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SCHIZOPHRENIA EMERGES OUT OF THE GRAVEYARD OF NEUROPATHOLOGISTS

BY KRISTEN COSBY

At the International Congress of Neuropathology in 1972, the famed neurologist Fred Plum summarized the pervading attitude towards schizophrenia in a now-infamous phrase: "Schizophrenia is the graveyard of neuropathologists." Plum thought that not only had nothing been learned about schizophrenia from the study of the brain, but that nothing could be learned. The human brain was still largely considered an unknowable organ. Plum's remark may seem counterintuitive from our current perspective—in the past two decades neuroscience has experienced a sort of renaissance. In vivo neuroimaging, neurophysiology, and postmortem neurochemical studies have allowed researchers to gather data on the activities of brain cells in normal and afflicted tissue as never before. What was once considered unknowable—the causes of human behavior, emotion, and motivation—now seems within our grasp. And the field of neuroscience is now a vast landscape, with seemingly endless possibilities for investigation.

David Lewis's approach to understanding and treating schizophrenia starts with the cognitive impairments associated with the disease.

ILLUSTRATION | NICOLE FICHERA

So where do you begin to try to understand schizophrenia? Historically, the study of schizophrenia has been problematic because of its evasive, heterogeneous nature. Different people contract the illness for different combinations of reasons (both genetic and environmental), and there is no diagnostic test for schizophrenia. Patients are diagnosed with the disease after the onset of the severest of symptoms: psychosis. In other words, treatment can only begin after the disease has significantly altered brain function.

Researchers eventually realized that the antipsychotic effects of chlorpromazine stemmed from its ability to block type 2 dopamine receptors.

Today, more than half a century after its introduction, psychiatrists still treat schizophrenia with derivatives of chlorpromazine.

But if the University of Pittsburgh's David Lewis—an MD, chair of Pitt's Department of Psychiatry, and UPMC Professor of Translational Neuroscience—is correct, the route to the next generation of therapies for schizophrenia will appear from looking elsewhere. Decades of research have convinced Lewis that we can identify and treat the disease better by understanding aspects of the disease you don't hear much about—people with schizophrenia struggle profoundly with working memory and certain other cognitive tasks. Patients with schizophrenia typically score 1 to 1.5 standard deviations below the mean on cognitive tests. They are likely to have trouble absorbing or manipulating the information needed to perform daily functions. Even something as basic as remembering and dialing a phone number is challenging when your working memory is impaired.

And unlike psychotic episodes, which can be treated, the cognitive impairments are considered permanent and constant.

Lewis has been hailed as one of the most innovative and creative contributors to the field of psychiatric illness by many of his peers, mentors, and even the director of the National Institute of Mental Health. Now a lot of people are watching to see how his approach unfolds. An alternative method of treatment based on Lewis's work is already in phase II trials.

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If a patient experiences delusions, hallucinations, and speech or cognitive impairments, has been ill for more than six months, and *cannot be diagnosed with any other condition*, a psychiatrist will give the diagnosis of schizophrenia. So the diagnosis is one of exclusion. It's uttered when nothing else can explain these symptoms.

In the early 1950s, a French pharmaceutical company developed and distributed chlorpromazine—the first effective treatment for schizophrenia and the first marketed (under the trademarked name Thorazine) antipsychotic—but its champions had no idea how the drug worked to reduce the effects of psychosis.

Lewis

In the past two decades, tissue studies have revealed a common neurochemical characteristic of schizophrenia: increased activity of the neurotransmitter dopamine at the basal ganglia (a group of interconnected nuclei near the upper brain stem and deep in the cerebral hemispheres that allow us to make voluntary body movements and to control speech and other social behaviors). The dopamine receptors control the neural signaling that influences important behaviors and certain kinds of memory.

When he was a psychiatry resident at the University of Iowa, Lewis encountered a number of patients who experienced hallucinations and delusions. His encounters with one young patient, an 18-year-old who suffered from schizophrenia, has remained with him.

"One of the things that really struck me about the cost of the illness for him was that although his hallucinations and delusions were suppressed with medication, he was still very impaired by his inability to engage in actions," Lewis recalls.

"There was this disconnection between his stated desires and his ability to make decisions, to take initiative, and to think through a course of actions that would be required to achieve his goals. My impression at the time was that he seemed to be trapped in a world that he didn't like, but unable to plan or take actions to get into a different world.

"That experience with him gave me an appreciation for the complexities and the burden of the illness." It also turned Lewis's attention to the study of psychotic disorders and how executive processes, like cognition and working memory, become disrupted.

Although schizophrenia is not diagnosed and, therefore, not treated until the onset of psychosis, many studies indicate the impairments in cognition are present much earlier in life—though not all people who demonstrate the cognitive challenges associated with the disorder are later diagnosed with it. According to Lewis, the opportunity to treat schizophrenia before the onset of psychosis lies in our ability to understand which neurocircuits malfunction in the brains of people with schizophrenia and in our ability to understand how healthy circuits and diseased circuits develop differently in adolescence. (To learn what Lewis and a number of researchers at Pitt are discovering about the effects of cannabis use during this vulnerable time, see p. 17.)

