NEUROSCIENCE

Averaged Brains Pinpoint a Site for Schizophrenia

Schizophrenia presents a bewildering array of symptoms—everything from social withdrawal to hallucinations and delusional behavior. And researchers trying to understand the neurological defects underlying this patchwork have generally approached it one piece at a time, trying to link specific symptoms to specific brain sites. Because cognitive function is impaired, for instance, some researchers have focused on the prefrontal cortex; because schizophrenics also suffer linguistic disturbances, researchers have also been eyeing another part of the cerebral cortex, the temporal lobes.

Nancy Andreasen of the University of Iowa calls the piecemeal approach "unparsimonious and conceptually unsatisfying." She thinks that she and her colleagues may be on the track of a more economical and satisfying explanation: a single, underlying neurological abnormality. To find the evidence, she says, what you have to do is look at the whole picture of the brain—using the right imaging technology.

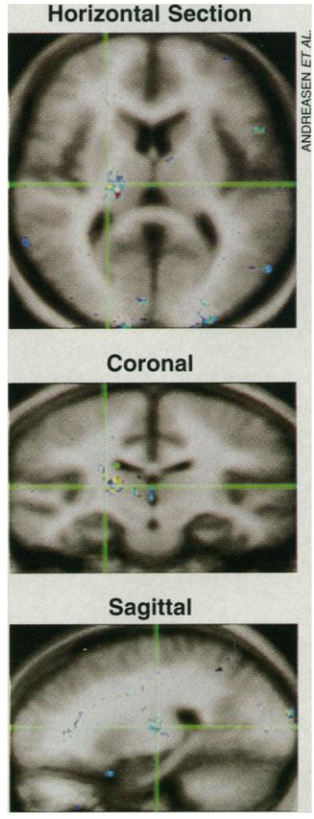
In work reported on page 294, Andreasen's group used a new technique called magnetic resonance image averaging to compare the brains of schizophrenic patients and normal controls. Their conclusion is that schizophrenic brains have an abnormality in the thalamus, a structure deep inside the brain that can be thought of (somewhat simplistically) as its central switchboard. If the Iowa group is right—and other researchers say the data are intriguing—this region of the brain could be responsible for the entire spectrum of schizophrenic symptoms.

Because schizophrenia mainly affects thought and emotion, efforts to find its cause have concentrated on the cortex, which is usually seen as the seat of these functions. Over the years, researchers have reported a wide variety of cortical abnormalities—such as unusual asymmetries in brain structure or biochemical disturbances—that seemed to be linked to schizophrenia. But these findings have had a habit of fading over time.

In the last decade, however, says psychiatrist Carol Tamminga of the Maryland Psychiatric Research Center at the University of Maryland, neuroscientists have come to understand that "subcortical" structures such as the basal ganglia and thalamus can exert powerful influences over cortical function. But so far, nothing more than subtle indications of thalamic abnormalities have turned up. And many of those hints came from studies of schizophrenic brains after death, from which meaningful conclusions about living brains are difficult to draw.

Magnetic resonance imaging (MRI) made it possible for Andreasen's group to follow up on these clues in living patients—and to gather far more detail than earlier studies. The Iowa group's scanner can image the brain in 124 vertical slices, each 1.5 millimeters thick, and complete the job in 10 minutes. Andreasen and her colleagues aren't the first to apply MRI to the search for brain abnormalities in schizophrenia, but they added steps that made the search more efficient and, they believe, more reliable.

Traditionally, MR images are analyzed by manually tracing and measuring their features, a technique Andreasen compares to medieval scribes "sitting around laboriously copying manuscripts. ... It takes forever to even measure a single structure in a large enough sample to be meaningful." Instead, the Iowa group introduced what Andreasen calls a "printing press" technology to standardize and speed up the process. First applied to MRI by Alan Evans and his colleagues at the Montreal Neurological Institute, the idea is to map each brain scan into a standard coordinate system to create a three-dimensional "average" brain. The advantage of the averaging, says Evans, is that it "removes the gross differences in brain size, orientation, and dimension, and allows you in an objective way to look at subtle anatomical or functional distinctions."



Key distinction? On images produced by subtracting "average" schizophrenic brains from controls, the differences *(colored spots)* are concentrated in the thalamus.

Andreasen and her colleagues followed this procedure with 40 normal people and 40 schizophrenics to create an average normal and average schizophrenic brain. They then subtracted the average schizophrenic brain from the normal version. What was left—the difference between the two averages—was the thalamus, which was smaller in the schizophrenic brains.

Although Andreasen believes the difference is real, she acknowledges the possibility of confounding factors and artifacts. MRI can be plagued by artifacts in the magnetic field, and the results might also be due to tissue differences that might not be biologically meaningful. Still, says Evans, the Iowa data "are very, very suggestive" of a real change in the thalamus.

It's a plausible site for a schizophrenic abnormality, says Andreasen, because the thalamus seems to act as the filter or gate for information reaching all cortical regions. If the filter were defective, the brain might be overloaded with information (or starved of it), and the result would be problems in understanding social cues, monitoring one's own speech, and interpreting the outside world. "All the symptoms of schizophrenia," she says, "could be explained by abnormalities in this crucial midline circuitry of the brain."

The underlying cause of this and other abnormalities in schizophrenia would still be mysterious, however. To Francine Benes, a neuroscientist at Harvard Medical School who accepts Andreasen's results, the first question is whether the changes in the thalamus are a symptom or a cause. The abnormalities are located quite near sites already under suspicion in schizophrenia, such as the prefrontal cortex, temporal lobes, and hippocampus. "You could argue this either way," says Benes. "You could argue that there are primary problems up in the cortical areas, and secondary changes occur by virtue of this in the thalamus. Conversely you could argue, as Dr. Andreasen does, that the pathophysiology flows from the thalamus up to the cortex."

Either way, Andreasen thinks the thalamus will prove a durable suspect in the search for schizophrenia's underlying brain abnormality. Unlike earlier hints of structural changes elsewhere in the brain, she says, the clues implicating it are based not on subjective interpretation of a few brains but on data from a large study population. The technique of averaging many MR images, she says, "has the great advantage of not forcing you to predict in a domain where we don't know enough to predict. I'm eternally impressed by how poor our ability is to predict anything about the human brain."

–Gary Taubes