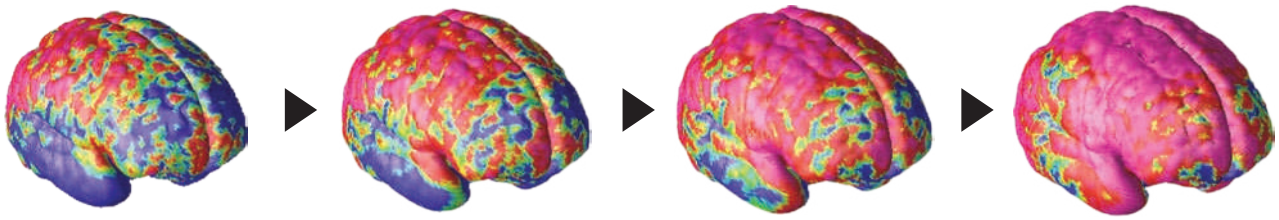
THE MAKING OF A TROUBLED MIND



Schizophrenia appears during adolescence. But where does one begin and the other end?

BY DAVID DOBBS

Rachel had just given birth to her third child when she became overwhelmed by the noise on the obstetrics ward, grew sharply paranoid about her sister, and in short order descended into her first schizophrenic episode. She was 28. Although it was only then that she started hearing voices — those of her family, distant screams, messages from spaceships — she and her psychiatrist came to see that there had been whisperings of this long before.

As a child — bright, but awkward both socially and physically — Rachel tended to keep to herself. She crammed her drawings full of the sort of elaborate fractal detail often seen in the work of psychotic artists. In her teenage years, some of her difficulties worsened. Acutely sensitive to noise, she was aware of the refrigerator cycling off and on, footfalls from the apartment next door, the traffic outside. Only in retrospect did any of these peculiarities seem ominous.

As Rachel's psychiatrist Robert Freedman explains in his book *The Madness Within Us,* where he writes about Rachel, that's how it is with the early flickers of paranoia, confusion, hypersensitivity and hallucination in people who develop schizophrenia. They often emerge exactly when adolescence is throwing the body and brain for a loop, and years before the disease manifests itself fully. "The problem with early symptoms," says Freedman, who is chair of psychiatry at the University of Colorado, Denver, and editor-in-chief of the *American Journal of Psychiatry*, "is

During adolescence grey matter is lost (pink), a process that may speed up in early-onset schizophrenia — hinting at the origins of the disease.

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that they're not very specific. At a time when thinking, emotion and behaviour change a lot anyway, these early indicators are very hard to separate from normality."

Even so, this overlap of schizophrenia's early signs with the hallmarks of adolescence has made this period a beacon to researchers. Over the past 20 years, studies have shown that the adolescent brain undergoes major developmental changes. Autopsy and imaging studies, for instance, have revealed that during childhood and adolescence the brain routinely prunes away vast numbers of synapses — the junctions between neurons across which electrical signals flow — and that this pruning seems to go on longer and farther in people with schizophrenia. Other work has shown that adolescence brings major upgrades to the neural networks that generate powers of judgement, cognition and behavioural control — building new circuits, remodelling old ones and discarding some altogether. The idea that schizophrenia arises from miscues or shoddy work in this complicated and delicate project has sparked a huge variety of research. Many basic neuroscientists are trying to work out what goes wrong on genetic, cellular, circuit and systems levels. Meanwhile, at the level of diagnostic practice, some researchers argue that subtle symptoms can not only be distinguished from normal adolescence, but can provide a reliable indicator of future disease.

In a pattern all too familiar to students of schizophrenia, none of these efforts has revealed the secret of this fiendishly complex disorder. One leading researcher, David Lewis, at the University of Pittsburgh's Western Psychiatric Institute and Clinic in Pennsylvania, has spent the past two decades exploring schizophrenia's developmental roots. Yet even Lewis says it's still too soon to know whether any given line of study, no matter how promising, is homing in on the schizophrenia puzzle's most essential component, if such a thing exists.