He is interested in the interactions of two kinds of cells in the dorsolateral prefrontal cortex, which is, not surprisingly, a region of the brain associated with cognition and working memory. The two types of neurons, pyramidal cells and chandelier cells, communicate using GABA neurotransmitters. (GABA is a molecule that determines when neurons are active and their level of activity.) The long, tree-like pyramidal cells span several layers of

the cortex. The chandelier cells talk only with pyramidal cells and powerfully control their activity. The pyramidal cells are responsible for much of the electrical signaling in the prefrontal cortex and are essential for cognition. Over the years, postmortem tissue studies (several of which Lewis's lab completed) have revealed that pyramidal cells in the brains of adults with schizophrenia are stunted. Lewis thinks that in adolescents likely to develop schizophrenia, the pyramidal cells and the chandelier cells fail to cultivate the kind of "relationship" necessary to create the strong, organized neural firing that produces healthy cognition. It's not clear whether this is caused by excessive synaptic pruning during adolescence or whether children born with a predisposition toward schizophrenia have fewer synapses to begin with.

The drug in a phase II clinical trial targets GABA transmissions from chandelier cells to pyramidal cells. The treatment has demonstrated an ability to improve synchronicity in the electrical activity of the prefrontal cortex and shown signs of improving working memory in patients with schizophrenia. Though the conceptualization of the precise role of chandelier cells in the circuitry of the prefrontal cortex has changed since the trials of the drug began two years ago, Lewis believes those cells remain a proper target for new drug therapies. "It turns out we think the drug should have the same beneficial effects, but perhaps for a different reason," says Lewis.

For Lewis, new information about synaptic activity that complicates a drug study is an advancement, not the source of a headache; it illuminates something new about the disease process. "The pursuit of drug development in psychiatry is rapidly changing because of our growing understanding of what's happening in the brain, in the illness, and how the brain normally functions," notes Lewis.

"This is an incredibly exciting time to be in psychiatry because of the advances that are being made in the basic sciences that are critical to our field," he adds. "We have the opportunity to consider novel linkages and relationships between different areas of investigation and with a level of resolution that is unprecedented."

Lewis's line of research into chandelier cells was featured in the Nov. 10, 2010, edition of *Nature*, which was well received by many of his colleagues. John Morrison, dean of basic sciences and the Graduate School of Biological Sciences at Mount Sinai, and a mentor of Lewis's during his days as a postdoc, says, "The therapy that's been used for schizophrenia for years has been dopamine based and that's … still useful in many ways, but I think [Lewis's] work will open up other therapeutic strategies for schizophrenia." These avenues could include both new drugs and cognitive behavioral therapies, which, Lewis speculates, might help strengthen and maintain healthy synaptic processes through, for instance, repetitive computer training.

Lewis is fond of sayings. His favorite was acquired from one of his mentors, Floyd Bloom, an MD, former editor-in-chief of *Science*, and former chair of the Department of Neuropharmacology at the Scripps Research Institute, who often asked his mentees, *Now that you know what you know, what do you know?*

Lewis uses this phrase so often that, three years ago, his graduate students gave him a bobblehead doll of himself with a voice recording that could be heard when a button on the doll is pressed. The recording is a chorus of his students repeating the line.

Now that you know what you know, what do you know? The question might seem redundant or simple, but Lewis's lab is all at once attempting to figure out schizophrenia's toll on cognition and working memory, as well as mapping the development of neurocircuitry in the prefrontal cortex during adolescence. And when you are taking on all that complexity, knowing what you know isn't always clear.

But the science is crystallizing. "When I entered the field of schizophrenia research," says Lewis, "there were lots of different opinions about the core clinical features of the illness and about the nature and location of the brain disturbances that resulted in those features. In the past two decades, the field has moved substantially to a more unified view of the core feature [cognitive deficits] and the underlying cortical circuits." Although less dramatic than delusions or hallucinations, cognitive deficits may provide avenues for earlier intervention.

When Lewis started his education as an undergraduate student of psychology and then a med student at Ohio State in the mid-70s, he intended to become a psychotherapist. But he was disappointed to find that practitioners working with patients suffering from psychiatric disorders concerned themselves primarily with theories of personality and human behavior rather than empirical studies of the brain.

WIKIPEDIA

Thorazine (aka, chlorpromazine) helped people with psychosis decades before anyone knew how the drug worked.

"The idea of using a solid empirical basis, a set of facts from experiments, using that to intervene therapeutically with someone, it just didn't exist then. Or at least I wasn't exposed to it," says Lewis, who also serves as director of both Pitt's Translational Neuroscience Program and of its NIMH Conte Research Center. He found that to be extremely problematic and limiting. He says, "I was disenchanted … People seemed to have abandoned a key principle of medicine, which is that you have to look at the organ that's diseased.

"You have to look at … the level at which it's organized, which, with the brain, is the circuits, the cells that form the circuits, the molecules that determine the functions of those cells. That kind of physiological basis wasn't there [when I was a student].

