FEATURE STORY

BRAIN CONNECTIVITY IN PSYCHIATRIC DISEASES

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Psychiatrist Daniel Mamah, MD, holds up four stylized images of the brain, each with a different pattern of white lines on it. "Do you see the differences?" he asks. "We have found four different patterns of white-matter abnormalities in people diagnosed with schizophrenia."

Mamah is discussing a recent paper, in which he and colleagues mapped the structural connections in patients' brains and then fed the data into a computer to identify patterns of connectivity. The computer algorithm was able to sort most of the 47 patients into one of four groups. The paper is the first published evidence that connectomics—the science of mapping connections between brain regions—can be used to subdivide the population of individuals with schizophrenia.

Schizophrenia used to be categorized based on symptoms, but the most recent iteration of the Diagnostic and Statistical Manual of Mental Disorders dropped the subdivisions on the grounds that symptoms do not correlate very well with underlying biology. Still, it is widely believed that schizophrenia comprises several distinct

Daniel Mamah, MD, and colleagues are working to provide a more accurate picture of what is going wrong in the brains of patients with schizophrenia and other psychiatric diseases.

disorders, even if currently they cannot be distinguished. Connectivity studies may provide a more accurate picture of what is going wrong in the brains of patients with this and other psychiatric diseases.

"The goal is to get to a point where we can parse out the different kinds of connectivity and link them to certain underlying etiologies," says Mamah. Different etiologies, he continues, would suggest different treatments for what is now classified as the same disease.

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Earlier this year, Mamah was awarded a five-year, $2.3 million grant to try to achieve that goal. The grant is one of only eight Biobehavioral Research Awards for Innovative New Scientists (BRAINS) awarded by the National Institute of Mental Health in 2015.

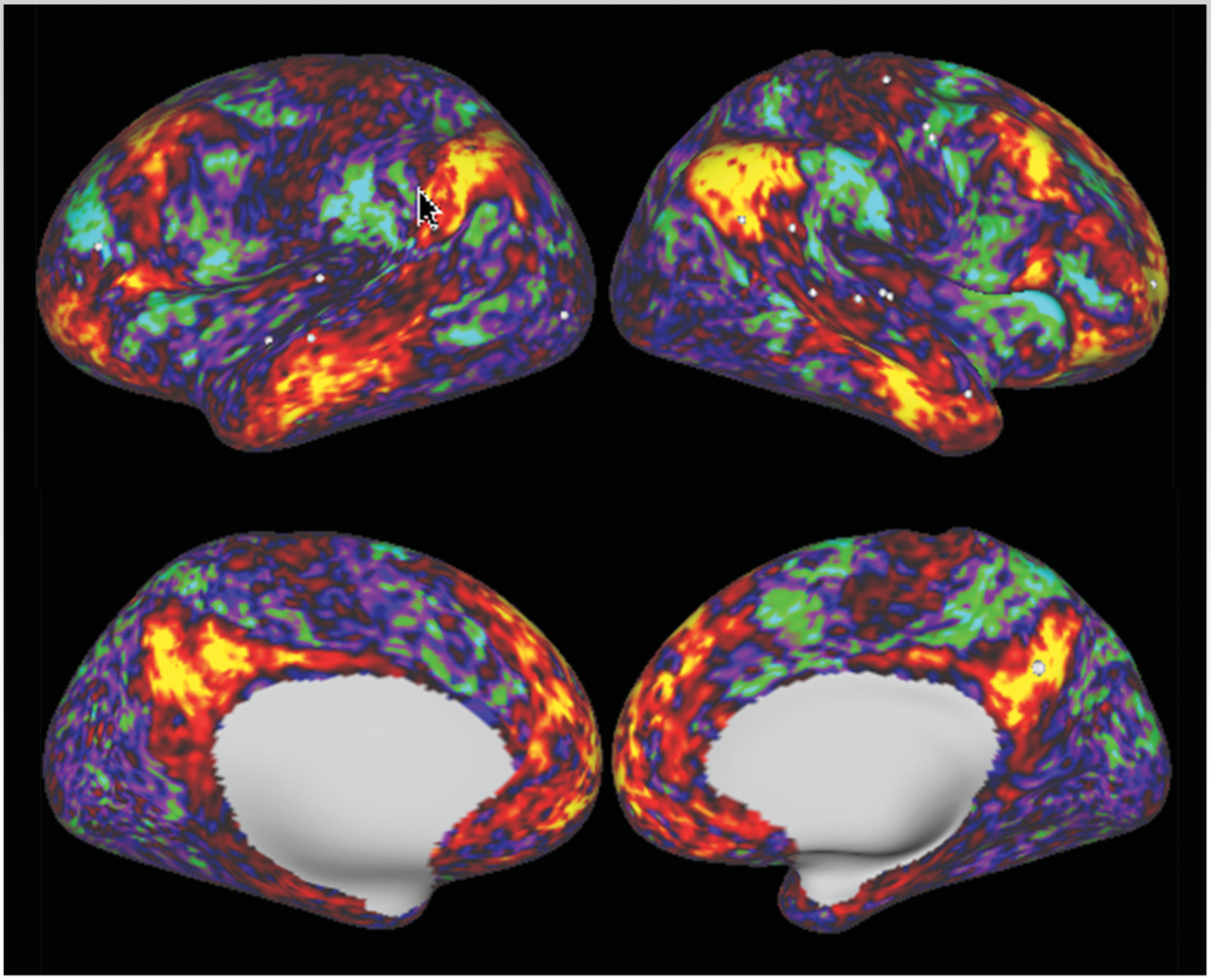
Mamah's BRAINS study applies the techniques developed for the Human Connectome Project (HCP)—a large-scale brain-imaging study of the connections within healthy adult brains—to schizophrenic and bipolar populations. Using HCP protocols, Mamah and colleagues will conduct resting-state and task-based studies of functional connectivity to look for abnormal patterns among their patients.