"It's more like getting a much better picture of one part of the elephant," he says, referring to the old parable of blind men collectively describing an elephant's nature by individually feeling its different parts. "I think it's working. When I talk with other researchers working other ideas, I'm encouraged that I'm onto something important, and even more encouraged that we all seem to be feeling our way around the same animal."

TEEN BRAIN

By many accounts, Lewis is running one of the more comprehensive and sustained attempts to explore normal and pre-schizophrenic adolescent brains. He is taking what neurologist and depression expert Helen Mayberg at Emory University School of Medicine in Atlanta, Georgia, describes as "one of the smartest, most creative and most promising angles I know of on schizophrenia".

Lewis has focused on a particular circuit in the dorsolateral prefrontal cortex (DLPFC), a multilayered region that is crucial to tying the threads of experience, memory, thought and emotion into a coherent, consistent view of the world (see 'Cellular culprits in schizophrenia'). The DLPFC builds and refines much of its complicated circuitry during childhood and adolescence, responding to both genes and experience. Much of Lewis's work examines the relationship, during this developmental period, between two types of cell: pyramidal neurons, which span several layers of the cortex; and chandelier cells, which sit near the base of the pyramidal cells. His concentration on them is one of those stubborn scientific projects that seems to produce little until, suddenly, it produces a lot.

Pyramidal cells, so called because their central bodies are triangular, generate much of the complex electrical signalling that takes place in the DLPFC and in the prefrontal cortex as a whole. Their effectiveness in this task depends heavily on the richness of branching in their long, tree-like forms. Multiple postmortem studies, including some by Lewis, show that in adults with schizophrenia, these pyramidal cells have smaller cell bodies and fewer of the protrusions called dendritic spines that receive input from synapses[1]. In the pyramidal cells in layer 3 of the DLPFC, which communicates extensively with other cortical regions and is key to powers of working memory that often falter in schizophrenia, Lewis found the dendritic spines reduced in number by about a quarter.

Most developmental neuroscientists suspected that this sparse branching resulted from aberrant synaptic pruning during adolescence. Pruning is a sort of clean-up job conventionally thought to eliminate weak synapses and leave strong ones. In schizophrenia, it was suspected, the pruning process hacked away indiscriminately, knocking out strong synapses along with weak ones.

In 2008, Lewis's team found evidence that argued against this idea in the brains of normal monkeys, whose PFCs develop along timelines comparable to those of humans[2]. The group found that the great majority of synapses in the layer 3 pyramidal neurons were functionally mature before pruning started. This left few immature or weak synapses to trim away. If this holds with healthy humans as well, Lewis argued, then schizophrenia cannot arise from a failure to select and prune away weak synapses, for there is not much to select. This and other discoveries led Lewis to offer an alternative hypothesis: that pyramidal cells in individuals with schizophrenia had weaker synapses before pruning ever began[1,3].

"We have to draw in dotted lines here," says Lewis. "But our suspicion is that early on, when someone destined for schizophrenia has an excess of synapses, the quality of the synapses doesn't matter so much, and the person does okay. Then later, when the pruning starts, the problems slowly become apparent, because they've lost their reserves."

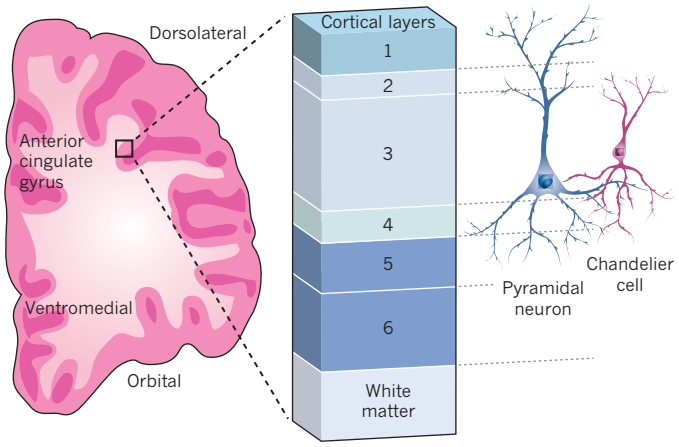
Lewis wanted to trace the story further back than that. What might be stunting the development of pyramidal cells in the first place? He suspected chandelier cells. Over the years, Lewis's group and others have built an increasingly strong case against the ornately branched chandelier cells, which seemed to communicate only with pyramidal cells. Lewis's autopsy work, for instance, had found that chandelier cells took huge hits in schizophrenia[4], with some proteins in their synapses reduced by about 40% — a sign that these junctions were not working normally.

