a noxious mix of emotions.



Photo by Graham Ramsay

**“A lot of clinicians, including myself until recently, would see young people in the early, prodromal phase of schizophrenia and wouldn’t understand what was going on. They seemed like they were psychotic, but they weren’t quite. It didn’t fit together,”** said Larry Seidman (right). **He, Anthony Giuliano, and colleagues are studying the prodromal phase in an effort to arrest and possibly prevent full-blown disease.**

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“A lot of what happens during this early phase is a growing fear and terror as odd things are happening to you. You’re losing your mind—it’s terrifying,” said Seidman.

### **Moving the Target**

For decades, indeed, ever since the early 20th century when the Swiss psychiatrist Eugen Bleuler coined the term

schizophrenia, researchers have focused on the full-blown manifestations of the disease. Over the past 10 years, motivated in part by the hope that they can pull people back from the brink of psychosis, Seidman and researchers around the world have been casting a wider net. In what some describe as a paradigm shift, they have been studying the earliest stage of schizophrenia, known as the prodromal phase, probing not just the cognitive deterioration but also social and emotional hallmarks of the disease.

In fact, Seidman and colleagues have gone back even earlier, beyond the prodromal phase. They are looking at behaviors and, through functional magnetic resonance imaging (fMRI), at the brains of people who do not display symptoms but are at high risk by virtue of having a close relative with schizophrenia. A fascinating pattern has recently emerged.

Working with MIT researchers Susan Whitfield-Gabrieli and John Gabrieli, Seidman, Heidi Thermenos, an HMS instructor in psychology in the Department of Psychiatry at BID, and colleagues have discovered that a constellation of brain regions that is typically turned down when people are attending to things in the outside world remains unusually active in people with schizophrenia and, to a lesser extent, in those at risk for the disease. What makes the findings, which appear in the Jan. 27 *Proceedings of the National Academy of Sciences*, especially intriguing is that this so-called default network is normally active when we are thinking about ourselves or about nothing in particular.

### **An overactive default network could help explain some of schizophrenia's most vexing features, the delusions and paranoia.**

Indeed, the researchers believe that an overactive default network could help explain some of schizophrenia's most vexing features, the delusions and paranoia. If this network is active, possibly even in overdrive, at the same time that you are engaged with the outside world, say watching TV, it could lead to self-oriented delusions, such as that the TV is talking directly to or about you.

The findings suggest an uncannily fitting scenario and yet mysteries remain, questions that Seidman and colleagues at HMS and elsewhere are addressing. Not all people in the prodromal phase go on to develop full-blown schizophrenia. Is there any way to predict who will develop disease? What is the course of psychosis at the behavioral and neurological levels? Can the disorder be stopped or prevented?

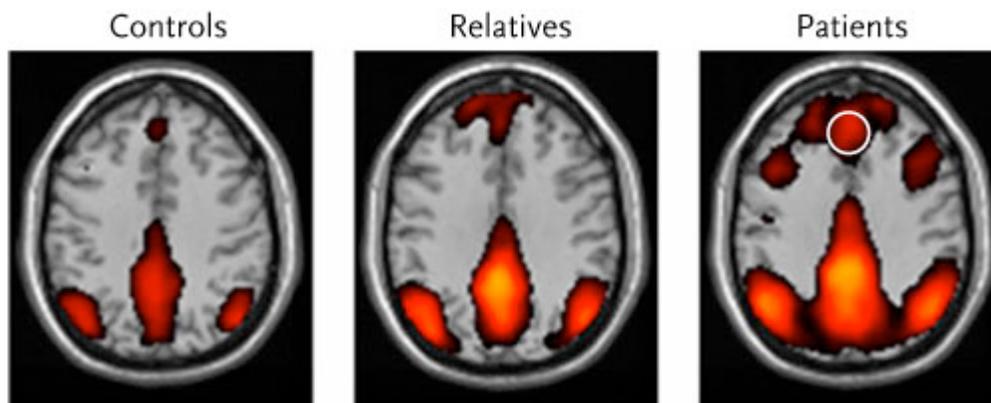
### **Uprooting Disease**

Though schizophrenia was known to run in families even in Bleuler's day, questions of risk and rescue were ignored for much of the 20th century. It was not until the late 1980s that researchers, spurred, in part, by pharmaceutical companies, began focusing on the first episode of full-blown schizophrenia in an effort to see if newer antipsychotic medications might allay or arrest the disease. The focus moved to even earlier periods in the 1990s. "People said, 'What if we start intervening before the illness begins?'" said Seidman.

In 1999, the National Institute of Mental Health gathered together several groups of researchers studying prodromal subjects and had them pool their resources in an effort to answer a basic question: what proportion of patients go on to develop full-blown schizophrenia? Seidman and colleagues, who had been using behavioral and imaging methods to study people with a family history of schizophrenia, were invited to add their at-risk sample. The consortium, known as the North American Prodromal Longitudinal Study (NAPLS), followed 291 clearly prodromal subjects for two and a half years and found that 35 percent of them went on to develop schizophrenia, findings reported in 2008.

Meanwhile, Seidman and colleagues had come across some puzzling findings in their fMRI data. A region of the frontal cortex, the dorsal lateral prefrontal cortex, was more activated in patients and at-risk subjects than in controls, yet the

frontal lobes of the brain were thought to be underactive in schizophrenia. Whitfield-Gabrieli, who had data showing this same apparently contradictory activation in another area of the brain, suspected the default network might be at play and, with Thermenos, Seidman and colleagues, embarked on a full-scale analysis.



Courtesy *PNAS* and Heidi Thermenos

***Disease by default.* The default network, an interconnected system of brain regions involved in self-reflection, was compared in patients with schizophrenia, first-degree relatives of people with the illness (considered to be at risk for the disease), and controls. In addition to displaying inappropriate activity during a mental task (see red areas in fMRIs), patients and relatives exhibited an unusual synchrony: brain regions that do not typically work together, such as the medial prefrontal cortex (white circle, far right) and certain other structures, were activated in a highly correlated manner.**

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The NAPLS researchers plan to look at the default network in the next phase of their work. The effort, dubbed NAPLS 2, is launching this month and will recruit 720 people over five years in an effort to understand what causes the conversion to psychosis.

Their ultimate goal is to find ways to catch and stop the disease, but Seidman and his colleagues are not waiting for those results. Next month, he, Anthony Giuliano, HMS instructor in psychology in the Department of Psychiatry at BID, and colleagues, with a grant from the Sydney Baer Foundation and support from the Massachusetts Department of Mental Health, will be launching a storefront clinic at the Massachusetts Mental Health Center.

“Our goal is to develop new treatment services for prodromal youths and young adults,” said Seidman. They plan to develop an innovative mix of pharmaceutical and talk therapy. “We want to help the person frame what’s going on so they can understand their symptoms and use some kind of cognitive control,” Seidman said. “Because in this prepsychotic phase, they are likely to still have more of their observing ego. They have more cognitive resources to understand what’s going on, even if they’re really struggling with it.”

—Misia Landau

Students may contact Larry Seidman at [lseidman@bidmc.harvard.edu](mailto:lseidman@bidmc.harvard.edu) for more information.

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