"That concept [of starting with the diseased organ] is not innovative at all. It just

hadn't been directly applied or completely applied to psychiatry," says Lewis.

After completing his internal medicine and psychiatry residencies at the University of Iowa, Lewis went on to (what's now called) the Scripps Research Institute as a visiting investigator in neuroscience and endocrinology. In December 1984, just after starting at Scripps, Lewis attended the annual meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico. At the conference, he heard two talks. The first demonstrated, using the first positron emission tomography (PET) imaging studies, that the prefrontal cortex of individuals with schizophrenia was clearly disturbed when they were conducting a task that involved working memory. The second, given by the late Patricia Goldman-Rakic, a PhD, was on the essential role of dopamine in working memory function in nonhuman primate studies.

When Lewis returned to his hotel room the night after the second talk, his mind was abuzz. He sat at his hotel desk scrawling notes, synthesizing what he saw as two clearly related studies of working memory. "It was a real lightbulb moment. … This was the strategy that would help me understand … the normal circuitry that contributes to working memory and how that circuitry is disturbed in schizophrenia."

Ten years of meticulous research passed between his lightbulb moment at the conference in San Juan and the publication of his first integrated study of postmortem tissue of people with schizophrenia and nonhuman-primate tissue. In 1991, he published his first paper on chandelier cells in the nonhuman primate cortex, the same cell type that his lab targeted in its development of the drug now in clinical trials. In 1998, he published his first paper on how chandelier cells are altered during schizophrenia.

When Lewis's predecessor, David Kupfer, now Pitt's Thomas Detre Professor of Psychiatry and professor of neuroscience and of clinical and translational science, became chair of the Department of Psychiatry at Pitt in 1983, he set out to build an "academic powerhouse." He recalls, "We really wanted to recruit some young people who, while being psychiatrists with MDs or MD/PhDs, would bring an element of strong basic science so that we could figure out better interventions, better drugs, better ways of thinking about prognosis, better understanding of genetics of all these disorders."

Lewis was his first recruit. While attending a series of talks at Floyd Bloom's lab at Scripps, Kupfer encountered the young man and was immediately struck by his proficiency with tissue studies.

After listening to Lewis's lecture, a colleague of Kupfer's who had accompanied him to the lab, turned to him and said, "He's the one!" From that moment on, Kupfer conspired to bring Lewis to Pitt. "Sometimes you can identify a star before he becomes a star. We were lucky to get him. He's what you call a productive Midwesterner!" Kupfer says, laughing.

Morrison, who was Lewis's mentor at the time of Kupfer's visit, agrees. "Perhaps as much as anyone who's ever trained with me, David took that training [in neurochemistry] and expanded it beautifully into all the approaches that he now takes into understanding human neurologic and psychiatric disorders. Twenty-five years later, he is still one of the leading figures who is bouncing between what he can use from the nonhuman primate and the diseased human brain. What he's been able to do is to show precisely what is disrupted in schizophrenia," says Morrison, referring to Lewis's stubborn pursuit of chandelier and pyramidal cells.

In the past 25 years, Lewis has published more than 250 papers, 65 book chapters, and two books. In the process, he has amassed a number of awards and acknowledgments of his work, including being chosen as the president-elect of the American College of Neuropsychopharmacology and a member of the Institute of Medicine. He is the only investigator in the United States to have simultaneously held a Senior Scientist award, a MERIT award, and a Conte Center Directorship from the National Institute of Mental Health.

Now he has his own saying that his graduate students repeat: *When a disease process is at issue, the answer is in the tissue.*

Every year since 1987, Pitt's psychiatry program has garnered more National Institutes of Health funding than any other psychiatry program in the country. It certainly has become a research powerhouse. What attracted Lewis to Pitt in the first place, and continues to impress him, is the strength of the faculty's research and the amount of collaboration that occurs within the department and with other members of Pittsburgh's neuroscience community.

"I think we've contributed to changing the mind-set about the importance of looking at tissue from people with psychiatric illnesses, schizophrenia in particular. And I think we helped contribute to raising the bar on the standard of how the work was done," says Lewis, who assumed the position of department chair in 2009.

"I see my role as chair now to stimulate people to find linkages and the points of intersection across their different strategies and approaches. Ultimately we need to have a fundamental understanding of brain circuits and their dysfunction, but we have to take that knowledge all the way through to applications in the real world of clinical care. We can know a lot about the illness, but if we don't bring the capacity to bear in the real world where our patients live and under the challenges that they face in society, we won't have accomplished the goal.

"We're trying to move the field into preemptive interventions. This is particularly important in psychiatry because many of the targets we treat are pretty far along in the disease process. In a sense, the treatment of schizophrenia today is the heart-disease equivalent to treatment after a patient has had a myocardial infarction. What we desire to do is to push the field so we are making interventions before the disease has a major functional impact."

In the case of schizophrenia, treating patients earlier in the disease process would allow doctors to assist patients in salvaging more of the neurocircuits necessary for completing cognitive tasks and preserving working memory. With a greater variety of targeted drug and cognitive therapies, we can hope that patients will be able to lead happier, more productive lives—and not be trapped in worlds they don't like. ■