For many years, everyone assumed that chandelier cells only had an inhibitory role: when 'talking' to pyramidal neurons, they said only 'calm down'. Then, about five years ago, a team led by Gábor Tamás at the University of Szeged in Hungary found that chandelier cells also have an excitatory role, sometimes shouting 'fire up'[5]. Groups led by Tamás, Lewis and others have all done work showing that the chandelier cells seem to be key contributors to the complex activity of their pyramidal neighbours. Last year, for instance, Karl Deisseroth's lab at Stanford University in California used sophisticated genetic techniques on mice to turn on and off a class of neurons that includes chandelier

CELLULAR CULPRITS IN SCHIZOPHRENIA

REF. 1

According to one hypothesis, schizophrenia may trace back to defects in pyramidal and chandelier cells in the dorsolateral prefrontal cortex that lead to clinical symptoms only in adolescence.



cells — and found that this started and stopped much of the animals' organized PFC activity[6].

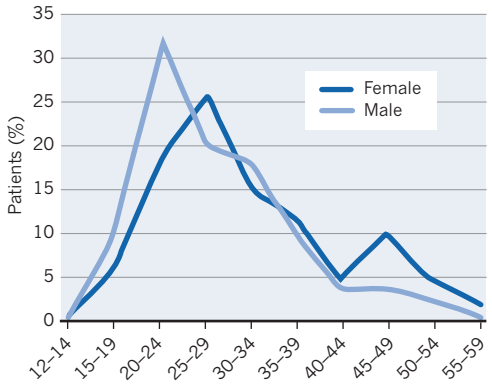
Lewis thinks that in people who later develop schizophrenia, chandelier cells fail at some crucial task of cultivating pyramidal cells during childhood or early adolescence. Together they do not generate the organized neural traffic required for building robust connections; and later, the weakness of both cell types leaves the PFC incapable of creating the vigorous, coordinated firing — including a type of electrical activity called gamma synchrony — that generates working memory. The result, subtle but increasingly apparent as synapses are pruned during adolescence, is a brain that can't consistently organize either its electrical activity or its thoughts: the shattered mind of schizophrenia.

Tom Insel, the director of the National Institute for Mental Health in Bethesda, Maryland, says that Lewis's model of this chain of dysfunction "provides something this field really needed: a framework for linking observations at the molecular, cellular and systems levels. We haven't had a story that crossed those levels of explanation before. And his story, whether it pans out in all its details or not, is invaluable for doing that."

While still thinking big, Lewis is filling in some of those details. Chandelier cells, for instance, signal using GABA, an inhibitory neurotransmitter. Lewis is trying to figure out whether errant GABA dynamics in schizophrenia are a cause of chandelier cell dysfunction or a compensation for it. He recently found that aiming an experimental drug at certain GABA receptors in chandelier and 'basket' cells (another kind of interneuron) boosted schizophrenia patients' gamma synchrony — and showed signs of improving their working memory. He's now trying to decide whether to aim another drug at those receptors or search for a different lever to pull — something that would reveal more cleanly the links among GABA, chandelier cells and the dysfunctions of schizophrenia. "You constantly have to balance this kind of close work with the big picture," he says.

ACCENT ON YOUTH

Distribution of age at first admission for schizophrenia in males and females.



