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TARGETING SCHIZOPHRENIA

Research shifts to examine role of myelin and suggests new therapies may be on the horizon

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Medicines that alter the brain chemical dopamine have worked for 50 years to calm the hallucinations and delusions of schizophrenia. So it was not a leap for researchers to set their sights on understanding the brain chemical's role, hoping it would spell out why one in every 100 people develops the devastating psychotic disorder.

But that hope hasn't been realized. Dopamine has given only hints about the illness.

The research road is taking a sharp turn. Investigators at Mount Sinai School of Medicine in Manhattan report results in an entirely different path that point to the involvement of myelin, the insulating sheath of nerve fibers.

Myelin, of course, is best known for its involvement in multiple sclerosis. This is the first time it has been strongly implicated in schizophrenia.

The findings have been " quite impressive," said Dr. Joseph Coyle, a professor of psychiatry and neuroscience at Harvard Medical School. "We have not had a new treatment target in 50 years. Having a different perspective may afford opportunities for new therapeutic approaches. It provides a very different look at the pathophysiology [abnormal changes] of the disease."

"We have assumed for 30 years that schizophrenia is a disease of the neurons," commented Dr. Fuller Torrey, a schizophrenia researcher and executive director of the Stanley Medical Research Institute in Bethesda, Md. "Now, all of this new data ... is making us question our assumptions."

The Mount Sinai researchers have identified abnormalities in glial cells, common and abundant cells in the brain's white matter. (The white matter contains the cells that support the higher cortical areas of the brain.) One type of glial cell in the white matter, called an oligodendrocyte, produces proteins that make myelin. Abnormalities in those cells corresponded to disruptions in the electrical connectivity of the brain in the schizophrenic patients studied.

"Think of it as a disconnection syndrome," said Mount Sinai's Dr. Kenneth Davis.

It is still too early to understand the exact damage, the Mount Sinai researchers say. But the

finding implicating myelin, first reported last year in the Proceedings of the National Academy of Sciences, suggests that the illness may be caused by improper connections in the brain's white matter that lead to mixed signals in the areas of the brain's gray matter that generate thought, emotion and behavior.

The Mount Sinai researchers have used gene chips (plates that contain thousands of genes) and brain scans to study schizophrenia, and the results suggest that many of the genes that control myelin are not functioning normally. The finding has sparked worldwide interest, and many labs in recent months have replicated the finding, said Davis, recently named dean of Mount Sinai.

For decades, scientists concentrated on the hallucinations and delusions that are the hallmark of the illness. But Davis and his colleagues have spent years defining and characterizing the more insidious symptoms that don't seem to get better with the antipsychotic medicines that effectively target dopamine.

Spending time with chronically institutionalized schizophrenics at Pilgrim Psychiatric Center in Brentwood, the researchers focused on their problems with thinking and organizing information, lack of motivation and inappropriate emotional and behavioral expressions.

They followed 1,103 elderly patients for at least five years, many of whom agreed to donate their brains at death.

At a recent celebration of Mount Sinai's 150 years, Davis presented findings from an analysis of the first few dozen patients' brain tissue. "You look for groups of genes that might tell a story about the disease," Davis said.

The results were compared to normal brain tissue.

"Only one group of genes showed underexpression," Davis explained - those associated with myelination, the process of insulating the brain's vast cellular communication network. "We saw a perfect separation between the patients' brains and the control group of brains. This is a pretty robust abnormality."

"We were staring at something new, which meant going somewhere we'd never been before," said Vahram Haroutunian, a Mount Sinai researcher who oversees many of the studies. "We were now in uncharted territory.

"At first we were skeptical. My tactic is to do my utmost to kill a finding. But we kept trying, and it wouldn't die." Is there direct evidence of myelin problems in schizophrenia?

Another Mount Sinai scientist, Patrick Hof, has found a 25 percent to 30 percent reduction in the number of oligodendrocytes in the diseased brains.

While there are no direct ways to look at myelin, some tools allow scientists to measure the organization of the fibers that send electrical messages from cell to cell in the white matter. Dr. Monte Buchsbaum, who heads Mount Sinai's brain scan lab, has found disorganization in the

way fibers flow across the brain.

At least four other labs have independently replicated these findings, Davis said.

Schizophrenia seems to strike most often in late adolescence or early adulthood. Interestingly, myelin doesn't finish its job coating the axons, the long terminals that branch off neurons, until then either. "It is a bit too much of a coincidence," Haroutunian said.

But the scientists don't know why the oligodendrocytes are sick and why the myelin that is made is abnormal, added Kelvin O. Lim of the University of Minnesota, who also has done ground-breaking work on white matter abnormalities in schizophrenia.

It's also too early to know what treatments might work. "It won't be as simple as replacing myelin," Davis said. The researchers know what is happening at the level of the gene but still don't understand what's going on at the protein level. It could be something else that is making the oligodendrocytes sick.

There is no evidence that schizophrenia is an autoimmune disease like multiple sclerosis, Davis added.

If the disorganized glial tracts of the white matter are laid down early in life, scientists suspect that symptoms could emerge at the same time the prefrontal cortex is called on to organize an adult life.