Explorations and revelations taking place in the medical school



A percolation model of the brain, borrowed from mathematicians, may help scientists wake up to how anesthesia and other puzzles of consciousness and cognition work.

PERCOLATING BRAINS

CONSCIOUSNESS AND COGNITION BECOME CLEARER | BY CHERYL ALKON

Some coffee drinkers claim they can't wake up or properly process information until they've downed their third cup of joe.

But how, exactly, does a noggin wake up? How is sensory information, like the heavy smell of a Colombian roast, transmitted across the brain and turned into an enticing thought? The mechanics of consciousness and cognition have been a puzzle for biologists and philosophers alike. Researchers at the University of Pittsburgh have come up with a new model explaining how the brain operates—and, well, it works like a coffeemaker.

With coffee production, water randomly flows through coffee grounds and a filter in a process called percolation. The liquid coffee eventually seeps into the bottom of the pot. Likewise, in the brain, information—in the form of external sensory stimulation such as images, sounds, or smells—gets processed as it travels through our neurons. This information moves from the thalamus, which acts like a relay station deep in the brain, to the cortex, where cognition and memory are formed and stored, explains Yan Xu, a PhD professor of anesthesiology, structural biology, and of pharmacology and chemical biology, and the vice chair for basic sciences in Pitt's Department of Anesthesiology.

This model is a way to grasp the complexity of the brain, Xu adds. "There are so many neurons in the brain. If you want to understand the general rules governing how the brain works, you will have to ignore some of the details," he says. "It's like the universe—you cannot study the details of every star. You have to abstract it out to understand the universe."

To abstract out brain workings, Xu and colleagues at Pitt and Carnegie Mellon University applied percolation theory from the field of mathematics. This approach illustrates the behavior of clusters that are connected directly or indirectly through other clusters and their connections.

Xu's team divided the brain into grids they called "nodes." ("Node" is a common term in neural network literature for groupings of cells or brain regions that are not anatomically defined.) Then the team calculated the probabilities that connections existed between the different nodes. Using a computer simulation, they found that the odds of a connection being present between nodes could be as low as 30 percent for the percolation of information to occur.

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The team's work, "Percolation Model of Sensory Transmission and Loss of Consciousness Under General Anesthesia," appeared in the Sept. 4 issue of *Physical Review Letters*, the premier physics journal published by the American Physical Society.

Xu, who has studied anesthesia mechanisms for the past 23 years and has been continuously funded by the National Institutes of Health for the past decade, says there are still many questions about how anesthesia works at the molecular and cellular levels. The percolation theory offers one explanation.

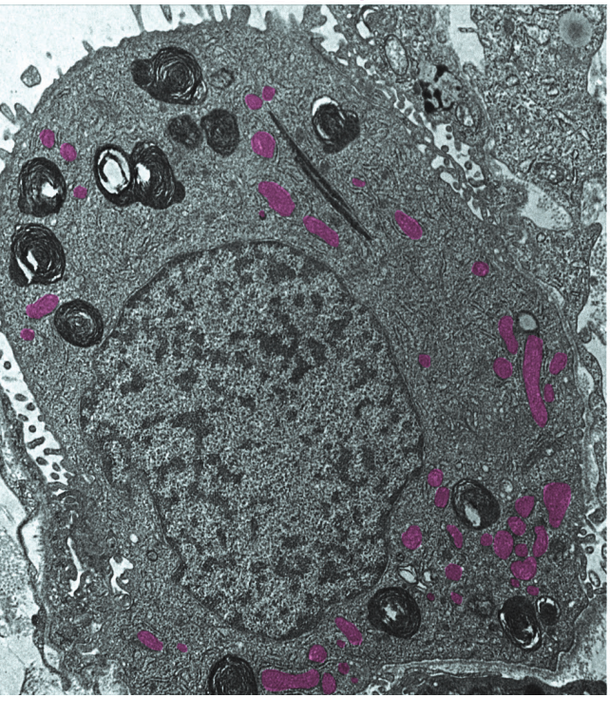
Xu's team validated their percolation model by showing that it reproduces key features clinically observed in recordings of brain activity when patients are transitioning from consciousness to unconsciousness under general anesthesia. In their model, changing a single variable that decides whether a connection is on or off can manipulate the system to replicate many of the changes that appear in brain waves when the mind is switched off under anesthesia.