SOURCE: M. CANNON & P. JONES *J. NEUROL. NEUROSURG. PSYCHIATRY* **60,** 604–613 (1996)

For Lewis, the balancing act means tracking and responding to other lines of research, such as the work of clinical psychiatrist Anissa Abi-Dargham at Columbia University, New York. Abi-Dargham is using brain-imaging tools to explore whether flaws in evolutionarily older, subcortical areas that use the neurotransmitter dopamine are driving developmental problems in PFC circuits, or whether the problems in the PFC alter dopamine function. Lewis considers these connections between research programmes another sign that schizophrenia study has advanced in the last decade or so. "Used to be," he says, "we just got tired of a hypothesis or hit a dead end and went onto something else. Now we're actually integrating hypotheses or testing one against another.

"Or if you want to put it another way," he says, laughing, "we're getting a bit more synchrony in these findings. The communication between the blind men is improving. The elephant is starting to come together."

RUNNING AHEAD

The focus on adolescent brain development that has been so valuable in research generates controversy among clinicians, however. Particularly contentious is the idea of clustering schizophrenia's early whisperings into a diagnosable 'prodrome' period during adolescence. (The term comes from a Latin word meaning 'running ahead'.) The disease is typically diagnosed in young adulthood (see 'Accent on youth').

The North American Prodrome Longitudinal Study, or NAPLS, is an eight-centre project formed in 2003 that has been testing ways to reliably diagnose people in such a prodrome stage and treat them with psychotherapy, cognitive training, family therapy or drugs in the hope of forestalling worsening problems. NAPLS's main diagnostic tool is a questionnaire it calls the Structured Interview for Prodromal Syndrome. It scores symptoms such as fragmented or unusual thoughts; family histories of psychosis; social or school troubles; and paranoia or other peculiarities of emotion, behaviour or thinking.

In 2008, the group reported on 291 adolescents and young adults that the questionnaire identified as being at 'very high risk' of developing schizophrenia or other psychotic disorders[7]. Within 2.5 years of screening, 35% suffered psychotic episodes. The NAPLS researchers say that a set of prediction algorithms derived from those results afterwards, and then run again on the same data, raises the screen's predictive accuracy to almost 80% — comparable, they say, to risk predictions for medical problems such as heart disease. The team says that this and other "strong evidence for the prodromal risk syndrome … raises the question of its evaluation for inclusion in *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)" or *DSM* — a move that would lead to wide use of such screens and interventions.

This gravely concerns some clinicians, who point to the unavoidable false positives. "You will inevitably tell people who are not really at risk of schizophrenia that they are 'at very high risk'," says Til Wykes, a King's College London clinical psychologist who specializes in mental health (see also page 165). The impact could go far beyond inappropriate use of antipsychotic drugs, she says. It could negatively affect how families, friends and the broader community treat that person, as well as their self-conception. "The anxiety this produces may even generate just the thing you're trying to protect against. And you're doing this to people who are what — 15, 16? This is a huge intervention to take with someone who may not be destined for schizophrenia."

Others feel that the benefits of improved treatment outweigh the risks of overdiagnosis. "I frankly don't understand this concern about diagnosing a prodromal period, and I find this concern about overtreatment misplaced," says William McFarlane, a psychiatrist who runs a prodromal diagnosis programme at the Maine Medical Center in Portland. McFarlane argues that inclusion in the *DSM* would bring consistency of diagnosis and treatment to more people.

Many of the scientists untangling schizophrenia's complex developmental threads don't believe they yet have the tools to reliably discern a prodromal period — let alone treat it. "We have better ideas about what's going on than we did in the past," says Lewis, "but we do not yet have a target, or an intervention for that matter, that has a high enough likelihood of success."

Freedman thinks the state of knowledge requires caution and humility. "Schizophrenia research is full of people who are sure they know what they're doing, and only later do we understand that the whole paradigm was off. Then we look back in amazement at how wrong they had it. I like to think everyone in my generation would be well aware of this history, and be reluctant to say we're there." ■

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