The HCP was designed to provide a baseline for studies like Mamah's. The five-year, $30 million project—funded by the National Institutes of Health and led by Washington University School of Medicine and the University of Minnesota—is the most comprehensive and finely detailed study of brain connectivity ever attempted.

The HCP is now wrapping up, and data for 900 participants have already been released to the public, along with all the methods used to obtain that information. The HCP team is currently cleaning the data for the final 300 participants and plans to release that information within a few months.

"Our HCP grant was used to determine the baseline and make everything publicly available," says neuroscientist Deanna Barch, PhD, an HCP investigator. "The idea is that other people will take the data and run with it. We are already beginning to see papers come out based on the first data set of 500 people, which we released in 2014."

Although the HCP was designed to provide a snapshot of healthy brains, the data could provide insight into psychiatric illnesses. People with a documented history of psychiatric illness were excluded, but those who had never been diagnosed were not, even if they self-reported psychiatric symptoms. "We made sure to include measures in the study that were relevant to psychiatric disorders," says Barch. "So there's a good amount of variation in depression, anxiety and substance use, and there's even a little bit of variation in self-reported psychotic experiences."



In these resting functional connectivity images, generated by the BRAINS study with an HCP Skyra scanner, the warm colors (red, orange, yellow) represent brain regions that are functionally connected with each other.

Image courtesy of Daniel Mamah, MD

The hope is that this kind of information could be used to diagnose and guide treatment of psychiatric illnesses. In the not-too-distant future, doctors could order a brain scan to determine a patient's illness subtype before beginning treatment, or to monitor treatment effectiveness by looking for normalization of the patient's connectivity pattern. "This scenario is definitely feasible," says Barch. "In terms of the technology, it would be no different than ordering an MRI scan for a broken bone. What we don't yet have is evidence of which aspects of brain connectivity or function we should be measuring." Mamah's BRAINS study could provide some of the first clues in that direction.

He holds up another set of pictures, this time of chest X-rays, to illustrate how that technology transformed doctors' ability to diagnose and treat chest pain decades ago. "Down the road, maybe we can figure out how to get the pattern of connectivity to normalize over time," he says. "But first we have to figure out what the patterns are, and what they mean." ■