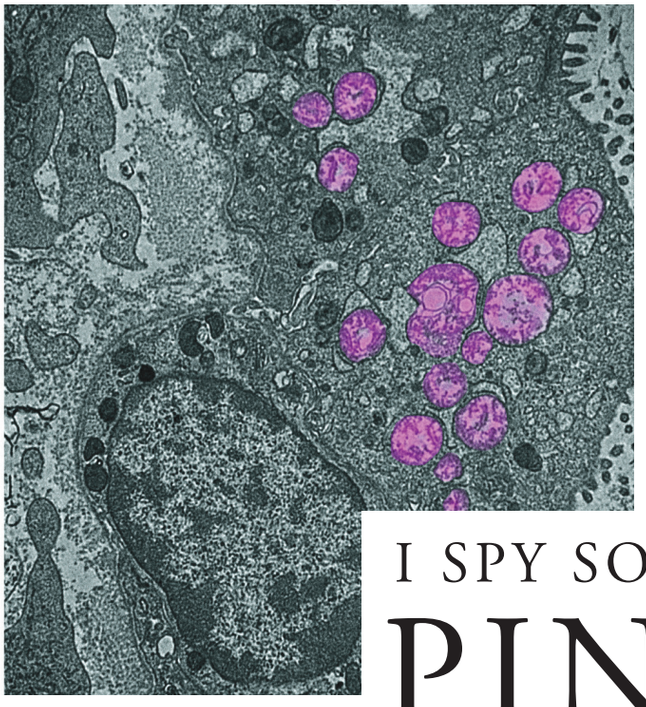
"What is remarkable from a theoretical point of view is that a simple abstract model can recapitulate essentially all salient features in a system as complex as the human brain when it transitions between conscious and unconscious states," Xu says.

Returning to the metaphor of the coffeemaker, if a sheet of plastic is covering the coffee grounds to prevent water from running through them, the coffee will never reach the bottom of the pot. "The brain is the same way—you can use anesthetics to interfere with the information flowing from one end to the other to block cognition," says Xu. "The theory allows you to understand the fundamental rules that govern how our mind works—and how anesthesia works to turn it off."

Xu says scientists can use the model to examine questions like how and whether the brain learns in various states of consciousness (including under anesthesia), how memories are formed and retrieved, and why there is a surge in high brain-wave frequencies in the EEG of a near-death patient. n

ILLUSTRATION BY STACY INNERST





The shape of mitochondria (fuschia) changes from small sausages in a healthy lung to swollen circles in a lung with idiopathic pulmonary fibrosis.

COURTESY MARTA BUENO AND JUDITH BRANDS

ONE DISEASE UNVEILS THE MECHANISM OF ANOTHER

BY KRISTIN BUNDY

I SPY SOMETHING PINK

Gray hair, wrinkles, perhaps a love of bath slippers—these are some of the universal signs of aging that we anticipate as we get older. Other age-related changes tend to be unique to each body. Some folks might not breathe as easily as they did during their racquetball days. Others might not remember what they did to pass the time yesterday. Although these ailments seem to be separate complications, there is new evidence that the underlying biology of some age-related diseases may not be so different after all.

One University of Pittsburgh team recently uncovered a connection between ailments of the lung and the central nervous system that tend to arise as we get older. Idiopathic pulmonary fibrosis (IPF), a progressive disease characterized by hardened connective tissue in the lung, might have ties to Parkinson's disease, which results from abnormal brain activity that first affects motor skills and can lead to dementia.

So how do the twain meet? The answer seems to lie in the mitochondria and how these sausage-shaped energy factories deal with aging and stress—a mechanism unknown in IPF until now.

Ana Mora, an MD and assistant professor of medicine in Pitt's Division of Pulmonary, Allergy, and Critical Care Medicine, and her team recently revealed the role mitochondria play in IPF. Those results were published in the February issue of *The Journal of Clinical Investigation*.

"Mitochondria was, for us, a natural target," Mora says. In IPF, the deposits of hardened connective tissue, or fibrosis, show up in the lung's alveolar epithelium; the epithelial cells contain the majority of the mitochondria in the lung, she says. "Any change in the mitochondria function probably makes [the cells] more vulnerable to injury and disease."

"And the second aspect that we thought was: [People investigating] age-related diseases have found that mitochondria also are an important factor for pathogenesis, especially [in] neurodegenerative diseases like Parkinson's."

Mora and her team began their investigation with IPF patient lung tissue samples they already had in the lab and confirmed that the epithelial mitochondria were indeed swollen, were less organized, and had accumulated in the cell, signifying insufficient mitophagy (the mitochondrion's inner quality control system).

Then they reviewed epithelial cells from lungs of healthy human donors of all ages and confirmed that mitochondria do become more dysmorphic and dysfunctional with age, but the effects are not as exaggerated as in patients with IPF. The team corroborated these results in mouse models.

"With age and stress, when we put [them] together, we can recapitulate the phenotype that we're seeing in the disease," says Mora. But age couldn't be the only factor that would lead to IPF; otherwise many more people would have the disease. So they began to think about the mechanism.

"We remembered that in Parkinson's disease, there has been a description of similar kinds of phenotypes, and they were associated with a mutation of a protein that is called PINK1," Mora explains.

