

Brain-Tied Gene Defect May Explain Why Schizophrenics Hear Voices

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SCIENTISTS have linked a genetic defect to a brain abnormality that might help explain a hallmark of schizophrenia: the inability to filter out irrelevant sounds and other distractions. That lack of filtering can result in a flood of heightened sensation that makes it nearly impossible to concentrate, and may be part of the reason schizophrenics hear voices and hallucinate.

The defect by itself does not cause schizophrenia, the researchers said, but it could be one of the risk factors that combine to bring on the devastating mental illness. And because their research involved a brain structure that responds to nicotine, they also proposed a most unusual theory: that nicotine might provide fleeting relief for some of the distressing symptoms schizophrenics feel, which might in turn explain their well-documented tendency to smoke heavily.

The new findings, reported today in *The Proceedings of the National Academy of Sciences*, are the first to link a genetic defect to a specific brain abnormality and a symptom of mental illness. But they are also the first evidence for a new theory in a field that has seen various genetic theories rise and fall, and other researchers regarded them with a mixture of interest and skepticism.

"It's intuitively very strong," said Dr. Richard Wyatt, head of neuropsychiatry at the National Institute of Mental Health. "It makes sense," he said. "It's important and exciting." But he added, "it will be more important if it can be replicated."

Dr. Solomon Snyder, director of the department of neuroscience at Johns Hopkins

University, said: "In contrast to virtually every study I've read about the genetics of any psychiatric illness, this one is integrated and has concrete meaning. It gives you the feeling they may be onto something with major importance." But he did not accept the proposed link between schizophrenia and smoking; the causes and effects of smoking are too complex to be so neatly explained, he said.

A more cautious position was taken by Dr. Steven Moldin, chief of the genetics research program at the schizophrenia branch of the mental health institute. "It's an intriguing finding," he said, "but it is certainly going to require confirmation in an independent sample of subjects by independent investigators."

According to the institute, schizophrenia affects more than two million Americans. Some 330,000 people a year are hospitalized because of the disease. Its cause is unknown, though a tangle of nature and nurture is suspected. Scientists think multiple genes are involved, along with environmental factors that may include injuries to the brain, and viral illness or malnutrition in the patient's mother during pregnancy.

Despite concerns about the preliminary nature of the findings presented today, other scientists praised the way the study was done.

Rather than blindly scanning the genes of patients with a disorder for a distinctive genetic trait, Dr. Robert Freedman, a professor of psychiatry at the University of Colorado and director of schizophrenia research at the Veterans Affairs Medical Center in Denver, and his colleagues based their approach on schizophrenics' well-known difficulty in filtering sensory input. Previous research had suggested that the problem might stem from an abnormality in brain function that could be detected in a laboratory.

When a normal person hears a tone, the brain makes an electrical response that can be measured, and if a second tone quickly follows the first one, the second response will be smaller. But schizophrenics are less able to inhibit the second response, and that seems to correlate with their poor performance on tests that measure the ability to pay attention.

The researchers studied 9 families with 104 members, including 36 schizophrenics. Thirty-five of the schizophrenics, and 22 of their normal relatives, showed the abnormal brain response on the tone test.

Next, assuming that the response was hereditary, the researchers began to study all the family members, looking for a genetic pattern common to those with the abnormal response and found a possible location for a genetic defect in an area on chromosome 15. At the same time, they conducted studies in rats to identify which parts of the brain cells were involved in the responses to the tone test. The key to a normal response -- and the

presumed source of trouble in schizophrenics -- turned out to be a structure called the alpha-7-nicotinic receptor, which responds to a chemical messenger, acetylcholine, as well as nicotine.

Another team pinpointed the location of the nicotinic receptor on chromosome 15, in the region that Dr. Freedman's team identified as a possible location for a defect.

Although Dr. Freedman thinks the gene his group is hunting will turn out to be the one for the nicotinic receptor, they have not proved it yet. Further studies in more patients are needed to prove that the abnormal response on the tone test is truly a manifestation of schizophrenia, and to pin down the gene that causes it, as well as mutations that interfere with its function.

But if the finding holds up, Dr. Freedman said, it would suggest that having defective or too few nicotinic receptors may predispose a person to schizophrenia. The fact that some healthy subjects appeared to have the same receptor abnormalities as their schizophrenic relatives would support the idea that the abnormality is a risk factor for schizophrenia, but cannot act alone to cause it.

Dr. Freedman said drug companies were trying to develop medications for schizophrenia that would stimulate the nicotinic receptors, in hope of providing longer-lasting -- and less hazardous -- relief than tobacco, which wears off almost immediately. In the meantime, he said, although he does warn schizophrenic patients that their symptoms might seem worse if they give up cigarettes, he still discourages smoking.

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