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Different mental disorders cause same brain-matter loss, study finds

February 4 2015

In a study analyzing whole-brain images from nearly 16,000 people, researchers at the Stanford University School of Medicine identified a common pattern across a spectrum of psychiatric disorders that are widely perceived to be quite distinct.

The meta-analysis of 193 peer-reviewed papers, to be published Feb. 4 in *JAMA Psychiatry*, reports a loss of gray matter in three brain structures that, although physically separate, participate in a network associated with high-level functions including planning and decision-making.

The findings call into question a longstanding tendency to distinguish psychiatric disorders chiefly by their symptoms rather than their underlying brain pathology.

In any given year, nearly one in five Americans meets the criteria for a diagnosis of psychiatric illness. "The idea that these disorders share some common brain architecture and that some functions could be abnormal across so many of them is intriguing," said Thomas Insel, MD, director of the National Institute of Mental Health, who wasn't involved in the study but is familiar with its contents.

The researchers drew on component studies that have been around for some time, said Insel. But these studies tended to focus on one or another psychiatric disorder in isolation, whereas the Stanford investigators "have stepped back from the trees to look at the forest and

see a pattern in that forest that wasn't apparent when you just look at the trees," Insel said.

"In many of these published studies we reviewed, researchers have tended to interpret their biological findings in terms of the one disorder they're focusing on," said Amit Etkin, MD, PhD, an assistant professor of psychiatry and behavioral sciences at Stanford and the study's senior author. Lead authorship is shared by Madeleine Goodkind, PhD, a postdoctoral scholar in Etkin's group, and Simon Eickhoff, DrMed, a professor of clinical neuroscience and medical psychology at Heinrich-Heine University Dusseldorf.

Similar gray-matter loss

Despite experienced clinicians' intuitive grasp of the blurred lines separating diverse psychiatric conditions, there's nonetheless often an assumption that these disorders, traditionally classified on the basis of predominant symptoms, are discrete in reality, noted Etkin, who is also an investigator at the Sierra-Pacific Mental Illness Research and Clinical Center at the Veterans Affairs Palo Alto Health Care System. "We tried to ask a basic question that hasn't been asked: Is there any common biological basis for mental illness?"

To address that question, he and his colleagues pooled data from 193 separate studies containing, in all, magnetic-resonance images of the brains of 7,381 patients falling into six diagnostic categories: schizophrenia, bipolar disorder, major depression, addiction, obsessive-compulsive disorder and a cluster of related anxiety disorders. Comparing the images with those from 8,511 healthy control subjects, the research team identified three separate brain structures, several centimeters apart from one another, with a diminished volume of gray matter, the brain tissue that serves to process information. These structures—the left and right anterior insula and the dorsal anterior

cingulate—are known to be parts of a larger network in the brain whose component parts tend to fire in synchrony. This network is associated with higher-level executive functions such as concentrating in the face of distractions, multitasking or task-switching, planning and decision-making, and inhibition of counterproductive impulses.

Gray-matter loss in the three brain structures was similar across patients with different psychiatric conditions, the researchers found.

These structures can be viewed as the alarm bell of the brain, Etkin said. "They work together, signaling to other brain regions when reality deviates from expectations—that something important and unpredicted has happened, or something important has failed to happen." That signaling guides future behavior in directions more likely to obtain desired results.

Some incongruities

In addition to gray-matter loss in these three structures, people diagnosed with major depression also had gray-matter loss in other structures, including the hippocampus and amygdala, two key areas involved in storing memories and processing emotion, respectively. Schizophrenia was marked by reduced gray matter in several other structures, as well as an increase in gray matter in a region called the striatum, which Etkin suggested may be due more to the antipsychotic medications prescribed for schizophrenia than to the disease process itself.

Further analysis showed that gray-matter shrinkage in the three implicated brain structures was independent of any medication effects or overlapping psychiatric conditions.

Next, Etkin and his colleagues turned to three large databases containing both structural and functional MRI scans of healthy subjects. Among

healthy people, gray-matter volume in the right and left anterior insula and the dorsal anterior cingulate correlated with performance on classic tests of executive function. Such a test might involve, for example, asking the test-taker to note the color of the word "blue," displayed in a color other than blue, after seeing it briefly flashed on a screen. This finding strengthens evidence that among psychiatric patients, the generally observed gray-matter loss in brain structures associated with executive function is behaviorally significant.

The discovery that psychiatric disorders typically studied in isolation from one another turn out to share a common structural deficit mirrors, in some respects, a genetic analysis conducted in 2013 by researchers at Massachusetts General Hospital that showed shared genetic glitches among several categories of mental illness, said Insel. But this is the first imaging study to do so, he said.

"I wouldn't have expected these results. I've been working under the assumption that we can use neuroimaging to help classify the different forms of mental illness," Insel said. "This makes it harder."

More information: *JAMA Psychiatry*. Published online February 4, 2015. DOI: 10.1001/jamapsychiatry.2014.2206

Provided by Stanford University Medical Center