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Biomarkers trump behavior in mental illness diagnosis

Here's how doctors decide which mental or neurological disorder their troubled patients suffer from: they ask questions like, "Are you hearing voices?" and "Do you feel like people are out to get you?"

Not all that different from how they used to do it about 100 years ago.

New techniques are set to radically change that approach—and perhaps define new categories within each disease—relying more on changes in physiology than in behavior.

"Now we're at the opposite end of the spectrum where we can take an unbiased look," says Stephen Glatt, a psychiatric geneticist at the State University of New York in Syracuse.

Delusions, hallucinations, disorganized thinking and other psychotic symptoms can result from schizophrenia, Alzheimer disease, bipolar disorder, manic depression or dementia. Even diabetes and syphilis can induce forms of psychosis.

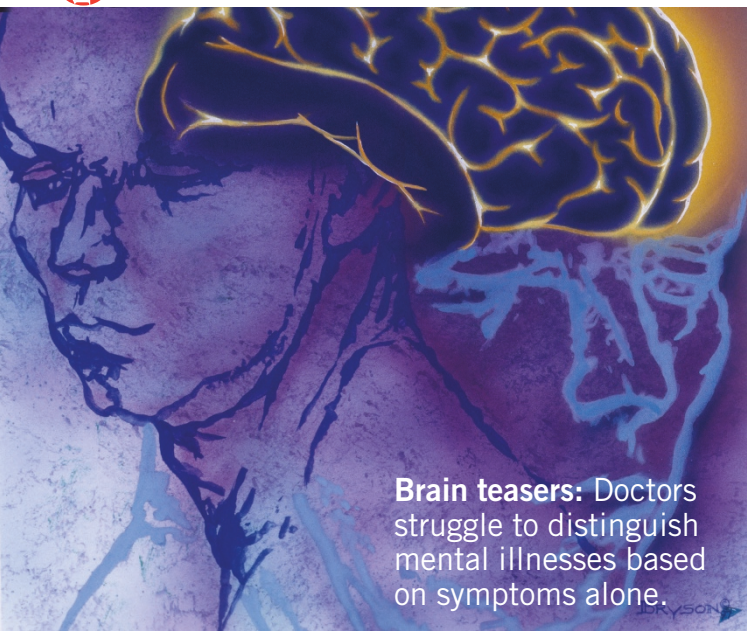
The answers to doctors' questions can help whittle down the categories somewhat, but it's far from a perfect science. Less than a third of individuals with these disorders respond to medications, most likely because they are being treated for the wrong one. The treatment for each illness can be drastically different, so pinning down the diagnosis is crucial.

Scientists are increasingly turning to biomarkers—such as genes or proteins in tissues, blood and body fluids—to distinguish between symptomatically indistinct illnesses.

"This is the holy grail of research," says Karoly Mirnics, associate professor of medical psychiatry at Vanderbilt University. Using techniques that have only become available in the past few years, scientists are looking at the brain, serum and spinal fluid and asking which combinations of genes or proteins might be expressed differently in these disorders.

The field is still far from ready for the clinic, but holds great promise: markers could allow for earlier treatment and a better prognosis, ultimately enabling scientists to intervene even before the full-blown disease strikes.

In one study published in November, researchers tested spinal fluid from patients at the first onset of schizophrenia. They found higher levels of a small protein derived from the protein VGF, known to be important for energy metabolism, and lower levels of the protein transthyretin compared with healthy controls. Post-mortem tissues of schizophrenic brains showed that same trend (*PLoS Med.* **3**, e428).



Brain teasers: Doctors struggle to distinguish mental illnesses based on symptoms alone.

Samples from individuals with Alzheimer disease and obsessive-compulsive disorder did not show those differences, but those from individuals with depression did.

"This is not really surprising because people who have a family history of schizophrenia are also much, much more likely to grow up with depression or other forms of mental illness," says Sabine Bahn, director of the Cambridge Centre for Neuropsychiatric Research.

To drill down to trends unique to a single disease, scientists are examining panels or 'pathways' of biomarkers. Even within the umbrella of a single disease as defined clinically, there may be several subtypes that could be distinguished at a molecular level.

For example, "It's very unlikely that a schizophrenic from one end of the spectrum to a schizophrenic on the other end of the spectrum will show the exact same biomarkers," says Mirnics.

In a study published in August, Bahn's group also found that treating schizophrenics who had had only one psychotic episode—but not more than one—corrected abnormal patterns in the expression of some metabolites, including glucose, lactate and acetate (*PLoS Med.* **3**, e327), underscoring the importance of early intervention.

Biomarkers are also revealing unexpected insights into the biology of diseases. For example, using gene chips, one team found that some pathways involved in energy and metabolism are affected in individuals with schizophrenia—which is consistent with Bahn's finding (*Proc. Natl. Acad. Sci. USA* **102**, 15533–15538; 2005). The role of metabolism, says Glatt, lead researcher of that study, "could be something that we are not yet even thinking about."

There are important caveats, however. Genetics could account for 50% or fewer of schizophrenia cases, for instance. Shifts in the expression of proteins that respond to external variables may be a more reliable predictor in those cases.

Many of the techniques also lack the sensitivity necessary to detect minute traces of molecules. Scientists will also need to monitor individuals over time, correcting for confounding factors such as the effects of previous treatment, nutrition and smoking as well as drug and alcohol abuse.

The most challenging aspect might yet turn out to be redefining a 100-year-old classification system. "That will be a major upheaval," Bahn says. "There may be problems in implementing them because it would change our entire way of thinking."

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