So the team probed into the potential "pinkness" of IPF epithelial cells. They found that the cells are deficient in PINK1. Mora's team collaborated with Pitt's Charleen Chu, an MD/PhD, professor of pathology, and the A. Julio Martinez Professor of Neuropathology, to study PINK1-deficient mice that had been used to study mitochondrial pathobiology and Parkinson's.

Mora and colleagues analyzed the mitochondria in the epithelial cells of the alveoli without the presence of PINK1 in these mice, and sure enough, they were spontaneously swollen, and the lungs showed deposits of collagen. They then challenged the PINK1 knockout mice with two different types of stressors. Again, the epithelial cells were more prone to die, and the lungs were more likely to develop fibrosis.

The team concluded that if a cell doesn't express enough PINK1, the mitochondria's shape and function become abnormal, and cells begin to fail as they work harder to repair and proliferate during injury. In IPF, instead of mending, the cells try to close the wound in an exaggerated way, which turns into fibrosis.

Despite the PINK1 mutation connection, scientists don't know whether patients with Parkinson's are at any more risk of having IPF or vice versa.

Mora says their next code to crack is understanding "other hallmarks of aging that bring susceptibility to disease." n



GETTY IMAGES

KIDS TELL IT LIKE IT IS

BY JENNY BLAIR

LISTEN UP, DOCS

Imagine you're an HIV-positive teen leaving a clinic appointment, and you're miffed because the doctor only talked to your mom. Then you spot a poster for a medical study looking to sign up youth, but the description is so complex that you can't figure out what the study involves.

It's easy for health care professionals to fail spectacularly at connecting with young people. But in Pittsburgh, youth are speaking up, and providers and researchers are listening. In two groups associated with the Division of Adolescent and Young Adult Medicine in the Department of Pediatrics at the University of Pittsburgh, young people discuss and create lasting change in how they interact with health care. It's all part of the division's philosophy, which underlies the respectful way its faculty interact with youth. (See "You Don't Understand!" *Pitt Med*, Spring 2015.) Division chief Elizabeth Miller, an MD and PhD anthropologist, sums it up this way: "If you're actually going to do work with adolescents, it's really helpful to have them involved."

ADVISING RESEARCHERS

Studying youth can be ethically and culturally rocky, but Pitt researchers who want to get it right can check in with the Youth Research Advisory Board (YRAB, pronounced *why-rab*). Every month, this group of young people gets together to advise faculty who want to reach out and study the teen and young adult demographic. Trained in research ethics from Pitt's Institutional Review Board and the Clinical and Translational Science Institute, YRAB members weigh in on questions like: Is this recruiting poster free of jargon? How can younger teens ethically participate if they'd rather their parents weren't involved?

"It's a really invaluable opportunity for investigators who are kind of in their heads and are only working with a research team on these things," says YRAB's supervisor, epidemiologist Heather McCauley, an ScD. "They can actually have youth as stakeholders in the development of their research projects."

When assistant professor of pediatrics Ana Radovic, an MD, was designing a confidential social media website for adolescents with depression, for instance, YRAB members warned her that an option to "like" content could discourage young people whose posts receive few likes.

"The group was very thoughtful about the specific needs of depressed adolescents and helped guide our design to be more patient centered," Radovic says.

ADVISING OTHER PATIENTS

Smoothing the transition from pediatric to adult health care is the *raison d'être* of the Children's Hospital Advisory Network for Guidance and Empowerment, or CHANGE. This group of young people discusses ways to make the transition easier, especially for youth who face barriers to care. Most CHANGE members are experts on these barriers, having coped for years with disabilities, chronic illnesses, and logistical hurdles like living in a rural area. So they're in a good position to support one another and advise parents and health professionals.

CHANGE and YRAB member Megan Marmol is a 20-year-old Carlow University student who lives with a chronic illness. She points out how fraught even a simple medical visit can be for a young person, like when a provider talks to parents instead of the patient herself.

"That causes tension between the parent and the young person," she says. Recognizing this, Pitt providers now make a point of seeing young people alone for the first few minutes of an appointment. CHANGE members have also suggested that potentially intimidating objects like speculums be stored out of sight, and they've reviewed the clinic's welcome letter to make it more patient friendly.

Marmol praises CHANGE for an inclusiveness that many youth might not often experience. After all, the very kids who often feel shunted aside in daily life—the one in a wheelchair, the one who is excluded from the general ed classroom—are often best acquainted with the complexities of obtaining health care. As they talk to one another and give presentations to those who attend CHANGE meetings, Marmol says they are learning to navigate the system with confidence.

"Their voice matters," Marmol says. "The more you can help people develop these leadership skills, their self-advocating skills, their voice—that changes everything." n